CHARLES BONNET SYNDROME: RESTING-STATE FUNCTIONAL CONNECTIVITY, MORPHOLOGY, NEUROCHEMICAL, AND PSYCHOSOCIAL CORRELATES

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A DISSERTATION SUBMITTED TO THE FACULTY OF GRADUATE STUDIES IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

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Abstract

Charles Bonnet Syndrome (CBS) is a debilitating phenomenon characterized by a triad of visual hallucinations, an absence of cognitive impairment, and vision loss that usually affects the ageing population secondary to age-related visual impairment. CBS mechanisms continue to be explored, and it is unknown whether the etiology, timing (early vs. late onset), and locus (central vs. peripheral) of vision loss drive different neurophysiological mechanisms that cause CBS hallucinations. Evidence also suggests that there may be an association between psychosocial health factors and change in CBS hallucinations during the COVID-19 pandemic. My dissertation describes three experiments that examine functional connectivity, morphology, neurochemical, and psychosocial correlates in CBS. My findings expand our understanding on the compensatory neuroplastic changes that occur in the visual cortex secondary to vision loss. Chapter II examines functional connectivity in resting state networks and global morphological changes in the brain. Chapter III examines the concentrations of excitatory and inhibitory neurometabolites in the visual cortex. Chapter IV explores psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity to examine whether they are associated with changes in the nature and frequency of CBS hallucinations during the COVID-19 pandemic. This information contributes to a better understanding of the neural correlates of CBS which affects the vulnerable ageing population.

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This PhD journey has been one of immense growth, both personally and professionally. It has been a challenging yet rewarding path that has shaped me in ways I could never have imagined. To all who have been a part of this experience, I thank you from the bottom of my heart.

Preface

“Hallucinations, like dreams, are constructed from the visual fragments in one’s mind, and the brain’s activity can generate vivid inner experiences even when deprived of external stimulation.

- Oliver Sacks, author of *Hallucinations* (p. 10)

Charles Bonnet Syndrome (CBS) is a fascinating phenomenon that lies at the intersection of neurology, ophthalmology, and psychology. It illustrates the brain's determination to create coherence and patterns, even when external sensory inputs are diminished. This phenomenon underscores the brain's adaptive capacity to maintain a sense of reality.

This dissertation represents the culmination of years of inquiry into the mechanisms underlying visual hallucinations in CBS including functional connectivity, morphology, neurotransmitter dynamics, and psychosocial health, aiming to contribute to the understanding of this condition that affects many but remains poorly understood.

The path to this research has been both challenging and rewarding. It has required interdisciplinary exploration, engagement with diverse methodologies, and a commitment to unraveling complex phenomena. This work reflects not only my scientific curiosity but also my deep respect for the individuals who shared their experiences as participants in my studies.

As I present this dissertation, I am reminded of the broader significance of CBS, not only as a medical condition but as a window into the brain’s resilience and adaptability. I hope this work inspires further inquiry and contributes meaningfully to the

ongoing conversation around CBS and related conditions.

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List of Abbreviations

^{1}H	Proton
2D	Two-dimensional
3D	Three-dimensional
3T	3 Tesla
AMD	Age-related macular degeneration
ART	Artefact detection tool
BOLD	Blood oxygen level-dependent
CAT	Computational anatomical toolbox
CBS	Charles Bonnet Syndrome
Cr	Creatine
cTBS	Continuous theta-burst stimulation
ctDCS	Cathodal transcranial direct current stimulation
CSF	Cerebrospinal fluid
dB	Decibel
ETDRS	Early treatment diabetic retinopathy study
fCSF	Cerebrospinal fluid volume fractions
FDR	False discovery rate
fGM	Grey matter volume fractions
fMRI	Functional magnetic resonance spectroscopy
FoV	Field of view
FWHM	Full-width half maximum
fWM	White matter volume fractions

GABA	Gamma-aminobutyric acid
GABA+	Combined 3 GABA methylene groups
Glx	Combined glutamate, glutamine, and glutathione
Hz	Hertz
ICD	International classification of diseases
i.u.	Institutional units
LGN	Lateral geniculate nucleus
MB	Multi-band
ME	Multi-echo
MEGA-PRESS	Mescher-Garwood point resolved spectroscopy
MoCA	Montreal cognitive assessment
MPRAGE	Magnetization-prepared rapid gradient echo
MRS	Magnetic resonance spectroscopy
NEVHI	North-east visual hallucination inventory
NMDA	*N*-methyl D-aspartate
NPI	Neuropsychiatric inventory
ppm	Parts per million
rTMS	repetitive transcranial magnetic stimulation
SPECT	Single-photon emission computed tomography
SPM	Statistical parametric mapping
TE	Echo time
Tedana	TE dependent analysis
TI	Inversion time

TR	Repetition time
V1	Primary visual cortex/ striate cortex
V2	Secondary visual cortex/ extrastriate cortex
V3	Association visual cortex 3/ extrastriate cortex
V4	Association visual cortex 4/ extrastriate cortex
V5	Association visual cortex 5/ extrastriate cortex
WHO	World Health Organization
Z_{cc}	Effect size for Crawford-Howell *t*-test

CHAPTER I

GENERAL INTRODUCTION

As humans, our ability to perceive and interpret the world is deeply rooted in our sensory systems, with vision playing a pivotal role in our daily experiences. However, when this vital sense begins to deteriorate, as seen in age-related visual impairments such as age-related macular degeneration, glaucoma, or cataracts, the brain undergoes changes to compensate for visual loss (Burge et al., 2016; Chan et al., 2021; Hernowo et al., 2014; Stein et al., 2021). According to the World Health Organization (WHO), 2.2 billion people worldwide face some form of visual impairment (Paré et al., 2023). While most of these cases face mild to moderate visual deficits, it is estimated that 43 million people suffer from blindness (visual acuity < 3/60 or <10° visual field around central fixation) and this prevalence is expected to increase due to a rise in eye diseases (Steinmetz et al., 2021). The phenomenon known as Charles Bonnet Syndrome (CBS) emerges as a striking example of the brain's response to significant vision loss, where vivid visual hallucinations occur in the absence of cognitive impairment (Teunisse et al., 1996). To date, CBS has only been reported in acquired vision loss, and it has not been reported in congenital blindness (Gilmour et al., 2009; Menon et al., 2003; Schadlu et al., 2009; Teunisse et al., 1996; Vukicevic & Fitzmaurice, 2008; Yacoub & Ferrucci, 2011). CBS hallucinations can be thought of as the visual analogue to phantom limb pain where a person continues to experience limb sensations even after the loss of a limb. In CBS, individuals continue to see vivid images of faces, animals, objects, patterns, or figures despite their vision loss. Over the last decade, there has been a 60% increase in the number of CBS studies, driven by its inclusion in the WHO international classification of diseases (ICD) - 11, which has brought greater attention to this condition (Jones et al., 2021). In this dissertation, I delve into the intricate neural

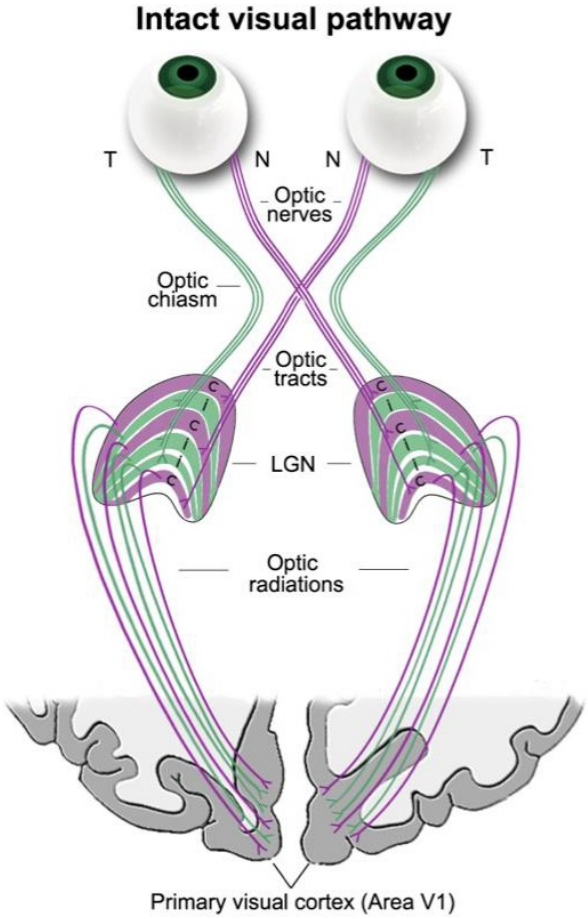
mechanisms associated with CBS and its psychosocial implications, exploring global brain as well as visual cortex changes. By examining these dimensions, this research aims to understand how the brain adapts to sensory deprivation through neuroplasticity and its implications for those affected by CBS.

Typical Visual System Processing

In the human visual system, the transmission of signals occurs along three main regions – the retina, the lateral geniculate nucleus (LGN) – a subcortical nucleus of the thalamus – and visual cortex. The retina is a photosensitive tissue that is comprised of light detecting photoreceptors known as rods and cones (Hussey et al., 2022). Rods function in low-light and motion detection while cones operate in bright light and are responsible for trichromatic color vision (Molday & Moritz, 2015). Visual stimuli are carried through retinal ganglion cells from each eye and converge at the optic chiasm where one half of the axons project ipsilaterally (uncrossed temporal fibres) and the other half projects contralaterally (crossed nasal fibres) to the LGN (la Vail et al., 1991). Projections of hemi-decussated retinal fibres from the LGN to the visual cortex influence the structural and topographic organization in striate and extrastriate cortices which receive visual information about the binocular visual field from both eyes. The primary visual cortex (V1) receives stronger visual input from the contralateral eye because projections from the nasal hemiretina (~53%) are greater than projections from the temporal hemiretina (~47%) (la Vail et al., 1991) (Figure 1.1).

Figure 1.1.

Schematic Illustration of an Intact Human Visual System



Note. Illustration of an intact visual system. Visual information is relayed from each eye through nasal (purple) and temporal (green) projections. Nasal fibres (crossed) project to the contralateral LGN while temporal (uncrossed) fibres project to the ipsilateral LGN. Visual information is relayed from LGN to primary visual cortex through optic radiations. Figure adopted from Kelly et al., 2014 (permission for this type of reuse is not required under the Creative Commons Attribution License (CC BY)).

V1 is the first cortical region that processes visual cues such as orientation of edges and lines (Liang et al., 2023). The secondary visual cortex (V2) integrates signals from V1 with an increased level of complexity and forms feedforward connections to extrastriate visual areas (V3-V5) and feedback loops with V1 to facilitate processing of visual information (Briggs et al., 2020; Callaway & Nassi, 2009; Marques et al., 2018; Sincich & Horton, 2005). Connections from V1 diverge into two specialized visual streams, namely the dorsal and ventral visual streams. The dorsal visual stream has specialized areas for spatial processing and visuo-motor tasks while the ventral stream has areas specialized in facial recognition, object vision, scene perception, as well as discrimination of visual features such as size, shape, colour, and brightness (Goodale & Milner, 1992; Mishkin et al., 1983; Sheth & Young, 2016). Research shows that functional connections from V1 to higher visual areas are complicated, following multiple reciprocal feedback and feedforward pathways such as V1 – V3, V1 – V2 – V4, and V1 – V4 that skip some inferior temporal areas along the ventral stream to facilitate parallel, multistage processing of visual information (Briggs et al., 2020). Connections from V1 to distant areas form extended territories and brain wide networks (Beckmann et al., 2005; Bianciardi et al., 2009; Fransson, 2006; Laumann et al., 2017), and synchronized activity between those regions could explain the neural underpinnings of cortical functions (Biswal et al., 1995; Biswal et al., 2010; Buckner et al., 2008; Fox et al., 2005; Fox & Raichle, 2007). When visual input from one or both eyes is disrupted, plastic changes alter the topographic organization and functional connectivity of the visual cortex (Kelly et al., 2014, 2019) and can lead to irreversible changes in cortical morphology and functional connectivity within brain networks (Marchesi et al., 2021).

Retinal changes are considered irreversible because they involve progressive degeneration of photoreceptors and retinal ganglion cells, which eliminates afferent visual input to the brain and cannot be regenerated, resulting in downstream cortical reorganization (Wong et al., 2014; Yoshimine et al., 2018; Yuan et al., 2021). This is observed in complex hallucinations that occur secondary to binocular vision loss where people who hallucinate faces or colors show distinct activation patterns in functionally specialized regions that are part of larger brain networks (ffytche et al., 1998). Visual hallucination content may hence be associated with functionally specialized regions such as fusiform cortex (face processing), parahippocampal cortex (place selectivity), lateral occipital cortex (object processing), and inferior temporal gyrus (visual features and pattern recognition) (Faillenot et al., 1997; Herath et al., 2001; Kanwisher & Yovel, 2006; Mormann et al., 2017; Mullin & Steeves, 2013; Weiner et al., 2018).

Cortical Adaptation to Vision Loss

Following vision loss, neuroplasticity occurs at a molecular level through activity-dependent changes in synaptic strength, primarily mediated by long-term potentiation (LTP) and long-term depression (LTD), involving *N*-methyl D-aspartate (NMDA) receptor activation, calcium influx, and downstream signaling cascades that regulate gene expression, and synaptic protein synthesis (Kandel et al., 2014). This neuroplasticity affords distinct global and local (visual system) structural brain alterations in grey matter through neuronal degeneration and/ or white matter through demyelination or axonal damage. For instance, significant reductions in grey matter volume, white matter volume, cortical thickness, and total surface area of the brain have been reported secondary to vision loss in congenital blindness as well as late blindness

from eye diseases such as diabetic retinopathy, glaucoma, cataracts, or retinal detachment (Atilgan et al., 2017; Jiang et al., 2009; Park et al., 2009; Wan et al., 2013). Moreover, studies have reported volume increases in the lateral, third, and fourth ventricles in optic neuropathy, retinal detachment, eye trauma, and glaucoma (Jonak et al., 2020; Leporé et al., 2010), further highlighting global measure changes in vision loss compared to healthy-sighted individuals. Even in the occipital lobe, vision loss has been associated with grey matter volume reductions in V1 (Aguirre et al., 2016; Jiang et al., 2015; Leporé et al., 2010; Maller et al., 2016; Manara et al., 2015), cuneus (Jiang et al., 2015; Voss et al., 2014; Wan et al., 2013), lingual gyrus (Jiang et al., 2015; Lee et al., 2014), superior occipital gyrus (Jiang et al., 2015), middle occipital gyrus (Jiang et al., 2015), left and right inferior occipital gyri (Voss et al., 2014), as well as occipital white matter volume reductions in cuneus (Voss & Zatorre, 2012), lateral and superior occipital gyri (Maller et al., 2016), and lingual gyrus (Maller et al., 2016; Wan et al., 2013). Unfortunately, due to limited regeneration secondary to vision loss, eye diseases such as age-related macular degeneration (AMD) that cause damage to retinal ganglion cells can lead to maladaptive neuroplastic changes to the morphology and functional connectivity of the visual brain (Yuan et al., 2021).

Age-Related Macular Degeneration

AMD is the most common form of retinal degenerative diseases and is the primary cause of blindness in older adults (Wong et al., 2014). Age is a major risk factor associated with AMD, and it is estimated that the prevalence of AMD will increase from 196 million in 2020 to 288 million in 2040 (Brown et al., 2019; Wong et al., 2014). Rods and cones are light sensitive photoreceptor cells located at the back of the retina next to

the retinal pigment epithelium, a cell layer that supports photoreceptors (Hussey et al., 2022). Rods operate in dim light while cones operate for colour detection under bright lighting conditions and are concentrated in the macula, the central part of the retina (Ingram et al., 2016). The fovea is a morphologically distinct area located inside the macula that consists of cones and yields high visual acuity (Bringmann et al., 2018).

AMD is characterized by damage to photoreceptors in the macula and leads to loss of vision in the central visual field and an irreversible reduction in detailed foveal vision either from accumulation of drusen, an extracellular material that disrupts the retinal pigment epithelium leading to oxidative stress, inflammation, and degeneration, or from abnormal immature blood vessel growth into the retina, that causes blood and fluid accumulation (Wong et al., 2014; Yoshimine et al., 2018). Decreased input from the retina leads to adaptations in visual circuitry where visual deprivation from the central scotoma (area of the visual field with partial or incomplete loss of vision) facilitates structural reorganization of the visual cortex. A cortical region representing central vision known as the lesion projection zone undergoes reorganization through compensatory neuroplastic mechanisms (Ferreira et al., 2017; Marc et al., 2007). Volumetric reductions occur in central regions of V1, and peripheral areas (known as preferred retinal locus) become more responsive to improve peripheral vision and relocate visual processing to the periphery as a compensation for the central scotoma (Burge et al., 2016; Hernowo et al., 2014).

There are distinct visual pathway alterations that are specific to retinal degeneration due to macular degeneration. Juvenile macular degeneration which occurs during childhood/ adolescence is associated with morphological changes along

the entire visual pathway in structures such as the optic nerve, optic chiasm, LGN, and visual cortex (Nuzzi et al., 2020). AMD which occurs in late adulthood is associated with structural alterations in the LGN and downstream structures and is characterized by a reduction in LGN volume, decreased grey matter density (proportion of grey matter/ neurons in a cortical tissue volume) in the posterior part of the calcarine sulcus, white matter changes in frontal regions (Boucard et al., 2009; Nuzzi et al., 2020), and an increased activation in association areas such as the prefrontal cortex, parietal lobule, intraparietal sulcus, and frontal and supplementary eye fields (Alahmadi et al., 2018). Moreover, there is a direct link between the severity of vision impairment with the progression of AMD and damage to optic radiation white matter projecting to V1 (Yoshimine et al., 2018). A prolonged state of vision loss from eye-diseases such as AMD, glaucoma, cataracts, optic neuropathies, or central retinal artery occlusions can lead to distinct functional connectivity patterns and morphological changes depending on the cause of vision loss. In a progressively ageing population, conditions like Charles Bonnet Syndrome (CBS) that arise from multiple coinciding eye-related pathologies pose several challenges to understanding the complex structural, functional, and neurochemical correlates related to the manifestations of the condition.

Ocular Tuberculosis

Ocular tuberculosis is a form of tuberculosis which is caused by intracellular bacillus Mycobacterium tuberculosis infection. Tuberculosis is estimated to affect more than 1.7 billion people worldwide but less than 1% of the United States population is affected by ocular tuberculosis, an extrapulmonary manifestation of the disease (Alvarez et al., 2009). The rare prevalence of ocular tuberculosis may be due to the fact

that it can manifest as a variety of ocular pathologies such as uveitis, papilledema, papillitis, or neuroretinitis (Albert et al., 2016) especially when laboratory tools such as polymerase chain reaction, gamma-interferon testing, and cultures may not be available in many clinical facilities. Ocular tuberculosis can affect various ocular tissues and manifests in a wide variety of clinical symptoms, depending on the pathophysiological changes to affected structures such as uvea, sclera, cornea, retina, conjunctiva, or optic nerve (Donahue, 1967). Diagnosis of ocular tuberculosis is challenging due to a lack of uniformity in diagnostic criteria. About 90% of ocular tuberculosis cases remain asymptomatic, and early detection and administration of steroidal treatment can reverse negative outcomes (Sridharan & Biswas, 2007). However, in rare cases, ocular tuberculosis may lead to retinal tears and scarring if not treated in a timely manner.

Since ocular tuberculosis can affect different structures, it is unclear how lesions to ocular structures impact cortical morphology and functional connectivity. In conditions like CBS where visual hallucinations occur secondary to vision loss from a myriad of eye diseases, no studies investigated morphological and functional connectivity alterations associated with ocular tuberculosis due to the rareness of its occurrence. Moreover, it is unclear how the co-occurrence of ocular tuberculosis with other eye pathologies could affect the brain's morphology and functional connectivity.

Charles Bonnet Syndrome

CBS is a debilitating phenomenon where individuals experience complex visual hallucinations secondary to vision loss. The leading visual system etiology associated with CBS is AMD (Vukicevic & Fitzmaurice, 2008), but other etiologies such as glaucoma, cataracts, Leber's hereditary optic neuropathy, central retinal artery

occlusion, and many more have also been implicated (Burke, 2002; Madill & ffytche, 2005; Tan et al., 2006; Toosy et al., 2006). It has been reported that one in five people with vision loss experience visual hallucinations (Potts, 2019). Reports on the prevalence of CBS have been variable depending on research criteria (Gordon, 2016). While some studies report that about 10% to 40% of individuals with visual impairment suffer from CBS (Abbott et al., 2007; Gilmour et al., 2009; Jacob et al., 2004; Manford & Andermann, 1998; Menon et al., 2003; Pankow & Luchins, 1997; Rovner, 2002; Skorin, 2005; Vukicevic & Fitzmaurice, 2008), others suggest that only 1% of visually impaired individuals experience CBS hallucinations (Schadlu et al., 2009; Yacoub & Ferrucci, 2011). Also, some studies indicate that CBS predominantly affects women (Crumbliss et al., 2008; Menon et al., 2003; Vukicevic & Fitzmaurice, 2008). Evidence shows that women are more likely to report and seek help on health issues (Galdas et al., 2005; Kuehner, 2017). It is hence unclear if women are physiologically more susceptible to CBS or whether they are more likely to report its occurrence. Moreover, it was previously thought that CBS hallucinations are transient and resolve after 3-18 months, but a survey by Cox and ffytche (2014) showed that in 75% of cases hallucinations continued after 5 years or more from onset. Another study showed that CBS hallucinations can persist even after 30 years from onset (Teunisse et al., 1996).

CBS is characterized by a triad of visual hallucinations, normal cognitive status/ lack of psychiatric illnesses, and ocular pathology. Hallucinations are visual percepts that occur without external visual stimulation. The deafferentation theory posits that a disruption or reduction of afferent retinal input leads to an increased activation/ hyperexcitability in visual cortical regions thereby causing CBS visual hallucinations

(Burke, 2002). CBS visual hallucinations can be categorized into two broad categories – simple and complex. Simple hallucinations involve flashes of light, lines, or simple shapes, while complex hallucinations present in the form of geometric patterns and complex images of faces, animals, and landscapes (Khan et al., 2008). Despite the variability in the manifestation of visual hallucinations, researchers have reported the occurrence of both simple and complex hallucinations in CBS (Firbank et al., 2022; Jones & Moosajee, 2021; Piarulli et al., 2021; Vacchiano et al., 2019). In fact, Zhuzhuni and colleagues (2018) described that simple and complex visual hallucinations are governed by the same mechanisms, except that simple hallucinations are associated with disruptions in early visual areas while complex hallucinations involve disruption of higher-order visually specialized areas. This was observed in CBS patients displaying increased activation in higher-order category-selective regions such as activation in fusiform regions with face hallucinations or in colour area V4 with coloured hallucinations (ffytche et al., 1998). One of the primary functions of V1 is to receive, integrate, and transmit visual information to V2, associative cortices, and higher order visual areas along the dorsal and ventral stream. V1 neurons respond to simple stimuli such as lines, orientation of edges, and direction of motion (Liang et al., 2023). Therefore, it is thought that disruption to afferent signals to V1 or occipital lesions produce simple visual hallucinations while lesions in specialized occipitoparietal and occipitotemporal regions which process more complex visual information such as faces, objects, and scenes are associated with complex visual hallucinations. It is also thought that a dysfunction in early visual cortex (V1 and V2) prevents the transmission of visual stimuli to higher-order visual areas leading to endogenous activation, thereby causing

complex visual hallucinations (Kazui et al., 2009). It is unclear however, why there is a variability in the type of CBS hallucinations and whether the underlying causes of vision loss (etiology, timing – early vs. late onset, and locus of visual field defect – central vs. peripheral) and their influence on visual pathway disruptions can predict the susceptibility to either simple or complex visual hallucinations.

CBS hallucinations greatly vary in their manifestation – stationary (Miyaoka et al., 2009) versus moving (Jan & del Castillo, 2012), colored (Bhatnagar et al., 2022; Miyaoka et al., 2009; Vacchiano et al., 2019) versus black and white (Liapis et al., 2021; Maruzairi & Joo, 2022), and they can be continuous (occurring at all times), episodic (lasting a few days or months before disappearing), or periodic (occurring on some days), lasting anywhere between a few seconds to hours or days (Burke, 2002; Madill et al., 2009; Menon et al., 2003; Schadlu et al., 2009) and one patient can experience multiple manifestations with varying frequencies. A key hallmark of CBS is an awareness that the visual hallucinations are not real (Teunisse et al., 1996). When CBS hallucinations are initially experienced, 80% of patients realize that they are not real (Gilmour et al., 2009; Menon et al., 2003; Rovner, 2006; Vukicevic & Fitzmaurice, 2008), and the remaining 20% who are initially confused by the hallucinations eventually realize that they are not real (Gilmour et al., 2009; Yacoub & Ferrucci, 2011).

Teunisse and colleagues (1996) proposed five diagnostic criteria to confirm whether a CBS diagnosis can be made. The criteria included:

1. At least one complex visual hallucination that occurred within the past 4 weeks.
2. A period between the first and last hallucination exceeding 4 weeks.
3. Full or partial retention of insight about the unreal nature of the hallucinations.

4. An absence of hallucinations in other sensory modalities.
5. An absence of delusions.

Visually impaired older adults between 70 – 85 years of age are most affected by CBS due to an increased prevalence of visual disorders with age (Abbott et al., 2007; Kinoshita et al., 2009; Menon et al., 2003; Schultz & Melzack, 1991; Teunisse et al., 1996, 1998). Typically, individuals with best-corrected visual acuity between 20/40 and 20/1600 experience CBS, but visual acuity between 20/300 and 20/800 has been reported to increase the likelihood of CBS especially when visual deficits are binocular (Gilmour et al., 2009; Kester, 2009; Menon et al., 2003). Nonetheless, in a recent retrospective study, it was shown that there was no association between binocular visual loss and CBS (Jones & Moosajee, 2021). The authors found that while some patients with binocular central, and/ or peripheral vision loss reported CBS hallucinations, others with vision loss in only one eye also reported visual hallucinations. This led the authors to the conclusion that a binocular loss of visual acuity is not a predictor for CBS onset, and they suggested that there should be no visual acuity threshold before physicians provide CBS education or further investigate the possibility of a CBS diagnosis (Jones & Moosajee, 2021).

Treatment Approaches

There is no current definitive treatment for CBS. Some studies reported that CBS hallucinations can be triggered by environmental factors such as bright environments, and several mitigation techniques are usually recommended such as looking directly at the hallucinatory images, moving one's eyes, blinking, walking towards the hallucinations, or closing one's eyes, to help stop the hallucination episodes (Anderson

et al., 2004; Jacob et al., 2004; Teunisse et al., 1996). However, while Teunisse and colleagues (1996) found that 67% of participants see hallucinations with their eyes open, hallucinations can be experienced even when eyes are closed and the implementation of these techniques is not always successful (Menon et al., 2003; Piarulli et al., 2021; Schultz et al., 1996; Vukicevic & Fitzmaurice, 2008).

Pharmacological treatments have also been administered but their success in mitigating hallucinations is variable. For instance, administering antipsychotics such as olanzapine, fumarate, and risperidone has been shown to partially or completely alleviate visual hallucinations (Asensio Sánchez et al., 2003; Burke, 2002; Cumurcu et al., 2005; Kester, 2009; Mansuri et al., 2022; Ogata et al., 2011; Schadlu et al., 2009; Unsalver et al., 2007). Anticonvulsants such as clonazepam, carbamazepine, valproate, and gabapentin, as well as cholinesterase inhibitors such as donepezil have also been shown to decrease or completely alleviate CBS hallucinations (Chaudhuri, 2000; Chen et al., 2001; Hori et al., 2000; Hosty, 1990; Paulig & Mentrup, 2001; Sarkar et al., 2017; Schadlu et al., 2009; Sonnenblick et al., 1995; Ukai et al., 2007). However, in some cases, antipsychotics, antidepressants, and anticonvulsants have been found to trigger hallucinations (Vitorovic & Biller, 2013). Also, most of these pharmacological interventions were administered in case reports, and there is a need for clinical and randomized controlled trials to establish an effective treatment for CBS hallucinations. Finally, other interventions such as non-invasive brain stimulation techniques, including cathodal transcranial direct current stimulation (ctDCS), 1 Hz repetitive transcranial magnetic stimulation (rTMS), and continuous theta-burst stimulation

(cTBS) have shown promising results in eliminating CBS hallucinations (Bodén et al., 2021; daSilva Morgan et al., 2022; Merabet et al., 2003). Future research should focus on longitudinal designs that explore the longevity of these effects to further examine the feasibility and dosage requirements of non-invasive brain stimulation techniques to mitigate and/ or alleviate CBS hallucinations. By understanding the underlying functional connectivity and morphological changes associated with CBS, treatment approaches can be formulated to cater to specific cortical locations affected by maladaptive neuroplasticity depending on the cause of vision loss.

Functional Connectivity and Morphological Changes in CBS

Previous research has indicated that visual hallucinations in CBS could be associated with changes in activation patterns across brain networks (ffytche et al., 1998; Martial et al., 2019; Vacchiano et al., 2019) and suggests alterations in the way the brain processes and integrates information following vision loss. Functional magnetic resonance imaging (fMRI) has emerged as a powerful method that employs blood-oxygen-level-dependent (BOLD) signals to capture temporal correlations in neural activity during task-induced changes or at rest. Resting-state fMRI explores synchronized activation of anatomically distinct areas that function as a unitary network at rest. These networks elicit activity in the absence of visual stimulation and are characterized by synchronous low-frequency (<0.1 Hz) fluctuations observed during sleep, rest, and light sedation (Fox et al., 2007; Greicius et al., 2008; Horovitz et al., 2008). One region may be involved in the intrinsic activity of multiple resting-state networks, albeit unequally (Beckmann et al., 2005; Bianciardi et al., 2009; Fransson,

2006; Laumann et al., 2017). These temporal correlations in the activity of anatomically distinct areas could highlight the neural underpinnings of different etiopathologies of the brain (Biswal et al., 1995; Biswal et al., 2010; Buckner et al., 2008; Fox et al., 2007; Fox & Raichle, 2007).

The perceptual attention deficit model suggests that decreased visual input leads to dysfunctional activation patterns in attention and perceptual networks, producing visual hallucinatory images (Collerton et al., 2005; Russell & Burns, 2014). In fact, in neurological conditions with visual hallucinatory manifestations such as Parkinson's disease, it has been suggested that visual hallucinations could arise from altered activity in resting-state networks (Onofrj et al., 2017; Shine et al., 2014). Therefore, it is plausible that even in CBS hallucinations that occur secondary to vision loss, improper functioning of these synergistic resting-state networks could contribute to the formation of visual hallucinations.

The default mode network and dorsal attention network are two large networks that have an antagonistic relationship and the activation of one network leads to the deactivation of the other. Neuroimaging studies show that the dorsal attention network is a task- positive network that modulates visual goal-directed tasks and visuospatial attention orientation (Shine et al., 2011), while the default mode network is a task-negative network that activates at rest or with internally directed tasks such as introspection (Buckner et al., 2008). Shine and colleagues (2011, 2014) observed that improper recruitment of the dorsal attention network - including regions such as the frontal eye fields, intraparietal sulcus, and lateral prefrontal cortex, responsible for perceptual visual processing, could explain the occurrence of visual hallucinations. The

authors also suggested that an overreliance on other networks such as the default mode network (including nodes in the precuneus, posterior cingulate cortex, and medial prefrontal cortex) may play a role in the formation of visual hallucinations (Shine et al., 2011, 2014). While the dorsal attention network is responsible for top-down modulation of visual goal-directed tasks, its activation is functionally concomitant with the deactivation of the default mode network. Visual hallucinations are thought to occur when there is a failure in dorsal attention network modulation, leading to dysfunctional default mode network activation patterns (Shine et al., 2014). Studies of individuals with CBS also show an association between visual hallucinations and decreased grey matter volume in areas within the dorsal attention network (Lawn & ffytche, 2021) further supporting evidence for dorsal attention network and default mode network dysfunctions. Neurological disorders with visual hallucinatory manifestations such as Parkinson's disease have also been associated with default mode network overactivity (Yao et al., 2014).

Network-level alterations in functional connectivity have not only been reported in visual hallucinations, but also with vision loss. In late blindness from eye diseases such as AMD, damage to macular photoreceptors leads to the formation of a cortical region known as the lesion projection zone which is deprived of bottom-up retinal input from the central retinal lesion (Zarbin, 2004). To compensate for that, individuals use part of their peripheral vision to perform visual tasks, and this forms an alternative cortical region known as the preferred retinal locus which processes visual input from the peripheral visual field (Bullimore et al., 1991; Fleming et al., 2024). Since the visual cortex is retinotopically organized, cortical areas representing central vision exhibit

different functional connectivity patterns compared to regions representing peripheral vision (Arcaro et al., 2015; Griffis et al., 2017; Striem-Amit et al., 2015). These differential patterns depend on the way a person uses their visual field for everyday tasks. For example, central visual fields are more strongly associated with category-selective regions for face recognition (fusiform regions) in the ventral occipital lobe since those tasks usually rely on central parts of the visual field for detailed foveal vision (Levy et al., 2001). In contrast, peripheral visual fields are associated with other regions of category selectivity such as identifying motion in area MT (Tootell et al., 1995; Yu et al., 2010). As such, with central vision loss, regions in the preferred retinal locus that now process input from the peripheral visual field undergo alterations in functional connectivity with category-selective ventral occipital areas (Sabbah et al., 2017). Specifically, afferented early visual areas representing peripheral vision show an increased positive connectivity with visual areas (cuneus), default mode network (precuneus, posterior cingulate), and category-selective regions in the ventral visual stream (fusiform, parahippocampal regions) (Sabbah et al., 2017). In contrast, deafferented early visual areas that receive input from the central scotoma display increased negative connectivity with cuneus, precuneus, posterior cingulate, and parietal regions such as the parieto-occipital sulcus, inferior parietal lobule, and intraparietal sulcus (Sabbah et al., 2017).

If the locus of visual field defects determines the direction of functional connectivity patterns between brain networks, it is possible that in CBS functional connectivity alterations depend on whether the etiology of vision loss affected central or peripheral visual fields. Several studies have examined individuals who developed CBS

from a myriad of visual pathologies including macular degeneration, glaucoma, cataracts, and Leber's hereditary optic neuropathy (Bhatnagar et al., 2022; Liapis et al., 2021; Piarulli et al., 2021; Teunisse et al., 1996; Vacchiano et al., 2019). It is unclear whether the differences in findings across studies could be explained by the variability in underlying causes of vision loss in CBS. For instance, CBS patients with cataracts and glaucoma show asymmetrical hyper-activation patterns in the lateral temporal cortex, striatum, and thalamus and this is not seen in CBS patients who lose their vision due to AMD (Adachi et al., 2000). Similarly, a 62-year-old male patient with simple and complex CBS hallucinations secondary to Leber's hereditary optic neuropathy showed increased activation patterns in V1, V2, cuneus, precuneus, and insula (Vacchiano et al., 2019), but a lack of activation of early visual areas has been suggested as a mechanism for CBS hallucinations secondary to retinal detachment and diabetic retinopathy (Kazui et al., 2009). As mentioned above, it is possible that the difference in underlying etiology and locus of visual field defects (central vs. peripheral) explains the distinct activation and functional connectivity patterns.

Another important consideration in CBS is the timing of vision loss – whether vision loss occurred early or late in life. Only one study examined resting-state functional connectivity of visual areas in a CBS patient with visual hallucinations due to retinitis pigmentosa, a peripheral eye disease that manifests early in life during critical periods of visual development (Kamde & Anjankar, 2023). In the study, the authors reported dysfunctional resting-state connectivity patterns between visual cortex and nodes of the default mode network (Martial et al., 2019). These findings are in line with vision loss research showing positive connectivity between visual areas representing

peripheral vision and default mode network (Sabbah et al., 2017). In contrast, functional connectivity alterations were not found in frontoparietal regions in the CBS participant (Martial et al., 2019), and this is unlike previous AMD research showing increased activation in frontoparietal regions (Alahmadi et al., 2018). As such, it may not be the "cause" alone but also the timing (early vs. late onset) and locus (central vs. peripheral) of vision loss that influences the direction of functional connectivity changes. Retinitis pigmentosa typically manifests in adolescence (Kamde & Anjankar, 2023) while AMD typically manifests in people over 60 years of age (Wong et al., 2014). The alignment in findings in blindness and CBS supports the notion that the mechanisms governing functional connectivity alterations may differ based on primary etiology, timing of vision loss, and locus of visual field defects.

Resting-state functional connectivity dysfunction in CBS extends beyond network-level disruptions in dorsal attention and default mode networks and has also been observed across multiple functionally specialized nodes. In a fMRI experiment, participants who hallucinated in colour demonstrated activation in the fusiform gyrus in an area corresponding to the colour centre, area V4 (ffytche et al., 1998). This was not observed in people who hallucinated in black and white where activity was observed outside V4. In contrast, people who hallucinated objects showed activation in the right middle fusiform gyrus in response to visually presented objects (ffytche et al., 1998). This hodotopic framework emphasizes that hallucination content may be related to the topological activation of functionally specialized areas (e.g., activation of face processing network with face hallucinations) and their connectivity with large-scale networks may be associated with long-term network alterations. Continuing their work,

the authors found that while viewing visual stimuli the control group showed activity along V1 and ventral visual stream, while CBS patients showed stimulus-evoked activity in the striate cortex that failed to extend to fusiform or lingual gyri (ffytche et al., 1998). These findings link network-level and node-level alterations in CBS: a disruption in visual signal transmission to higher-order cortical areas may lead to endogenous activation of these category-selective regions, thereby forming complex visual hallucinations (Kazui et al., 2009). As previously mentioned, central visual fields are more strongly associated with ventral face and object regions, e.g., face recognition (fusiform) (Levy et al., 2001, Sabbah et al., 2017), while peripheral fields show stronger associations with motion-selective cortex (MT/MT+) (Tootell et al., 1995; Yu et al., 2010). As such, in CBS from central vision loss, altered connectivity between central field brain representations and category-selective regions may be related to how visual areas and category-selective regions connect. Given this functional specificity, it is reasonable to expect corresponding structural changes depending on the locus of visual field defects.

Morphologically, studies consistently show that compared to healthy controls, areas of V1 that receive information from the damaged macula in AMD (central, late onset) undergo a reduction in grey matter volume and cortical thinning due to deprivation of retinal input from the central scotoma (Alcauter et al., 2011; Boucard et al., 2009; Ferreira et al., 2017; Kitajima et al., 1997; Plank et al., 2011). Individuals with AMD also show a reduction in frontal white matter volume and along anterior brain regions (Cavaliere et al., 2020; Hernowo et al., 2014; Reislev et al., 2016). Consistent with AMD studies, CBS secondary to AMD is associated with a widespread decrease in

white matter fractional anisotropy in the thalamus and its connections, especially along the anterior commissure (Firbank et al., 2022). Individuals with CBS secondary to AMD also show decreased grey matter volume in areas within the dorsal attention network (Lawn & ffytche, 2021) further supporting evidence for dorsal attention network and default mode network dysfunctions. However, while individuals with central vision loss from AMD show significantly thinner primary visual cortex in areas that receive visual input from the central macular lesion, peripheral regions show an increase in cortical thickness possibly due to compensatory recruitment of V1 areas corresponding to spared retinal areas of peripheral vision (Burge et al., 2016). This indicates that structural changes may vary in CBS depending on the locus of visual field defect associated with the underlying etiology of eye disease. Contrary to CBS from central vision loss, those who develop CBS secondary to glaucoma and cataract show morphological changes in occipital, temporal, and parietal cortices (Adachi et al., 2000). However, even within occipital regions, morphology is inconsistent across studies. In a single case study of an 86 year-old patient with CBS from bilateral cataracts and open-angle glaucoma, there were no marked changes in primary (V1), secondary (V2), and associative visual areas (Adachi et al., 2000) but atrophy was observed in the temporal lobes (Adachi et al., 1994). In contrast, hereditary retinal disorders such as retinitis pigmentosa (peripheral, early-onset) are associated with decreased grey matter volume in the middle occipital gyrus and cuneus, and decreased cortical thickness in several occipital regions including the cuneus, lingual, and fusiform gyri (Martial et al., 2019).

Despite the above-mentioned structural changes in CBS, it is still unknown why only some individuals with vision loss develop CBS. For instance, A CBS patient

secondary to retinitis pigmentosa showed decreased grey matter volume in the occipital lobe compared to healthy controls (Martial et al., 2019). However, late-blind controls showed similar reductions in occipital grey matter volume. This indicates that individuals with CBS and eye-disease controls (without hallucinations) may demonstrate similar morphological patterns. A major limitation in current CBS research is the methodological inconsistencies across studies, grouping participants with different underlying etiologies rather than investigating each etiology separately (Doeller et al., 2021; Hahamy et al., 2021; Jones & Moosajee, 2021; Karagöl, 2021; Russell et al., 2018; Teunisse et al., 1996). Some studies investigate CBS participants with central retinal abnormalities, without stating the exact eye disease diagnosis (Russell et al., 2018), and others recruit participants with a combination of glaucoma and AMD (Nair et al., 2015), AMD with Parkinson's disease (Lerario et al., 2013), AMD, glaucoma, and cataracts (Jan & del Castillo, 2012), glaucoma and cataracts (Miyaoka et al., 2009), AMD, glaucoma, cataracts, and retinitis pigmentosa (Firbank et al., 2022), bi-occipital ischemic lesion (Zhuzhuni et al., 2018), AMD, glaucoma, and diabetic retinopathy (Teunisse et al., 1996), and Leber's hereditary optic neuropathy (Vacchiano et al., 2019). While some of these studies are case reports, this mixing of etiopathologies obscures etiology-specific mechanisms and limits interpretability and cross-study comparisons. Depending on the type of eye disease, distinct visual system alterations can occur (Chan et al., 2021; Ferreira et al., 2017; Marc et al., 2007; Stein et al., 2021; Zhang et al., 2019). Glaucoma is a progressive optic neuropathy characterized by degeneration of retinal ganglion cells, LGN neuronal loss, and increased intraocular pressure leading to peripheral vision loss through insufficient optic nerve perfusion (Chan et al., 2021). Despite the difference

in underlying pathophysiological mechanisms between AMD and glaucoma, studies have grouped CBS participants with both these eye-diseases into one group (Firbank et al., 2022; Jan & del Castillo, 2012; Teunisse et al., 1996). Individuals with advanced glaucoma show retinotopic reductions in grey matter volume in the anterior calcarine sulcus, and decreased resting cerebral blood flow in occipital poles (Zhang et al., 2015). Other studies have found a decreased cortical thickness in area V5 and MT+ complex in patients with early glaucoma (Yu et al., 2014). Li and colleagues (2012) also found that the decrease in grey matter volume extends beyond visual areas into regions such as the supramarginal gyrus, inferior, and superior frontal regions (Li et al., 2012). Due to this grouping of CBS participants with different etiologies, CBS research has reported contradictory findings.

Adding to the complexity of how different mechanisms of vision loss elicit distinct morphological and functional connectivity alterations, ageing introduces specific structural changes that affect the brain's structural integrity and functional connectivity. Morphologically, ageing is characterized by cerebral atrophy, volume loss, ventricular enlargement, and sulci widening (Blinkouskaya et al., 2021). The volume and weight of the brain decrease by approximately 5% per decade after the age of 40 (Peters, 2006). Grey matter fractions decrease from 52.35% in the fourth decade of life to 50.49% at 80 years of age, while white matter fractions similarly decrease from 47.63% to 40.29%. In the context of CBS, these age-related changes are heightened by specific structural alterations that occur with vision loss. A combination of factors such as functional connectivity alterations, structural changes, ageing, and vision loss add another layer of complexity to understanding the visual hallucinatory manifestations of CBS.

Neurochemical Correlates in Visual Hallucinations

In addition to functional and morphological correlates in CBS, previous deafferentation research suggests that neurotransmitter concentrations could fluctuate secondary to deprivation of retinal afferent input to the visual cortex (Yacoub & Ferrucci, 2011). This is demonstrated through increased neurotransmitters in presynaptic vesicles, increase in glutamatergic *N*-methyl D-aspartate (NMDA) receptors, and a decrease in gamma-aminobutryic acid (GABA) receptors in the postsynaptic neuron. Thus, the neurochemical correlates of inhibitory (GABA) and excitatory (glutamate) neurometabolites could add a more holistic insight into the underlying neurophysiological mechanisms of CBS. There are currently no studies that investigated visual cortex neurometabolite concentrations in CBS. However, in a case report of a 94-year-old woman with CBS secondary to AMD and cataracts, the authors discussed that with visual impairment, GABA-active drugs such as Zolpidem which bind to GABA receptors may interfere with GABA functioning and disrupt visual cortex afferents thereby causing visual hallucinations (Stofler et al., 2004). Proton magnetic resonance spectroscopy (^{1}H-MRS) is a useful in-vivo method that quantifies metabolites through the resonance properties of hydrogen nuclei in a specific voxel in the brain. The method isolates neurometabolite signals in reference to creatine and water - a combined glutamate, glutamine, and glutathione signal (referred to as Glx) at 3.75 ppm and a combined signal of three GABA methylene groups at 3 ppm (combined signal known as GABA+) (Mescher et al., 1998a; Mullins et al., 2014).

In the visual system, the dynamic interplay between glutamate and GABA, the primary excitatory and inhibitory neurotransmitters, respectively, is essential for

functioning (Isaacson & Scanziani, 2011). Retinal ganglion cell functioning is dominated by glutamate receptors, and GABA is formed by the decarboxylation of glutamate in GABAergic interneurons (Schmidt-Wilcke et al., 2018). Due to the close link between glutamate and GABA in production, function, and reuptake, reductions in the concentration of one could impact the other (Bang et al., 2023) and effective inhibitory GABAergic modulation is essential for efficient glutamatergic neurotransmission (Boccuni & Fairless, 2022). Visual cortex glutamatergic signals decrease with the progression of eye diseases further highlighting that the loss of visual input affects glutamatergic levels and signaling (Bang et al., 2023). In fact, there is a temporal relationship between GABA and glutamate concentrations in the visual cortex (Rideaux, 2020). In a recent study of fifty-eight young healthy participants, Rideaux (2020) found that when participants had their eyes closed, visual cortex GABA and glutamate concentrations had opposing temporal dynamics, i.e., a decrease in GABA predicted an increase in glutamate approximately 120 seconds later. However, it is unclear if this opposing temporal dynamic is at play in CBS. Visual stimulation is associated with increased glutamate concentrations in the visual cortex (Bednařík et al., 2015, Betina Ip et al., 2017, Kurcyus et al., 2018, Lin et al., 2012, Mangia et al., 2007, Schaller et al., 2013) and this suggests a strong involvement of glutamate during the processing of visual stimuli. However, results have been inconsistent about GABA concentrations where one study found a decrease in GABA during visual stimulation (Mekle et al., 2017), while others could not replicate these findings (Bednařík et al., 2015, 2018; Kurcyus et al., 2018; Mangia et al., 2007; Schaller et al., 2013). While increased glutamate concentrations were associated with excitatory neural responses as expected

(Schallmo et al., 2019), another study showed that GABA did not play a major role in a visual task and increasing inhibition with lorazepam, a GABA agonist, did not increase visual spatial suppression (Schallmo et al., 2018). This led to the notion that visual cortical inhibition may extend beyond the inhibitory effects of GABA.

When there is a lack of sensory visual input, the visual system undergoes massive reorganization. However, the role of neurotransmitters in this cortical reorganization is unclear. In CBS, it is unclear how a combined effect of vision loss and age influences neurotransmitter concentrations especially since neither a decrease in visual acuity nor severe visual impairment are required to make a CBS diagnosis (ffytche, 2007; Jurišić et al., 2018; Karagöl, 2021; Teunisse et al., 1995). Moreover, the literature reports contradictory findings about visual cortex GABA levels with ageing. In a post-mortem human study of different age groups, it was found that there was a decrease in enzymes responsible for GABA production with ageing (age between 69 to 80 years) (Pinto et al., 2010). This was supported by other studies which found lower GABA concentrations in the visual cortex of older adults (Chamberlain et al., 2021; Simmonite et al., 2019; Zuppichini et al., 2024). On the contrary, another study found an increase in visual cortex GABA and decrease in glutamate levels with ageing (Pitchaimuthu et al., 2017). These contradictory findings pose a challenge and further add complexity to inferences made about the neurochemical correlates in CBS.

Psychosocial Correlates in CBS Hallucinations

CBS arises from changes in visual sensory processing secondary to vision loss and different functional, morphological, and neurochemical alterations could be implicated in the occurrence of visual hallucinations. Although the literature shows the

physiological changes involved in CBS, it has been suggested that CBS may be associated with changes in psychosocial health measures. CBS predominantly affects older adults given that it is primarily associated with age-related eye diseases. In a vulnerable population like the elderly, social isolation and decreased quality of life which are associated with ageing have been shown to impact psychosocial health and the occurrence of CBS visual hallucinations (Gloster et al., 2020; Lebrasseur et al., 2021). In a study of 360 individuals with CBS, 25% of participants described their visual hallucinations as unpleasant, and this could negatively impact the quality of life of people who experience these hallucinations (Khan et al., 2008). In fact, Cox & ffytche (2014) found that out of 492 CBS patients, 45% were negatively affected by fear-inducing hallucinations. This is supported by another study that showed that 32% of CBS patients had a negative emotional response to their visual hallucinations (Teunisse et al., 1996). It is hence possible that there may be negative impacts on psychosocial health depending on the type of hallucinations experienced by individuals with CBS.

Psychosocial health measures have been previously explored in individuals with CBS. While one study found that there was no relationship between depression and CBS visual hallucinations (Boxerman et al., 2015), another reported that patients with visual hallucinations were more likely to report feelings of depression (Jackson et al., 2005). It has also been reported that 25% of CBS participants experience anxiety (Menon et al., 2003), and people with CBS score worse in anxiety, depression, and social dysfunction compared to visually impaired controls without hallucinations (Scott et al., 2001). While these findings cannot infer causality between CBS and psychosocial health, they may imply that CBS is related to psychosocial health suggesting a role of

visual hallucinations in psychological processes of these individuals.

The COVID-19 pandemic and other global incidents provide important insight on psychosocial health in older adults. For instance, an exacerbation in previously benign visual hallucinations was observed after the Australian bushfires (Cameron et al., 2009). During the COVID-19 pandemic older adults experienced adverse effects on their mental health due to the implementation of public health safety measures to reduce virus transmission (Gloster et al., 2020). Psychosocial health measures such as social isolation and loneliness measurably increased among older adults during the COVID-19 pandemic (Donovan & Blazer, 2020), and social isolation contributes to a decrease in quality of life in older adults (Lebrasseur et al., 2021). Even in terms of hallucination characteristics, a study found that 56% of CBS participants experienced an increase in the frequency of their hallucinations and 47% reported changes to the nature of their hallucinations during the COVID-19 pandemic lockdown (Jones et al., 2021b). Moreover, 67% of their CBS participants reported greater feelings of loneliness, and loneliness was higher in older participants (Jones et al., 2021b). This highlights that in an ageing population CBS visual hallucinations may contribute to greater feelings of loneliness. Despite these findings, the study used qualitative responses about the experiences of CBS patients during the COVID-19 pandemic but did not use validated outcome measures. Further investigation into CBS visual hallucinations and their relation to psychosocial health measures using standardized and validated outcome measures is warranted to allow objective quantification of psychosocial measures and enable generalization.

Another important factor that must be considered when evaluating the visual

hallucinatory experiences in CBS is the provision of appropriate support and education to these individuals. Providing appropriate support and education has been shown to alleviate fear and mental health concerns faced by people who experience CBS hallucinations (Hughes, 2013; Karson et al., 2022). In fact, Menon (2005) reported that 63% of patients feared being labelled as “insane” (Menon, 2005). This explains why the majority of participants (73%) do not report their visual hallucinations to their doctors (Teunisse et al., 1996). This is further compounded by the lack of CBS awareness even among healthcare providers. In a Canadian study, it was reported that 55% of physicians were completely unaware of CBS, and 85% of physicians never provided CBS information to patients with visual impairment (Gordon & Felfeli, 2018). Cox and ffytche (2014) also found that one-third of the patients believed that their healthcare professionals did not know about CBS, and this could pose as a challenge because accurate information about CBS could decrease negative outcomes at onset by 20%. Despite the inevitable growing prevalence of CBS amongst the ageing population, physicians often misattribute these hallucinations to psychological conditions, thereby adversely affecting the assessment, diagnosis, and treatment of individuals who suffer from the condition (Cox & ffytche, 2014; Gordon & Felfeli, 2018). Teunisse and colleagues (1996) reported that only 16 out of their 60 participants consulted their doctors about their hallucinations and out of those participants, only one received a proper diagnosis. Since CBS is highly underreported, this magnifies the issue of lack of awareness - it has been reported that out of 200 patients, 80% of patients were completely unaware of CBS (Singh et al., 2014). Moreover, out of 492 CBS patients, 67% reported not knowing about the condition at onset of symptoms (Cox & ffytche,

2014). On the contrary, in an association for people with macular diseases, 87% of patients were aware of CBS as opposed to only 29% in the general population. This highlights the importance of support groups and how proper education to clinicians and patients can drastically improve outcomes in individuals with CBS.

In an ageing population, where anxiety, loneliness, and social isolation are prevalent, psychosocial health could impact patients and affect their overall quality of life and well-being. If CBS hallucinations are associated with psychosocial health, the lack of awareness and education may further exacerbate CBS hallucinations and negatively impact quality of life. The awareness and understanding of CBS among both healthcare professionals and patients are crucial not only for accurate diagnosis and effective management but also for addressing the psychosocial correlates associated with the syndrome.

General Purpose and Hypotheses

The primary aim of this dissertation is to advance our understanding of the underlying neural correlates of CBS hallucinations by examining the physiological correlates in a case of CBS secondary to AMD and with a history of ocular tuberculosis. Moreover, this dissertation aims to examine psychosocial health measures in a group of individuals with CBS to explore the association between psychosocial correlates and change in CBS hallucinations. Through a multi-faceted investigation that explores functional connectivity, morphological, neurochemical, and psychosocial correlates, this research is structured around three key chapters, each addressing distinct but interrelated aspects of CBS. Chapter II investigates the resting-state functional connectivity within specific brain networks and functional nodes, particularly those involved in visual processing, to identify potential disruptions or alterations that could be associated with hallucinations in a single-case of CBS. Additionally, Chapter II explores morphological measures such as brain tissue volume, and cortical thickness in a CBS patient compared to healthy controls. Chapter III examines the neurochemical correlates of visual hallucinations by measuring concentrations of visual cortex glutamate and GABA in a case of CBS. Finally, chapter IV focuses on psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity to assess whether they are associated with changes in nature and frequency of CBS hallucination during the COVID-19 pandemic in a group of CBS participants. Chapter IV also explores the association between vision loss and changes in CBS hallucinations during the pandemic. Together, these chapters aim to contribute to our understanding of CBS hallucinations, offering insights into both their physiological and psychosocial

correlates.

Chapter II

Previous studies have suggested that visual hallucinations in CBS could be associated with dysfunctional activation patterns across nodes within the visual, default mode, dorsal attention, and salience networks. These alterations may not only be a consequence of visual impairment but also normal aging, which affects the brain's structural integrity and functional connectivity. By using a resting-state fMRI paradigm, chapter II further investigates the functional connectivity and morphology in a single case of CBS following AMD and ocular tuberculosis compared to healthy controls with normal or corrected-to-normal vision, focusing on brain networks and their potential role in the manifestation of visual hallucinations. The single case studied in this research has a unique and rare ocular history and investigating the physiological mechanisms in this patient will help add to the body of literature, addressing questions on whether there are common neurophysiological changes irrespective of blindness etiology in CBS or whether morphological and functional connectivity patterns in CBS hallucinations depend on vision loss etiology, timing of vision loss (early vs. onset), and locus of visual field defect (central vs. peripheral). Previous findings have shown an alteration in functional connectivity between visual areas and category-selective regions along the ventral visual stream in visual hallucinations. For instance, face hallucinations have been associated with increased activation in fusiform regions known for face perception (ffytche, 1998). Moreover, the parahippocampal gyrus, a category-selective region for scene perception in the ventral visual stream has been shown to exhibit increased negative connectivity with occipital regions (occipital pole and lateral occipital) in visual

hallucinations from Parkinson's disease and Lewy body dementia (D'Antonio et al., 2022). Therefore, I predicted that CBS is associated with increased negative connectivity between visual areas and the temporo-occipital fusiform (faces), inferior lateral occipital cortex (objects), temporo-occipital inferior temporal gyrus (patterns), and parahippocampal gyri (scenes). Moreover, I predicted that CBS is associated with increased negative connectivity between visual areas and nodes in the default mode network such as precuneus and posterior cingulate gyrus. This is based on previous evidence showing altered default-mode network functional connectivity in individuals with vision loss from central visual field defects (Sabbah et al., 2017), Parkinsonian visual hallucinations (Yao et al., 2014), and CBS secondary to retinitis pigmentosa (Martial et al., 2019). Further, I predicted an increased positive connectivity in CBS between the visual areas and the intraparietal sulcus, a dorsal attention network node, demonstrating a disruption of antagonistic relationships between default mode and dorsal attention networks. The intraparietal sulcus has been previously implicated in the occurrence of visual hallucinations. In a lesion study, Wang and colleagues (2024) found that a lesion in the left intraparietal sulcus was associated with peduncular hallucinosis (Wang et al., 2024). Moreover, transcranial magnetic stimulation to the intraparietal sulcus evoked less cortical activity in Lewy body dementia hallucinators (Leodori et al., 2023). In addition, individuals who experience visual hallucinations from Parkinson's disease and Lewy body dementia display increased positive connectivity between the supramarginal gyrus (a node of the salience network) and occipital regions namely the occipital pole and lingual gyrus (D'Antonio et al., 2022). I predicted that the supramarginal gyrus will display increased positive connectivity with visual areas in

CBS. Finally, I predicted that CBS will be associated with decreased grey matter volume and cortical thickness in visual areas in line with previous evidence showing decreased grey matter volume and cortical thickness in CBS secondary to retinitis pigmentosa (Martial et al., 2019).

Chapter III

To date, no studies have investigated neurometabolite concentrations in the visual cortex of individuals with CBS. Considering the temporal dynamics observed between excitatory and inhibitory neurometabolites and the inconsistent findings about the inhibitory role of GABA in visual processing, this experiment aims to explore the dynamics of visual cortex glutamate and GABA in a single case of CBS. While studies have found increased visual cortex glutamate (Bednařík et al., 2015, 2018; Betina Ip et al., 2017; Kurcyus et al., 2018; Lin et al., 2012; Mangia et al., 2007; Schaller et al., 2013) and a decrease in GABA during visual stimulation (Mekle et al., 2017), there is no evidence on the changes in visual cortex neurometabolite concentrations in CBS. The possibility of CBS demonstrating unique glutamate and GABA dynamics warrants further investigation into the neurochemistry of the visual cortex. Understanding the potential links between glutamate, GABA, and visual hallucinations in CBS could not only elucidate the neurochemical basis of these phenomena but also contribute to broader theories of cortical reorganization and the role of neurotransmitters in visual processing. This could potentially lead to the development of pharmacological treatments for CBS. I hypothesized that glutamate levels will be higher in the CBS case compared to healthy controls based on the deafferentation theory and proposed hyperexcitability of visual areas that arises as a compensation for the lack of retinal

stimulation. I also predicted that GABA concentrations will be lower in CBS compared to healthy controls due to a possible dysfunction in inhibitory mechanisms that prevent the formation of visual hallucinations.

Chapter IV

Although it is well-documented that CBS arises from changes in visual sensory processing secondary to vision loss, and different functional, morphological, and neurochemical alterations may be implicated in the occurrence of visual hallucinations, the association between CBS hallucinations and psychosocial health measures remains underexplored. The ageing population, particularly those affected by CBS, often experience heightened levels of anxiety, loneliness, and social isolation, which could theoretically exacerbate visual hallucinations and impact their quality of life. A previous study employed qualitative survey questions to report the subjective experiences of individuals with CBS during the COVID-19 pandemic and found an association between the nature of hallucinations and loneliness (Jones et al., 2021b). By employing quantitative methodologies and standardized outcome measures, this chapter aimed to examine whether psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity were associated with changes in the nature and frequency of CBS hallucinations during the COVID-19 pandemic. By examining psychosocial health factors as well as vision status, this will help us understand whether changes to visual hallucinations experienced by individuals with CBS are related to psychosocial health or the natural course of progression of vision loss. I hypothesized that vision status will be associated with changes in the nature and frequency of CBS hallucinations during the COVID-19 pandemic, further supporting the notion that CBS is

primarily a physiological phenomenon; Changes in CBS hallucinations during the COVID-19 pandemic may be related to the progression of eye disease rather than psychosocial health. Since the duration of time lived with vision loss has been shown to be associated with psychosocial health (Bonsaksen et al., 2025; Munaw & Tegegn, 2022; Williams et al., 1998) , I predicted that time since hallucination onset which indicates how long a person has lived with hallucinations in months will be associated with psychosocial health measures. Therefore, this study aimed to broaden our understanding of CBS as a multifaceted condition.

Together, my neuroimaging exploration of resting-state functional connectivity and neurochemical correlates of a single CBS participant, and self-reported psychosocial data from a group of CBS participants will contribute to a more comprehensive understanding of the underlying mechanisms of CBS. This information will help us better understand visual cortical plasticity that occurs in CBS secondary to visual deprivation. The insights gained do not only enhance the theoretical framework surrounding CBS but also inform the development of more targeted therapeutic interventions. For instance, non-invasive brain stimulation techniques could potentially target the hyperexcitability of areas implicated in visual hallucinations and understanding neurochemical (excitatory and inhibitory) visual cortex correlates can help develop pharmacological treatments to mitigate and/ or alleviate CBS hallucinations. Ultimately, this dissertation seeks to bridge gaps in the current literature and pave the way for future studies in this complex and underexplored area.

CHAPTER II

RESTING-STATE FUNCTIONAL CONNECTIVITY AND MORPHOLOGY IN A CASE OF CHARLES BONNET SYNDROME SECONDARY TO AGE-RELATED MACULAR DEGENERATION AND OCULAR TUBERCULOSIS

Kinakool, A. N., Moro, S. S., Cohan, R., Rafique, S. A., & Steeves, J. K. E. (2026). *Resting-state functional connectivity and morphology in a case of Charles Bonnet Syndrome secondary to age-related macular degeneration and ocular tuberculosis* [Manuscript in preparation]. Department of Psychology, York University

Abstract

Charles Bonnet Syndrome (CBS) is characterized by complex visual hallucinations that develop secondary to vision loss, often from multiple coinciding diseases such as age-related macular degeneration (AMD), glaucoma, or cataracts. CBS hallucinations are not well understood but may arise from the hyperexcitability of visual brain areas as a result of deafferentation following vision loss. Several studies exploring CBS secondary to vision loss report varying findings. Since functional connectivity patterns and morphology may differ based on the etiology of vision loss, it is important to investigate functional connectivity and morphology in cases of CBS secondary to unique etiologies. We employed seed- based connectivity and voxel-based morphometry to investigate resting-state functional connectivity and morphology, respectively, in a unique case of an 80-year-old male (Patient A.P.) with CBS secondary to AMD and a history of ocular tuberculosis. Compared to healthy controls, the right and left occipital poles showed increased negative connectivity with the precuneus and posterior cingulate cortex in Patient A.P. Moreover, the right cuneal cortex displayed increased positive connectivity with the right thalamus, and the functional connectivity between the left lingual gyrus and inferior lateral occipital cortex showed a trend toward increased negative connectivity in A.P. There were no differences between Patient A.P. and healthy controls in grey matter volume, white matter volume, total intracranial volume, and cortical thickness. These findings suggest an alteration in resting-state functional connectivity between networks involved in visual processing but no morphological changes in a single case of CBS following AMD and a history of ocular tuberculosis.

Visual hallucinations are percepts that occur in the absence of external visual stimulation and can be broadly categorized into simple (lines, dots, flashes of light) and complex (patterns, faces, objects, animals, or landscapes) hallucinations (Khan et al., 2008). Charles Bonnet Syndrome (CBS) is a debilitating phenomenon where visual hallucinations arise secondary to vision loss, often from age-related eye diseases. While age-related macular degeneration (AMD) is the most prevalent ocular pathology associated with CBS (Vukicevic & Fitzmaurice, 2008), other conditions such as glaucoma, cataracts, retinitis pigmentosa, Leber's hereditary optic neuropathy, and central retinal artery occlusion have also been implicated (Burke, 2002; Madill & ffytche, 2005; Martial et al., 2019; Tan et al., 2006; Toosy et al., 2006).

The pathophysiology of CBS is complex, and several neural mechanisms have been proposed to explain how visual hallucinations emerge following visual sensory deprivation. Among these, visual deafferentation – the partial or complete loss of bottom-up afferent sensory input to the visual cortex – is widely regarded as the driving mechanism of cortical hyperexcitability and CBS hallucinatory experiences (Burke, 2002; Kester, 2009; Rovner, 2006; Schadlu et al., 2009). Deafferentation-related changes are not limited to the visual cortex but influence broader cortical systems through network-level adaptations that may underlie hallucinatory experiences.

In the healthy brain, brain functions rely on the synchronous activity of large-scale functional networks – groups of anatomically distinct regions whose spontaneous activity is temporally correlated (Fox et al., 2007; Greicius et al., 2008; Horovitz et al., 2008). Resting-state functional magnetic resonance imaging (fMRI) enables the exploration of network connectivity by measuring the temporal correlation of

spontaneous blood-oxygen-level-dependent (BOLD) signal fluctuations between brain regions. Resting-state fMRI provides a powerful method for examining intrinsic network dynamics at rest (without visual stimulation).

To date, only one resting-state fMRI study has examined CBS involving a patient with visual hallucinations secondary to retinitis pigmentosa (Martial et al., 2019). The study reported altered functional connectivity between the visual cortex and nodes of the default mode network and salience network, but not in frontoparietal regions (Martial et al., 2019). In contrast, AMD has been associated with increased activation in frontoparietal regions (Alahmadi et al., 2018). These findings highlight a crucial and often overlooked point: distinct etiologies of vision loss – differing in onset, anatomical location of disruption, and pathophysiological mechanisms – are associated with unique patterns of functional connectivity and morphology. For instance, retinitis pigmentosa typically manifests in adolescence and leads to peripheral vision loss (Kamde & Anjankar, 2023), whereas AMD develops later in life (typically after 60 years of age) and primarily affects central vision (Wong et al., 2014). It is likely that cortical reorganization and neuroplastic adaptations that occur in CBS vary depending on early-onset versus late-onset or central versus peripheral visual field loss.

The deafferentation theory posits that the loss of bottom-up afferent sensory input to the visual cortex secondary to vision loss results in hyperexcitability of visual regions, serving as the driving mechanism of spontaneous visual percepts that characterize CBS hallucinations (Burke, 2002; Kester, 2009; Rovner, 2006; Schadlu et al., 2009). Evidence from functional imaging supports this interpretation. In a fMRI study, ffytche et al. (1998) found that while healthy controls viewing visual stimuli

showed activation in V1 and along the ventral visual stream, CBS participants displayed stimulus-evoked activity confined to the striate cortex, which failed to extend to higher-order brain regions. These localized changes within lower-level visual areas have also been observed in studies using single-photon emission computed tomography (SPECT) where hyperactivity in early visual areas was reported in two CBS patients with distinct etiologies (retinal detachment and diabetic retinopathy) (Kazui et al., 2009). The authors proposed that dysfunction within the early visual areas may disrupt the transmission of visual signals to higher-order cortical areas, leading to endogenous activation of these regions and the formation of complex visual hallucinations (Kazui et al., 2009). This indicates that deafferentation leads to alterations in excitability of early visual areas, and since these regions form integral nodes within larger brain networks, local changes in their activity may influence overall network functional connectivity.

In the healthy brain, several brain regions form nodes of larger scale networks that are responsible for specific functions (Beckmann et al., 2005; Binciardi et al., 2009; Fransson, 2006; Laumann et al., 2017). For instance, the dorsal attention network is a task-positive network that modulates visual goal-directed tasks and visuospatial attention orientation, and includes nodes such as the frontal eye fields, intraparietal sulcus, and lateral prefrontal cortex (Shine et al., 2011). In contrast, the default mode network is a task-negative network that activates at rest or with internally directed introspection, and includes nodes such as the precuneus, posterior cingulate cortex, and the medial prefrontal cortex (Buckner et al., 2008). These two networks operate in an antagonistic manner where the activation of one network is functionally concomitant with the deactivation of the other (Buckner et al., 2008; Fox et al., 2005; Shine et al.,

2014). When sensory input diminishes, dorsal attention network engagement decreases and the default mode network becomes dominant, leading to altered modulation between internal and external directed modes of visual processing (Shine et al., 2014). This framework links cortical hyperexcitability following vision loss and network-level disruption - a loss of afferent input perturbs early visual areas, which in turn disrupts the reciprocal interactions between task-positive dorsal attention and task-negative default mode network. Empirical findings support this framework where this network-level disruption between internal and external processing has been associated with visual hallucinations in perceptual disorders such as Parkinson's disease (Shine et al., 2011, 2014).

Adding to this evidence, Martial and colleagues (2019) reported increased positive connectivity between secondary visual cortex and the precuneus, a key node in the default mode network in CBS. In their study, the patient developed CBS secondary to retinitis pigmentosa. In contrast, Sabbah et al. (2017) observed increased negative connectivity between visual regions and nodes of both the default mode (precuneus and posterior cingulate cortex) and dorsal attention (intraparietal sulcus) networks in late blindness due to central vision loss. The directionality of these connectivity changes may reflect differences in etiology and timing of visual loss. Retinitis pigmentosa, typically early-onset with peripheral vision loss, involves long-term adaptations and large-scale organization that occur during the critical periods of visual development (Kamde & Anjankar, 2023). In contrast, central visual field disorders such as AMD are late onset, usually after 60 years of age and initially affect central foveal representations (Wong et al., 2014). Given these distinctions, it is plausible that unlike peripheral visual

field defects, individuals who develop CBS from central vision loss such as AMD will exhibit increased negative connectivity between early visual areas and nodes of the default mode and dorsal attention networks, reflecting a disruption of their antagonistic relationship between task-positive and task-negative visual processing.

While deafferentation-driven network-level alterations may explain the global imbalance between internally and externally directed brain processes associated with visual hallucinations, it is important to look beyond brain networks and examine changes along specific regional nodes. The ventral visual stream contains category-selective regions, and CBS research has shown that hallucination content is linked to their activation. In an fMRI study, ffytche and colleagues (1998) reported that CBS participants who hallucinated in colour showed activation in colour area V4, whereas those who hallucinated in black and white showed activity outside V4. Similarly, participants who hallucinated faces showed activation in the left middle fusiform gyrus, a region specialized in face processing (ffytche et al. 1998). Importantly, in eye disease controls without hallucinations, visual stimuli were associated with V1 activation that propagated along the ventral visual stream. In contrast, activation in the CBS group was confined to striate cortex and failed to extend to extrastriate or fusiform regions (ffytche et al., 1998). This supports the evidence that in CBS, bottom-up transmission of signals from early visual areas to higher-order category-selective areas is disrupted, leading to their spontaneous endogenous activation, thereby giving rise to complex visual hallucinations (Kazui et al., 2009).

In the healthy brain, the visual cortex is retinotopically organized, where central and peripheral field representations are functionally linked to different higher-order

regions depending on their visual role. (Arcaro et al., 2015; Griffis et al., 2017; Striem-Amit et al., 2015). Central visual fields are more strongly associated with category-selective regions for face recognition (fusiform regions) in the ventral occipital lobe since those tasks typically rely on central parts of the visual field for detailed foveal vision (Levy et al., 2001). In contrast, peripheral visual fields are associated with other regions of category selectivity such as identifying motion in area MT (Tootell et al., 1995; Yu et al., 2010). With central vision loss, early visual areas that represent afferented or spared peripheral visual fields show increased positive connectivity with secondary visual areas (cuneus), default mode network (precuneus, posterior cingulate), and category-selective regions in the ventral visual stream (fusiform, parahippocampal regions) (Sabbah et al., 2017). In contrast, early visual areas that represent input from the central scotoma show increased negative connectivity with cuneus, precuneus, posterior cingulate, and parietal regions such as the parieto-occipital sulcus, inferior parietal lobule, and intraparietal sulcus (Sabbah et al., 2017). AMD is a late-onset, central visual field disorder. It is plausible that in CBS secondary to AMD, early visual areas representing the deafferented central visual field will show increased negative connectivity with category-selective regions such as the fusiform (faces), lateral occipital cortex (objects), and parahippocampal (scenes).

In terms of morphology, structural brain changes depend on the part of the visual field that is deafferented. In AMD, a late-onset central field disease, studies show thinning of V1 regions corresponding to the central scotoma, and an increase in cortical thickness in V1 areas that correspond to spared retinal areas of peripheral vision (Burge et al., 2016). Studies also show that areas of V1 that receive information from the

damaged macula undergo a reduction in grey matter volume and cortical thickness due to deprivation of input from the central scotoma (Alcauter et al., 2011; Boucard et al., 2009; Ferreira et al., 2017; Kitajima et al., 1997; Plank et al., 2011). AMD is also associated with reductions in frontal/ anterior white matter (Cavaliere et al., 2020; Hernowo et al., 2014; Reislev et al., 2016).

Although vision loss is associated with structural brain changes, it remains unclear whether CBS-related morphology reflects the etiology of vision loss. Specifically, do CBS cases with AMD (central field loss) differ morphologically from CBS secondary to peripheral field disorders? A major challenge to this question is the methodological inconsistencies across studies, grouping participants with different underlying etiologies rather than investigating each etiology separately (Doeller et al., 2021; Hahamy et al., 2021;Jones & Moosajee, 2021; Karagöl, 2021; Russell et al., 2018; Teunisse et al., 1996). Some studies investigate CBS with central retinal abnormalities, without stating the exact eye disease diagnosis (Russell et al., 2018), and others recruit participants with a combination of glaucoma and AMD (Nair et al., 2015), AMD with Parkinson's disease (Lerario et al., 2013), AMD, glaucoma, and cataracts (Jan & del Castillo, 2012), glaucoma and cataracts (Miyaoka et al., 2009), AMD, glaucoma, cataracts, and retinitis pigmentosa (Firbank et al., 2022), bi-occipital ischemic lesion (Zhuzhuni et al., 2018), AMD, glaucoma, and diabetic retinopathy (Teunisse et al., 1996), and Leber's hereditary optic neuropathy (Vacchiano et al., 2019). While some of these studies are case reports, this mixing of etiopathologies obscures etiology-specific mechanisms and limits interpretability and cross-study comparisons.

Structural alterations in CBS may differ depending on the underlying etiology of eye disease. In CBS secondary to AMD, diffusion studies report decreased white-matter fractional anisotropy in the thalamus and its connections, particularly along the anterior commissure (Firbank et al., 2022). Other studies also describe decreased grey matter volume in cerebellar areas within the dorsal attention network in CBS linked to AMD (Lawn & ffytche, 2021), suggesting structural alterations in CBS with central vision loss may extend beyond the primary visual cortex. In contrast, CBS secondary to glaucoma and cataract is associated with morphological changes in occipital, temporal, and parietal cortices (Adachi et al., 2000). Even within occipital regions, an 86 year-old patient with CBS from bilateral cataracts and open-angle glaucoma, there were no marked changes in primary (V1), secondary (V2), and associative visual areas (Adachi et al., 2000) but atrophy was observed in the temporal lobes (Adachi et al., 1994). However, grey matter volume and cortical thickness reductions were observed in visual areas of an 85-year-old CBS case with retinitis pigmentosa (Martial et al., 2019). These findings highlight that morphological changes differ depending on parts of the visual field that are deafferented, but they do not explain why only a subset of people with vision loss develop CBS. For instance, decreased grey matter volume (middle occipital gyrus, cuneus, and superior parietal lobule) and cortical thickness (occipital regions including the cuneus, lingual and fusiform gyri) have been reported in CBS secondary to retinitis pigmentosa, a peripheral visual field disorder (Martial et al., 2019). However, late-blind controls without hallucinations showed similar occipital grey matter reductions (Martial et al., 2019), suggesting that these structural changes may reflect patterns of visual deprivation rather than CBS.

Taken together, the literature indicates that structural changes in CBS may be shaped by the locus of deafferentation (central vs. peripheral) and etiology. In AMD (late-onset, central visual field loss), there is a thinning of V1 areas corresponding to the central scotoma as opposed to the relative thickening of regions representing peripheral vision (Burge et al., 2016). Concurrently, cross-study comparisons are challenging considering the mixing of etiologies in CBS research, especially when some morphological effects may reflect visual deprivation rather than CBS, as late-blind controls show similar pattern to CBS secondary to retinitis pigmentosa (Martial et al., 2019). Reports across different etiologies (AMD, glaucoma, cataracts, hereditary retinal disease) also points to non-uniform morphological profiles. Considering the above challenges, this study investigated a unique case of CBS secondary to AMD, with a history of ocular tuberculosis.

The literature suggests that visual deafferentation in CBS (i) disrupts large-scale network connectivity, (ii) alters functional coupling of category-selective regions along the ventral visual stream in relation to hallucination content, and (iii) displays structural changes that vary with etiology, age of onset, and central vs. peripheral field involvement. The present study aims to characterize resting-state functional connectivity and morphology in a single-case of CBS with central vision loss secondary to AMD and a history of ocular tuberculosis, testing three hypotheses: 1. Increased negative connectivity between early visual areas and nodes of the default-mode and dorsal attention networks, 2. Increased negative connectivity between early visual areas and category-selective regions along the ventral visual stream, and 3. Decreased grey matter volume and cortical thickness in visual areas consistent with AMD-related

structural changes.

Materials and Methods

Written informed consent was obtained and ethics approval (e2023-119; approval period: 13th April 2023 – 10th April 2025) for this study was granted by the York University Office of Research Ethics in accordance with the Declaration of Helsinki.

Patient A.P.

Patient A.P. was an 80-year-old right-handed, male diagnosed with CBS. Patient A.P was diagnosed with bilateral AMD following vision loss that began 12 years prior, at 68 years of age. Patient A.P. also had a history of ocular tuberculosis in the left eye (diagnosed and treated, 10 years prior at 70 years of age), and bilateral cataracts (treated, 5 years prior in 2018). Upon assessment, binocular visual acuity was 0.9 logMAR (left eye – 0.8 logMAR; right eye – 1.02 logMAR) and there was no history of other neurological or neuropsychiatric disorders. Patient A.P. showed no measurable stereoacuity (Stereo Optical Company Inc., Chicago, IL). He reported a history of depression and anxiety for which he was intermittently treated with Lorazepam. The patient was not on Lorazepam when he was tested.

Standard vision testing was performed to assess monocular and binocular visual acuity using the early treatment diabetic retinopathy study (ETDRS) vision chart (Precision Vision, La Salle, IL). Colour vision was assessed using the Farnsworth D-15 (LUNEAU Ophtalmologie, France). Patient A.P.'s screening also included the Neuropsychiatric Inventory (NPI) which assesses psychopathology (Cummings et al., 1994) and the North-East Visual Hallucinations Interview (NEVHI) which assesses emotion, cognition, and behaviour associated with visual hallucinations (Mosimann et al., 2008). The Montreal Cognitive Assessment (MoCA)-Blind scale was used to

evaluate cognitive status and indicated normal cognitive functioning (Wittich et al., 2010). A summary of findings is presented in Appendix B.

Patient A.P.'s visual hallucinations included two rainbow colored spinning halos, green faces, twinkling trees, comic faces and figures, and lattice structures in the sky along his entire visual field. He occasionally saw cars while crossing the street and a tiger coming down the stairs. The hallucinations occurred several times a week, lasted from seconds to hours, and were exacerbated by bright light. Although he reported that the hallucinations were irritating, he never experienced frightening images. He did not report any other sensory hallucinations such as auditory, olfactory, or tactile.

Healthy Control Participants

In-Person Participants

Eight older healthy controls (*Mage* = 75.75 years; *SD* = 5 years; age range = 67 – 81 years; 5 females), with no history of neurological or psychiatric disorders were tested in this study. All participants were right-handed and had normal or corrected-to-normal vision (binocular visual acuity ≥ 0.06 logMAR) and normal stereoacuity. None of the participants presented with colour vision defects (Farnsworth D-15 test). All participants had normal cognitive status as assessed by the MoCA (Nasreddine et al., 2005). The screening form for healthy controls is presented in Appendix C.

Data Repository Participants

Additionally, 17 age-matched healthy controls (M_{age} = 73.41 years; *SD* = 6.17 years; age range = 66 – 85 years; 10 females), with normal or corrected-to-normal vision, normal cognition (MoCA scale), and no visual hallucinations (assessed through the Lewy Body Composite Risk Score) were included from an OpenNeuro dataset

(OpenNeuro Dataset ds005892 - doi:10.18112/openneuro.ds005892.v1.0.0). Participants underwent a resting-state fMRI scan with their eyes closed (details of protocol available in (Kemp et al., 2025)). In total, 26 participants' data (Patient A.P. and 25 healthy controls) were included in the analysis (Controls M_{age} = 74.16 years; *SD* = 5.82 years; age range = 66 – 85 years; 15 females). There was no difference in age between Patient A.P and healthy controls, $t(24) = 0.98$, $p = 0.335$, $z_{cc} = 1.003$.

Functional Magnetic Resonance Imaging (fMRI)

For the nine tested participants (Patient A.P. and 8 healthy controls) who were tested in person, a multi-band multi-echo (MB-ME) resting-state fMRI T2*-weighted echo-planar sequence with a 32-channel high-resolution brain array coil was acquired with a Siemens MAGNETOM® Prisma 3 Tesla MR scanner (52 slices, slice thickness = 3 mm, repetition time (TR) =1000 ms, echo time (TE) = 12.4, 30.15, and 47.9 ms, flip angle = 50°, spatial resolution of 3 mm voxel size based on 80 X 80 image matrix and field of view (FoV) = 240 mm, delay = 0, slice order = interleaved, acquisition time = ~ 10 mins) at the York MRI Facility in the Sherman Health Sciences Research Centre at York University. Head motion was minimized by secure padding around the participants' head. The scan was acquired in a dark room, and the participants were given eye masks to block out any additional light during the scan. Participants were instructed to stay awake, keep their eyes closed under the mask, and not to think of anything in particular.

A high-resolution T1-weighted image was acquired with a T1 magnetization-prepared rapid gradient echo (MPRAGE) imaging sequence - T1-weighted 3D gradient echo with 192 slices, (TR) = 2300 ms, (TE) = 2.26 ms, inversion time (TI) = 900 ms,

slice thickness = 1 mm, flip angle = 8°, FoV = 256 mm, slice order = ascending, acquisition time of approximately 5 mins. Using the T1-weighted anatomical images, cortical thickness and total intracranial volume were computed for regions across different brain networks in the left and right hemisphere. None of the participants reported falling asleep. Patient A.P. did not experience any visual hallucinations during the scan.

For the 17 healthy participants from the data repository, the resting-state scan was acquired using a 3T Siemens TrioTrim scanner – Echo-planar imaging, TR = 2000 ms, TE = 29 ms (details of protocol in OpenNeuro Dataset ds005892 - doi:10.18112/openneuro.ds005892.v1.0.0; Kemp et al., 2025). Participants were scanned with their eyes closed.

Data Analysis

Structural and functional data were analyzed using the CONN toolbox version 22.a (Nieto-Castanon, 2022) and SPM version 12 (Welcome Department of Imaging Neuroscience, UCL, London, United Kingdom) in MATLAB R2024b (The MathWorks Inc., Natick, MA, United Kingdom).

For the multi-echo data, TE-dependent analysis (tedana), an open-source, community-developed python library package for denoising multi-echo fMRI data was used to retain BOLD data and attenuate non-BOLD signals as part of the denoising and data cleaning process (DuPre et al., 2021; Kundu et al., 2011, 2013). Preprocessing was performed using a flexible preprocessing pipeline in CONN. The preprocessing pipeline included realignment, slice-time correction, outlier detection, direct segmentation and MNI normalization, and smoothing. The artifact detection tool (ART)

identified potential outliers and scrubbed acquisitions with a framewise displacement above 0.9 mm or global BOLD signal above 5 standard deviations. Temporal band-pass filtering removed frequencies below 0.008 Hz or above 0.09 Hz and focused on slow-frequency fluctuations while accounting for motion and physiological noise. Functional data were resampled to 2 mm isotropic voxels and structural data were resampled to 1 mm isotropic voxels. Spatial smoothing was performed using spatial convolution with a 6 mm full width at half maximum (FWHM) Gaussian kernel to increase BOLD signal-to-noise ratio and mitigate functional and gyral structure variability across subjects. Quality control of preprocessed and denoised data is provided in Appendix D.

Seed-based functional connectivity, an analysis method that examines temporal correlations between a seed region and targets across brain networks was used by computing Fisher-transformed *Z* coefficients from r values between regions. Predetermined seeds included seeds from visual areas: left and right occipital poles, left and right cuneal cortex, and left and right lingual gyri. A priori targets were determined based on previous research including - default mode network: precuneus, and posterior cingulate cortex; ventral visual stream: temporo-occipital fusiform cortex, inferior division of the lateral occipital cortex, temporo-occipital part of the inferior temporal gyrus, anterior and posterior divisions of the parahippocampal gyrus; dorsal attention network: intraparietal sulcus; salience network: supramarginal gyrus, and thalamus. A Crawford Howell *t*-test was used to compare seed-to-target connectivity of Patient A.P. and the healthy controls. The Crawford-Howell test is a modified *t*-test that compares a single test score to a sample mean. The Crawford-Howell *t*-test also computes the effect size (z_{cc}) which represents the number of standard deviations a single case value deviates

from the control group mean (Crawford et al., 2010; Crawford & Howell, 1998). A connection threshold of *p*-uncorrected < 0.05 was used and a correction for multiple comparisons was computed at a threshold of *p*-FDR < 0.05.

For morphological measures, voxel-based morphometry was employed using computational anatomical toolbox (CAT-12), a statistical parametric mapping (SPM) segmentation tool that computes total intracranial volume and absolute volume of grey matter, white matter, and cerebrospinal fluid (CSF) for each participant. Cortical thickness of visual and non-visual regions was computed using the FreeSurfer analysis suite v7.4.1 (https://surfer.nmr.mgh.harvard.edu/) where individual subject maps were parcellated into distinct anatomical regions using Desikan-Killiany atlas (Desikan et al., 2006). The Crawford-Howell *t*-test compared total intracranial volume, absolute brain tissue volumes, and cortical thickness of Patient A.P. to that of the healthy control group (Crawford & Howell, 1998).

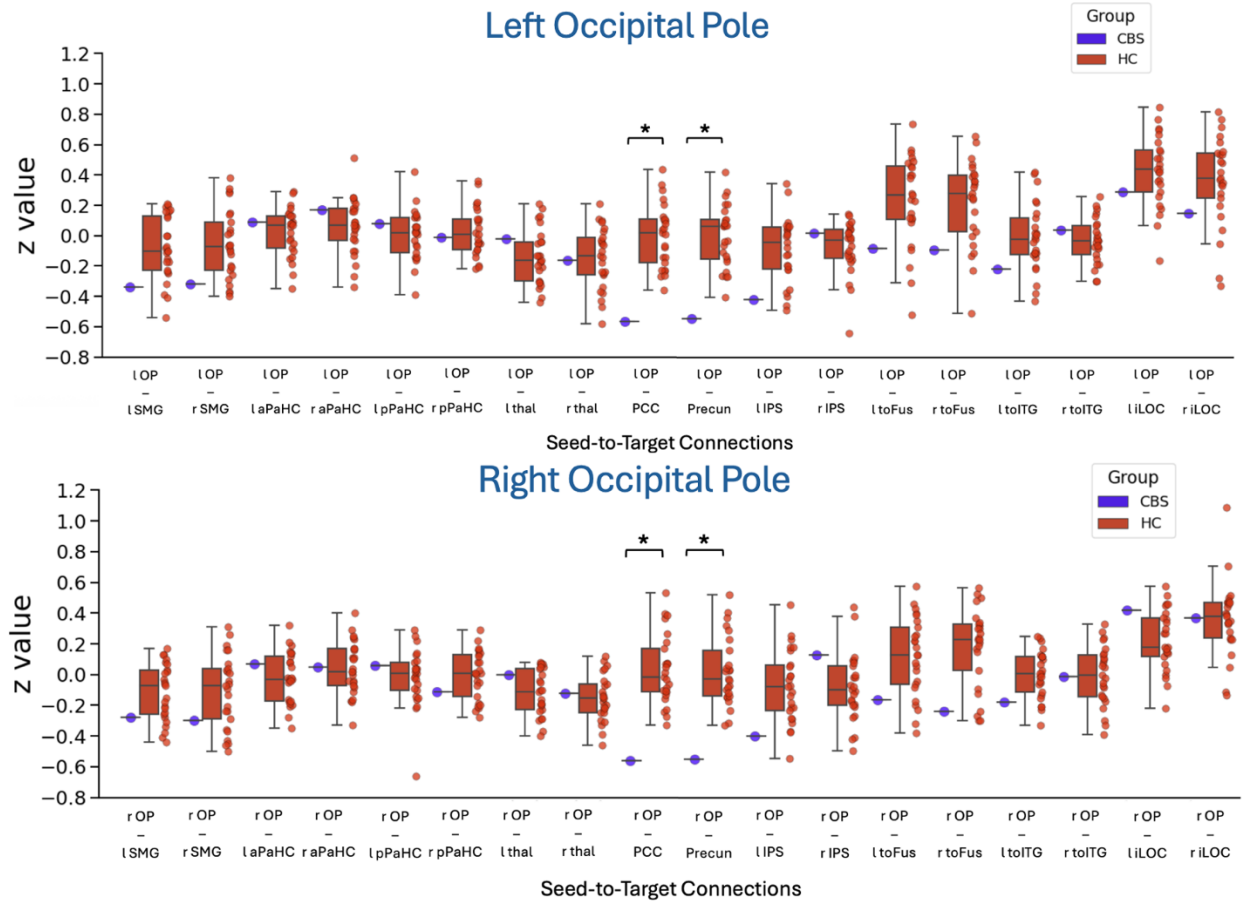
Results

Seed-Based Functional Connectivity

Resting-state functional connectivity was examined between seed regions including the occipital pole, cuneal cortex, and lingual gyrus and targets including precuneus and posterior cingulate cortex of the default mode network, temporo-occipital fusiform cortex, inferior division of the lateral occipital cortex, temporo-occipital part of the inferior temporal gyrus, anterior and posterior divisions of the parahippocampal gyrus along the ventral visual stream, intraparietal sulcus in the dorsal attention network, supramarginal gyrus of the salience network, and the thalamus. Compared to healthy controls, Patient A.P. showed increased negative connectivity between the left and right occipital pole and the precuneus and posterior cingulate cortex. Moreover, the right cuneal cortex displayed increased positive connectivity with the right thalamus in Patient A.P. compared to healthy controls. Finally, functional connectivity between the left lingual gyrus and inferior lateral occipital cortex showed a trend toward increased negative connectivity in Patient A.P. compared to healthy controls. Seed-to-target functional connectivity values of individual participants for each seed-to-target connection are illustrated in Figure 2.1 for occipital poles, Figure 2.2 for cuneal cortex, and Figure 2.3 for lingual gyrus. Appendix E displays Crawford Howell *t*-test results for each seed-to-target connection for occipital pole (Table E.1.), cuneal cortex (Table E.2.), and lingual gyri (Table E.3.).

Figure 2.1.

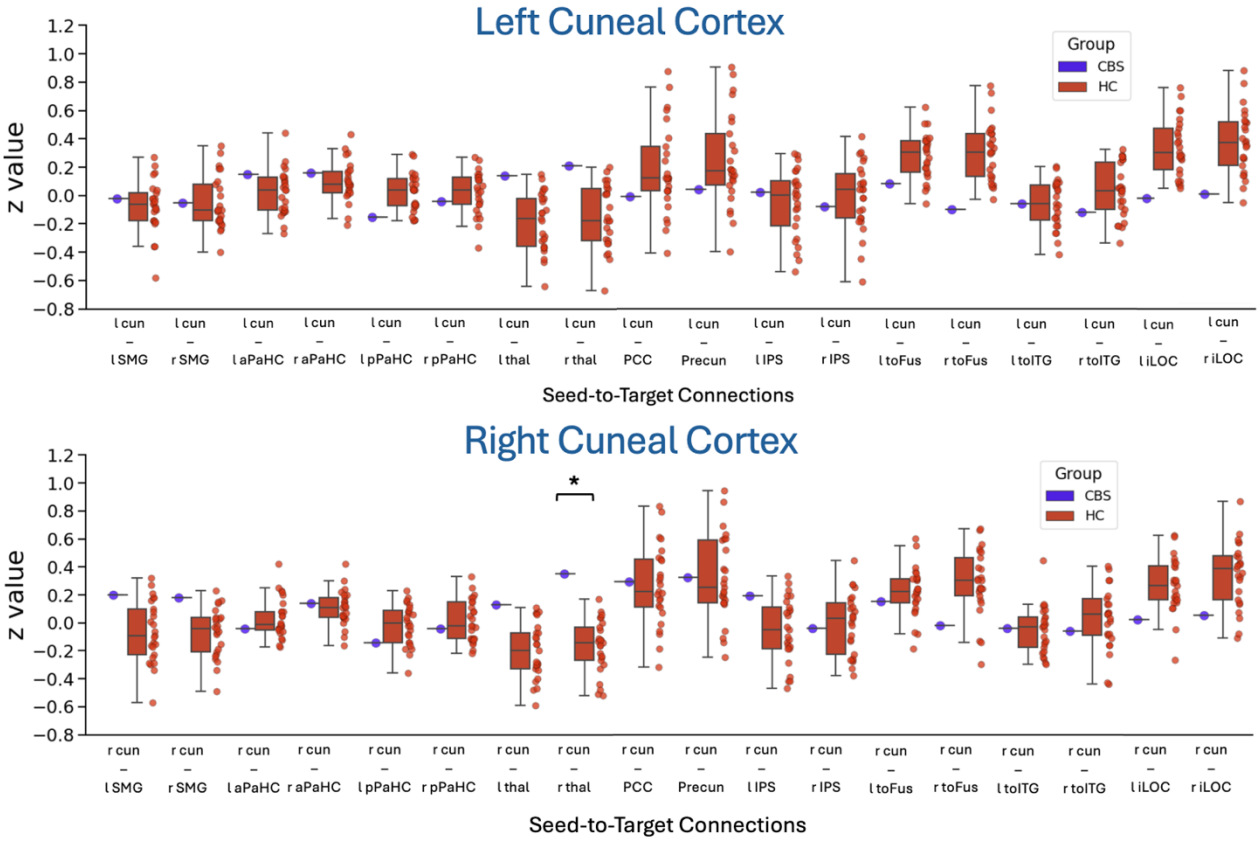
Occipital Pole Seed-to-Target Connectivity



Note. Seed-based functional connectivity Fisher-transformed z values between occipital poles and target regions in Patient A.P (blue) and healthy controls (orange). l = left; r = right; OP = occipital pole; SMG = supramarginal gyrus; aPaHC = anterior parahippocampal gyrus; pPaHC = posterior parahippocampal gyrus; thal = thalamus; PCC = posterior cingulate cortex; Precun = precuneus; IPS = intraparietal sulcus; toFus = temporo-occipital fusiform; toITG = temporo-occipital inferior temporal gyrus; iLOC = inferior lateral occipital cortex. *Significance is set to *p*-uncorrected (*p*-unc) < 0.05; *p*-FDR < 0.05

Figure 2.2.

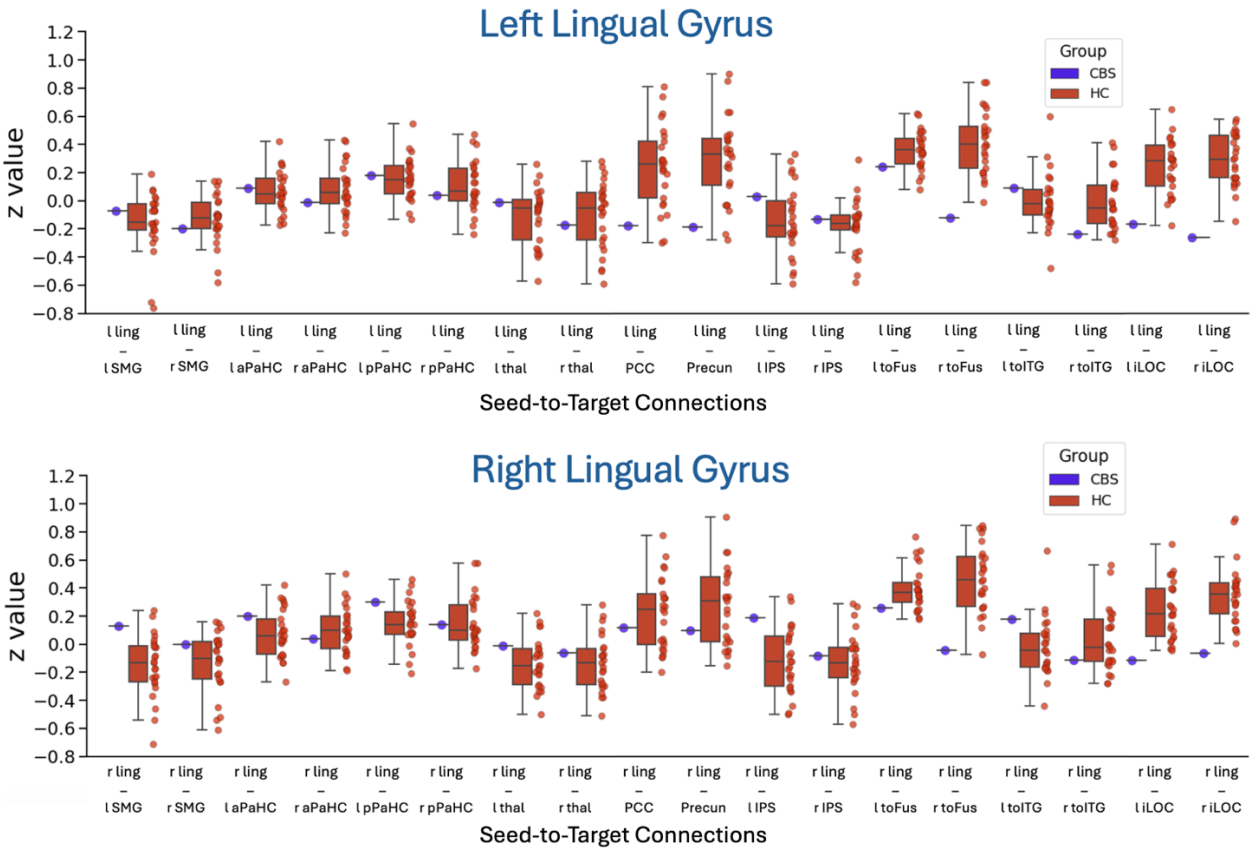
Cuneal Cortex Seed-to-Target Connectivity



Note. Seed-based functional connectivity Fisher-transformed z values between cuneal cortices and target regions in Patient A.P (blue) and healthy controls (orange). l = left; r = right; OP = occipital pole; SMG = supramarginal gyrus; aPaHC = anterior parahippocampal gyrus; pPaHC = posterior parahippocampal gyrus; PCC = posterior cingulate cortex; Precun = precuneus; IPS = intraparietal sulcus; toFus = temporo-occipital fusiform; toITG = temporo-occipital inferior temporal gyrus; iLOC = inferior lateral occipital cortex. *Significance is set to *p*-uncorrected (*p*-unc) < 0.05; *p*-FDR < 0.05

Figure 2.3.

Lingual Gyrus Seed-to-Target Connectivity



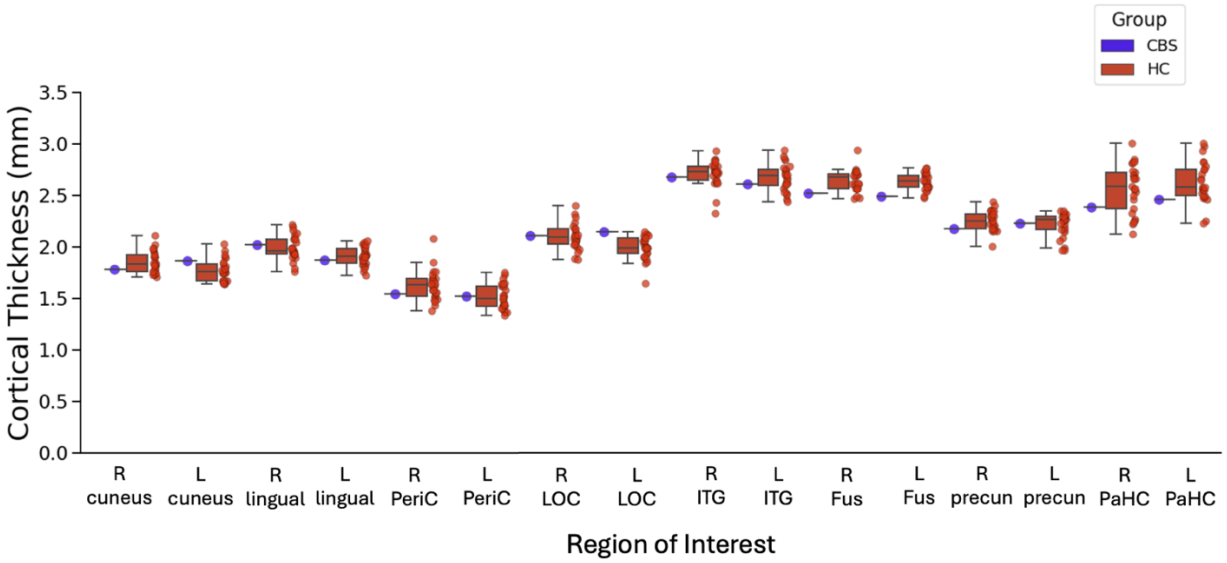
Note. Seed-based functional connectivity Fisher-transformed z values between lingual gyri and target regions in Patient A.P (blue) and healthy controls (orange). l = left; r = right; OP = occipital pole; SMG = supramarginal gyrus; aPaHC = anterior parahippocampal gyrus; pPaHC = posterior parahippocampal gyrus; PCC = posterior cingulate cortex; Precun = precuneus; IPS = intraparietal sulcus; toFus = temporo-occipital fusiform; toITG = temporo-occipital inferior temporal gyrus; iLOC = inferior lateral occipital cortex. *Significance is set to *p*-uncorrected (*p*-unc) < 0.05; *p*-FDR < 0.05

Morphological measures

Cortical thickness was examined for occipital regions: cuneal cortex, lingual cortex, pericalcarine, lateral occipital cortex; ventral visual stream: inferior temporal gyrus, fusiform, parahippocampal cortex; and the default mode network: precuneus. There was no difference in cortical thickness between Patient A.P. and healthy controls across brain regions. Figure 2.4. illustrates the difference in cortical thickness between Patient A.P. and healthy controls. Cortical thickness values and Crawford Howell *t*-test results comparing Patient A.P. and healthy controls are presented in Table E.4.

Figure 2.4.

Comparison of Cortical Thickness between Patient A.P. and Healthy Control Group

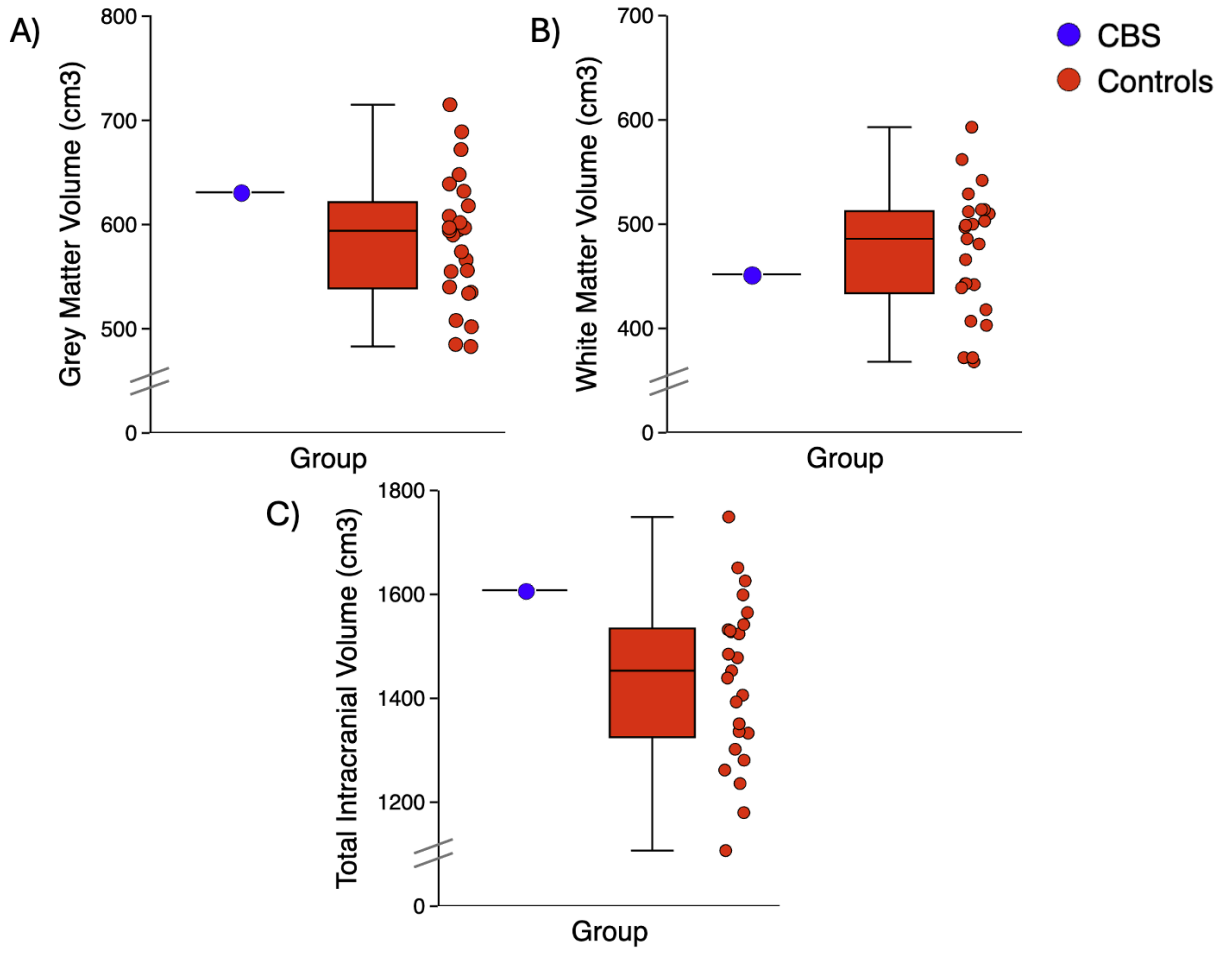


Note. Box plots depicting comparison of cortical thickness (mm) between Patient A.P. (blue) and healthy control group (orange). R = right; L = left; PeriC = pericalcarine; LOC = lateral occipital cortex; ITG = inferior temporal gyrus; Fus = fusiform; Precun = precuneus; PaHC = parahippocampus. No significant difference in cortical thickness of Patient A.P. compared to healthy control group ($p < 0.05$).

Crawford-Howell *t*-tests were conducted to compare total intracranial volume (cm^3), brain tissue volume for grey matter and white matter between Patient A.P. and healthy controls. There was no difference between Patient A.P. and healthy control group for total intracranial volume, absolute grey matter, or white matter volume. Grey matter volume, white matter volume, and total intracranial volume for Patient A.P. and healthy controls are presented in Figure 2.5. Crawford Howell *t*-test results comparing Patient A.P. and healthy controls are presented in Table E.5.

Figure 2.5.

Comparison of Brain Tissue Volume in Patient A.P. and Healthy Controls



Note. Boxplots depicting comparisons of brain tissue volume (cm^3) of A) grey matter, B) white matter, and C) total intracranial volume between Patient A.P. (blue) and healthy controls (orange). *Significance at $p < 0.05$.

Discussion

The present study investigated resting-state functional connectivity and morphology in Patient A.P. who developed CBS secondary to AMD and had a history of ocular tuberculosis. Compared to healthy controls, Patient A.P. showed increased negative connectivity between the right and left occipital pole and the precuneus and posterior cingulate cortex, nodes of the default mode network. Patient A.P. also showed increased negative connectivity between the right cuneal cortex and the right thalamus. Moreover, A.P. displayed a trend toward increased negative connectivity between the left lingual gyrus and the inferior lateral occipital cortex, a functionally specialized region along the ventral visual stream. Morphologically, cortical thickness did not differ between Patient A.P. and healthy controls across visual and non-visual regions. There was no difference in grey matter, white matter, or total intracranial volume between A.P. and healthy controls.

Network-Level Mechanisms: Etiology Specific Deafferentation-Driven Alterations in Large-Scale Networks

In CBS, deafferentation secondary to vision loss is proposed to induce hyperexcitability in early visual areas, thereby altering the functional connectivity between nodes of large-scale networks (Burke, 2002; Kester, 2009; Rovner, 2006; Schadlu et al., 2009). The default mode network is a task negative network that activates at rest (Buckner et al., 2008). During visual processing, an increase in visual input leads to the deactivation of the default mode network and other task-positive networks take over the processing of visual information (Shine et al., 2011, 2014). The antagonistic relationship between default mode (task-negative) and dorsal attention (task-positive) networks is crucial, as the dorsal attention network facilitates top-down

modulation of goal-directed visual tasks, and its activation is functionally concomitant with the deactivation of the default mode network. Previous research proposed that CBS visual hallucinations result from improper dorsal attention network recruitment and overreliance on the default mode network suggesting that a failure of the dorsal attention network to properly modulate activity leads to dysfunctional default mode network activation patterns, potentially contributing to visual hallucinations (Shine et al., 2011, 2014). Similar disruptions have also been observed in hallucinatory states such as schizophrenia, and LSD-induced hallucinations (Müller et al., 2018; Whitfield-Gabrieli & Ford, 2012), where improper default-mode network modulation may lead to excessive internally directed attention orientation during rest thereby forming visual hallucinations. In Patient A.P., a lack of visual input was associated with increased negative connectivity between early visual areas (left and right occipital pole) and the precuneus and posterior cingulate cortex, nodes of the default mode network. These findings are in line with our hypothesis and consistent with late blindness from central vision loss, in which early visual areas representing deafferented central visual fields show increased negative connectivity with nodes of the default mode network (Sabbah et al., 2017). In contrast, a CBS case with retinitis pigmentosa – an early-onset, peripheral visual field degeneration – showed increased positive connectivity between visual areas and the precuneus (Martial et al., 2019). The findings from this study support an etiology and timing dependent network reorganization – late onset central visual loss (AMD) aligns with stronger negative visual-default mode coupling, whereas early-onset peripheral loss may yield more positive coupling patterns (Wong et al., 2014; Kamde & Anjankar, 2023).

Patient A.P. also displayed increased positive connectivity between the right

cuneus and right thalamus. This pattern is in line with altered thalamo-cortical connectivity in CBS secondary to vision loss. Diffusion findings in CBS associated with AMD demonstrate reduced fractional anisotropy in thalamic pathways, specifically along the anterior commissure (Firbank et al., 2022), indicating the involvement of thalamo-cortical commissural connections. Functionally, thalamic hyper-activation has also been described in CBS secondary to cataract and glaucoma (Adachi et al., 2000). These results across different etiologies support the view that deafferentation in CBS disrupts thalamo-cortical circuits, potentially as part of broader network-level reorganization.

Functional Node-Level Mechanisms: Altered Coupling of Visual Areas and Category-Selective Regions

Adding to thalamo-cortical connectivity alterations, prior work suggests functional node-level disruptions where hallucination content (such as faces or objects) may be associated with activation of category-selective regions of ventral occipito-temporal regions. For example, a hallucination involving faces may involve activation within the face processing network which includes the fusiform face area and the occipital face area, and colour hallucinations involve activation in colour area V4 (ffytche et al., 1998). In this study we found a trend toward increased negative connectivity between the left lingual gyrus and inferior lateral occipital cortex, a region specialized in object recognition (Biederman, 1987; Mullin & Steeves, 2011). Previous work shows that stimulus-evoked activity remains confined to the striate cortex in CBS and fails to propagate to higher-order nodes (ffytche et al., 1998; Kazui et al., 2009). Our results support the theory that visual deprivation from vision loss prevents signal transmission from early visual areas (V1 and V2) to higher-order visual regions, thereby leading to endogenous activation of

these specialized areas that produce complex visual hallucinations (Kazui et al., 2009). This aligns with A.P.'s hallucinations of objects (such as the tiger and cars) and supports previous work showing that CBS involves altered connectivity between visual areas and higher-order visual processing regions in the ventral stream (ffytche et al., 1998).

Retinotopic organization further constrains which higher-order regions are preferentially implicated, depending on visual field representations. For instance, central field representations are more strongly linked to face/object regions in ventral occipito-temporal cortex (Levy et al., 2001), whereas peripheral field representations are more associated with motion-selective regions (MT/MT+) (Tootell et al., 1995; Yu et al., 2010). This implies that distinct functional connectivity patterns depend on the etiology of visual loss and the region of visual field that is affected (Arcaro et al., 2015; Griffis et al., 2017; Striem-Amit et al., 2015). Within this framework, the observed lingual-inferior lateral occipital cortex trend in this study is consistent with central-field deafferentation in AMD, and in line with our hypothesis that visual areas representing deafferented central visual fields would be more negatively coupled with category-selective regions along the ventral visual stream (ffytche et al., 1998; Sabbah et al., 2017; Levy et al., 2001).

Structural-Level Mechanisms: Etiology and Visual Field Specific Morphological Changes

While our findings highlight functional connectivity alterations, no morphological differences were observed in total intracranial volume, grey matter volume, and white matter volume in Patient A.P compared to healthy controls. Similarly, cortical thickness of visual and non-visual areas did not differ between our control group and Patient A.P.,

in contrast to Martial et al. (2019), who found lower cortical thickness in a CBS participant with retinitis pigmentosa compared to healthy controls. Two key factors may explain these discrepancies. In our study, Patient A.P. started experiencing vision loss when he was 68 years of age when he was diagnosed with AMD in 2011. A.P. developed CBS visual hallucinations at 77 years of age, 9 years after his vision started deteriorating. The CBS participant in Martial and colleagues' (2019) study was 85 years of age (diagnosed with CBS at 80 years) and started experiencing progressive vision loss at the age of 3 years from retinitis pigmentosa. The difference in time course of vision loss could explain the difference in morphological findings across the studies. Specifically, losing vision during the critical periods of visual development may be associated with different neuroplastic changes compared to losing vision in adulthood, after the visual system is fully mature. Moreover, the control group in Martial and colleagues' (2019) study was generally younger with a large variability in age ranging from 31 years to 72 years (Martial et al., 2019). The volume and weight of the brain decrease by approximately 5% per decade after the age of 40 (Peters, 2006). Grey matter fractions decrease from 52.35% in the 4th decade of life to 50.49% after 80 years of life, while white matter fractions similarly decrease from 47.63% to 40.29%. A combination of brain changes from retinitis pigmentosa and the age difference between their CBS participant and controls may have contributed to these morphological differences, as cerebral atrophy, volume loss, and other age-related changes, such as decreased grey and white matter fractions, intensify with aging and may be exacerbated by vision loss (Blinkouskaya et al., 2021).

It remains unclear what differentiates blindness from CBS. In CBS secondary to

retinitis pigmentosa, decreased grey matter volume and cortical thickness were also observed in late blind controls (Martial et al., 2019), suggesting that these structural changes may reflect vision loss rather than CBS visual hallucinations. Across the broader literature, structural findings vary with etiology – for instance, temporal lobe atrophy was observed without V1/ V2 changes in CBS secondary to glaucoma and cataracts (Adachi 2000, 1994). In this study, there were no changes to grey matter, white matter, or total intracranial volume in CBS. Previous AMD studies report thinning of V1 in zones corresponding to the central scotoma and relative preservation in peripheral representations (Burge et al., 2016; Alcauter et al., 2011; Boucard et al., 2009; Ferreira et al., 2017; Kitajima et al., 1997; Plank et al., 2011). AMD is also associated with reductions in frontal/ anterior white matter (Cavaliere et al., 2020; Hernowo et al., 2014; Reislev et al., 2016) and CBS secondary to AMD has been associated with reduced fractional anisotropy in the thalamus and anterior commissure (Firbank et al., 2022). In this study, we present a unique single-case study of Patient A.P. who developed CBS secondary to AMD and ocular tuberculosis. It is possible that the complicated ocular history of our case explains the difference in results.

We show an alteration in functional connectivity between visual areas and default mode network, and ventral visual stream but no morphological changes in Patient A.P. compared to healthy controls. Taken together, these findings indicate that in a CBS case with late-onset vision loss from AMD and a history of ocular tuberculosis, there network-level alterations between visual areas and the default-mode network, and node-level alterations with retinotopically organized category-selective regions corresponding to the phenomenology of visual hallucinations. To date only one study

has examined resting-state functional connectivity of brain regions, specifically in a CBS patient with visual hallucinations due to retinitis pigmentosa (Martial et al., 2019). Even within the scope of CBS that develops from eye diseases, several eye diseases can coexist in the aging population. The participant in this study lost his vision secondary to AMD and had a history of ocular tuberculosis which complicates the interpretation of results, as each eye-disease related etiology may contribute differently to the observed functional connectivity patterns. It may be that the timing of vision loss (whether vision loss occurs early or later in life), location of visual field disruption (central versus peripheral visual field loss), and etiology of vision loss are all critical factors in how changes in the brain manifest in CBS.

Conclusion

There is a growing body of CBS neuroimaging research that continues to be explored, especially considering the complexity of the condition and the wide range of etiologies that can cause CBS. Patient A.P had a rare case of CBS which developed secondary to AMD with a history of ocular tuberculosis and displayed altered thalamocortical, visual areas, default mode network, and ventral visual stream functional connectivity. CBS predominantly affects older adults who may experience multiple coinciding pathologies. This adds complexity to understanding the neurophysiological mechanisms involved in CBS hallucinations especially since functional connectivity and morphology can vary depending on the underlying vision loss etiology, timing of vision loss (early vs. late onset), and visual field defects (central vs. peripheral). The impact of these factors on functional and structural brain changes in CBS requires further exploration, particularly with respect to how different etiologies and their mechanisms of neuroplasticity shape neural alterations. Future research should focus on disentangling the roles of different eye diseases and the timing of vision loss in contributing to the functional connectivity and structural brain changes seen in CBS to move beyond a broad understanding of CBS as a unitary phenomenon.

Acknowledgements

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CHAPTER III

NO ALTERATIONS IN VISUAL CORTEX NEUROTRANSMITTER CONCENTRATIONS IN A CASE OF CHARLES BONNET SYNDROME SECONDARY TO AGE-RELATED MACULAR DEGENERATION AND OCULAR TUBERCULOSIS

Kinakool, A. N., Moro, S. S., Cohan, R., Rafique, S. A., & Steeves, J. K. E. (2026). No alterations in visual cortex *neurotransmitter concentrations in a case of Charles Bonnet Syndrome secondary to age-related macular degeneration and ocular tuberculosis* [Manuscript in preparation]. Department of Psychology, York University

Abstract

Charles Bonnet Syndrome (CBS) is a phenomenon characterized by visual hallucinations that occur secondary to vision loss. The hallucinations may be associated with hyperexcitability and inhibitory connectivity of visual cortical networks. How excitatory and inhibitory neurometabolites may play a role is unknown. We measured visual cortex glutamate (Glx; combined glutamate, glutamine, and glutathione) and gamma-aminobutyric acid (GABA+; combined 3 GABA methylene groups) levels in a single-case study of CBS. Magnetic resonance spectroscopy (MRS) was examined in a voxel within the visual cortex of an 80-year-old male (Patient A.P.) who developed CBS secondary to age-related macular degeneration (AMD) and ocular tuberculosis compared to fifteen age-matched control participants with normal or corrected-to-normal vision and normal cognitive functioning. There was no difference in visual cortex Glx and GABA+ concentrations in A.P. compared to healthy controls. Visual hallucinations in a single case study of CBS following AMD and ocular tuberculosis may not be associated with changes in visual cortex neurometabolite concentrations.

The visual system undergoes massive reorganization when there is a lack of sensory visual input (Marchesi et al., 2021). Charles Bonnet Syndrome (CBS) is a phenomenon that occurs secondary to vision loss often from age related degenerative visual impairments that progress to blindness such as age-related macular degeneration (AMD), glaucoma, or cataracts. CBS is characterized by a triad of visual hallucinations, normal cognitive status and lack of psychiatric illness, and ocular pathology (Teunisse et al., 1996). Visual hallucinations are visual percepts that occur without any external visual stimulation. For instance, individuals with CBS may experience hallucinations of visual images ranging from simple images such as lines, dots, or flashes of light to more complex images such as faces, animals, figures, patterns, or objects (Khan et al., 2008). These hallucinations occur when a disruption of visual input leads to hyperexcitability of deafferented areas of the visual cortex (Coltheart, 2018).

In vision, retinal ganglion cell functioning is dominated by glutamate receptors, but an effective inhibitory modulation by γ-aminobutyric acid (GABA) is essential for efficient glutamatergic neurotransmission (Boccuni & Fairless, 2022). At a cellular level, glutamate and GABA are closely linked in production, reuptake, and function (Bang et al., 2023), but it is unclear how their concentrations relate to CBS visual hallucinations that arise from vision loss. There is a dynamic temporal relationship between GABA and glutamate concentrations in the visual cortex during resting-state (eyes closed) (Rideaux, 2020). In a magnetic resonance spectroscopy (MRS) paradigm with healthy individuals, a decrease in visual cortex GABA+ predicted an increase in glutamate approximately 120 seconds later (Rideaux, 2020). It is still unknown however, how this

opposite temporal dynamic in glutamate and GABA concentrations may relate to the hyperexcitability of visual areas in visual hallucinations that arise from CBS.

Processing of visual stimuli is associated with increased glutamate concentrations in the visual cortex (Bednařík et al., 2015, 2018; Betina Ip et al. 2017; Kurcyus et al., 2018; Lin et al., 2012; Mangia et al., 2007; Schaller et al., 2013) but it is still unknown whether CBS visual hallucinations that may arise from hyperexcitability of visual areas are governed by increased occipital glutamate concentrations. Further, the role of GABA in visual processing is less clear although it has been implicated in top-down modulation of visual perception (Frangou et al., 2019), modulation of surround suppression of visual stimuli (Angelucci et al., 2017), and facilitation of perceptual dominance of visual cortex neurons (Lunghi et al., 2015; Pitchaimuthu et al., 2017; Robertson et al., 2016; Shapley et al., 2003). However, pharmacological interventions show that administering lorazepam, a GABA agonist, does not increase visual spatial suppression indicating that visual cortical inhibition may extend beyond the inhibitory effects of GABA (Schallmo et al., 2018). While one study found a decrease in GABA during the presentation of a visual checkerboard stimulus (Mekle et al., 2017), others did not replicate these findings (Bednařík et al., 2015, 2018; Kurcyus et al., 2018; Mangia et al., 2007; Schaller et al., 2013).

When there is a lack of sensory visual input, the visual system undergoes massive cortical reorganization (Merabet & Pascual-Leone, 2010). However, the role of neurotransmitters in this cortical reorganization is unclear. In CBS, it is unclear how a combined effect of vision loss and age influences neurotransmitter concentrations especially since neither a decrease in visual acuity nor severe visual impairment are

required to make a CBS diagnosis (ffytche, 2007; Jurišić et al., 2018; Karagöl, 2021; Teunisse et al., 1995). Moreover, the literature reports contradictory findings about visual cortex GABA levels with ageing. In a post-mortem human study of different age groups, it was found that there was a decrease in enzymes responsible for GABA production with ageing (age between 69 to 80 years) (Pinto et al., 2010). This was supported by other studies which found lower GABA concentrations in the visual cortex of older adults (Chamberlain et al., 2021; Simmonite et al., 2019; Zuppichini et al., 2024). On the contrary, another study found an increase in visual cortex GABA and decrease in glutamate levels with ageing (Pitchaimuthu et al., 2017). These contradictory findings pose a challenge and further add complexity to inferences made about the neurochemical correlates in CBS.

Currently, there are no studies that examined visual cortex glutamate and GABA concentrations in CBS. CBS can occur secondary to various eye-diseases, and distinct etiopathological mechanisms governing those eye-diseases may influence visual cortex neurometabolite concentrations. Moreover, it is unclear how a combination of CBS visual hallucinations, vision loss, and ageing affect neurometabolite concentrations. Here, we sought to investigate concentrations of visual cortex glutamate (Glx, a combined glutamate, glutamine, and glutathione) and GABA (GABA+, a combination of 3 GABA methylene groups) in a unique case of CBS secondary to AMD and ocular tuberculosis.

Materials & Methods

Ethical approval was obtained from York University Office of Research Ethics (ethics certificate: e2023-119) and written consent was obtained from all participants.

Standardized vision testing included visual acuity testing using the standardized early treatment diabetic retinopathy study (ETDRS) vision chart (Precision Vision, La Salle, IL), color vision using the Farnsworth D-15 (LUNEAU Ophtalmologie, France), and stereoacuity using the Random Dot Stereo Butterfly and Stereotest – Circles (Stereo Optical Company Inc., Chicago, IL). Visual field perimetry was assessed in Patient A.P. and six out of the 15 healthy controls using the EyeSuite™ OCTOPUS 300 (version 2.3.0) (Haag-Streit International, Switzerland) using the OP2/ M static examination procedure which assesses visual field deficits. Mean retinal sensitivity was recorded and compared between Patient A.P. and the healthy control group.

Patient A.P.

An 80-year-old right-handed male participant with CBS (Patient A.P.) was included in the study. A.P. started experiencing vision loss in 2011 when he was diagnosed with AMD and reported experiencing visual hallucinations since 2020. A.P. also had a history of ocular tuberculosis in his left eye (diagnosed in 2013), and bilateral cataract removal surgery in 2018. Upon assessment, he had binocular visual acuity of 0.9 logMAR (left eye – 0.8 logMAR; right eye – 1.02 logMAR) and had no history of other neurological or neuropsychiatric disorders. He reported a history of depression and anxiety for which he was intermittently treated with Lorazepam.

Patient A.P. underwent screening and completed standardized outcome measures including the Neuropsychiatric Inventory (NPI) which assesses

psychopathology (Cummings et al., 1994) and the North-East Visual Hallucinations Interview (NEVHI) which assesses emotions, cognitions, and behaviours associated with visual hallucinations (Mosimann et al., 2008). A.P. showed no measurable stereoacuity (Stereo Optical Company Inc., Chicago, IL). The Montreal Cognitive Assessment (MoCA) -Blind scale which evaluates participants with visual deficits was also administered (Wittich et al., 2010) and Patient A.P. had normal cognitive functioning. Detailed screening for A.P. is provided in Appendix B.

Patient A.P.'s visual hallucinations included two rainbow colored spinning halos, green faces, twinkling trees, comic faces and figures, lattice structures, cars while crossing the street, and a tiger coming down the stairs. He did not report any multisensory hallucinations (auditory, olfactory, or tactile). A.P.'s hallucinations were exacerbated by bright light and were visible along the entire visual field. They occurred several times a week and lasted seconds to hours. Patient A.P, did not report experiencing any visual hallucinations during the experiment and scan.

Healthy Controls

A group of fifteen age-matched healthy controls with no neurological or neuropsychiatric illnesses were also included in the study (7 females, Mean age (SD) = 72.6 (5.7) years). Out of the 15 healthy controls, 9 participants' data were collected as part of a collaborative project with the University of Waterloo. The MRS acquisition protocol exactly matched the protocol used in this study (resting-state with eyes closed). All healthy control participants were right-handed and had normal or corrected-to-normal vision. Participants underwent screening to rule out any neurological or psychiatric disorders. The MoCA scale indicated normal cognitive functioning of all healthy controls

(Nasreddine et al., 2005) and the Farnsworth D-15 test indicated that none of the participants had colour vision defects.

Magnetic Resonance Imaging

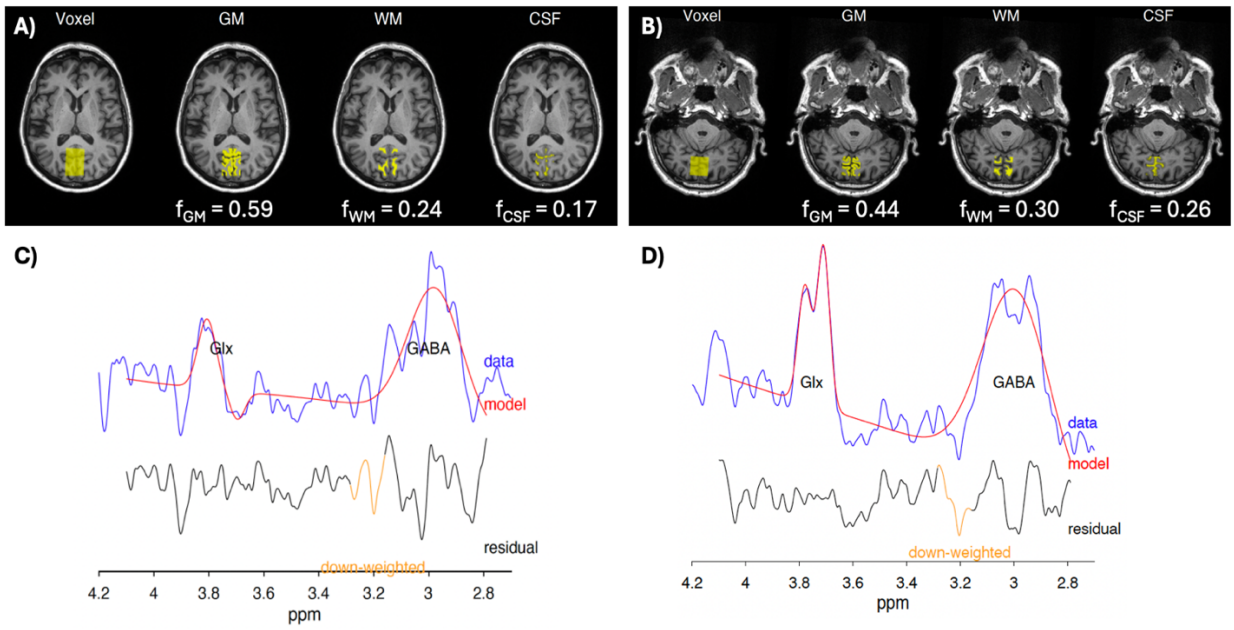
Structural magnetic resonance imaging and magnetic resonance spectroscopy (MRS) data were acquired with a 3 Tesla Siemens Magnetom® Prisma magnetic resonance scanner with a 32-channel high-resolution array head coil (Siemens, Erlangen, Germany). A T1 magnetization-prepared rapid gradient echo (MPRAGE) imaging sequence acquired high-resolution T1 weighted images - T1-weighted 3D gradient echo with 192 slices, repetition time (TR) = 2300 ms, echo time (TE) = 2.26 ms, inversion time (TI) = 900 ms, slice thickness = 1 mm, flip angle = 8°, field of view (FoV) = 256 mm, slice order = ascending, acquisition time of approximately 5 minutes.

For MRS, the Mescher-Garwood Point Resolved Spectroscopy (MEGA-PRESS) J- difference editing technique was used to acquire proton (^{1}H) MR spectra using a 25 mm^3 voxel placed medially in the visual cortex with participants' eyes closed under an eye mask in a dark room. This technique isolates a combined glutamate, glutamine, and glutathione signal (referred to as Glx) at 3.75 ppm and a combined signal of three GABA methylene groups at 3 ppm (combined signal known as GABA+) (Mescher et al., 1998b; Mullins et al., 2014). The volume of interest was centered on the calcarine sulcus with the lower edge aligning with the cerebellar tentorium and avoiding any non-brain tissue like cerebrospinal fluid or sagittal sinus (Figure 3.1). The following parameters were used: TR = 3000 ms, TE = 68 ms, spectral width = 1500 Hz, sinc-Gaussian editing pulses (nominal full-width at half maximum [FWHM] bandwidth = 50.55 Hz) applied at 1.9 parts per million (ppm) "edit-ON" and 7.5 ppm "edit-OFF", VAPOR

water suppression (FWHM bandwidth = 60 Hz), averages = 32, repeated four times for a total of 128 “edit-ON” and 128 “edit-OFF” averages, number of samples = 2048. An unsuppressed water reference scan was also performed to obtain a tissue concentration reference (averages = 10). The total acquisition time was approximately 30 minutes.

Figure 3.1.

Proton (^{1}H) MR Spectra Acquired from Visual Cortex



Note. MRS voxel placement and probabilistic partial volume voxel maps following GannetSegment tissue segmentation for A) one healthy control and B) Patient A.P.; Tissue volume fractions of grey matter (f_{GM}), white matter (f_{WM}), and cerebrospinal fluid (f_{CSF}) within the voxel used to provide tissue-corrected estimates for Glx and GABA+ concentrations. C) Healthy control and D) Patient A.P. spectral model fitting for Glx and GABA+ representing raw data (blue) and model fit (red), and down-weighting of artifact signals (yellow). Glx = combined glutamate, glutamine, and glutathione; GABA = gamma-aminobutyric acid.

Data analysis

MRS data were analyzed using a linear combination model on Gannet (v3.3.1; Baltimore, Maryland, United States; https://www.GABA+MRS.com) which performs batch analysis of edited difference spectrum double Gaussian fit (Edden et al., 2014) and SPM12 (statistical Parametric Mapping; Welcome Centre for Human Neuroimaging; London, United Kingdom; https://www.fil.ion.ucl.ac.uk/spm). GannetSegment using SPM segmentation calculated fractions of grey matter volume (f_{GM}), white matter volume (f_{WM}), and cerebrospinal fluid volume (f_{CSF}) within the visual cortex voxel. Details of gannet analysis methods are presented in Appendix F.

All statistical analyses were conducted in R Studio (v 2023.12.1+402; Vienna, Austria; www.R-project.org). The Crawford-Howell *t*-test was used to compare visual field perimetry measure of mean retinal sensitivity between Patient A.P. and six out of the 15 healthy controls who performed the visual field test (Crawford & Howell, 1998) and to compute effect size (Crawford et al., 2010). Similarly, Glx and GABA+ were compared between Patient A.P. and the healthy control group (Crawford & Howell, 1998). Analyses were conducted for Glx and GABA+ concentrations in reference to creatine. An alpha level of 0.05 was used.

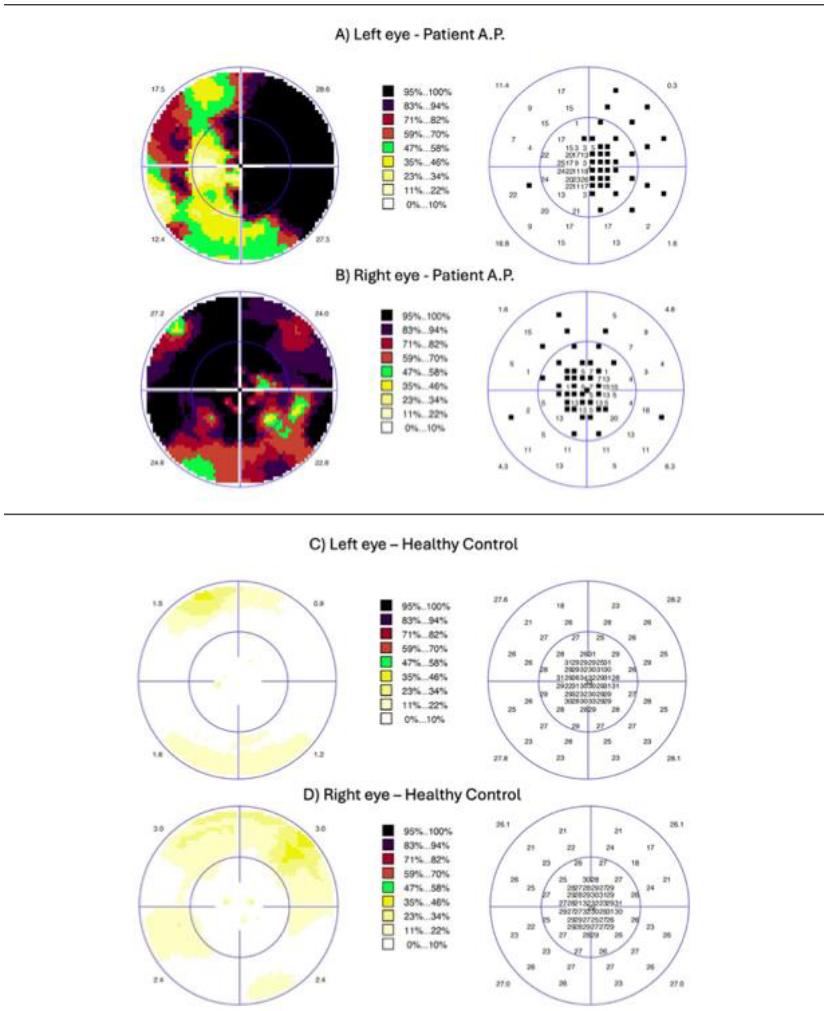
Results

Visual Field Measures

A Crawford-Howell *t*-test compared mean retinal sensitivity between Patient A.P. and six of the healthy controls for each eye. Patient A.P. had lower mean retinal sensitivity (mean retinal sensitivity = 7.4 dB) in the left eye compared to the six healthy controls (mean (SD) = 25.17 (1.88) dB), $t(5) = -8.75$, $p < 0.001$, $zcc = -9.45$. Similarly, A.P. had a significantly lower mean retinal sensitivity (4.2 dB) in the right eye compared to healthy controls (mean (SD) = 24.47 (1.63) dB), $t(5) = -11.51$, $p < 0.001$, $zcc = -12.44$. This confirms poor visual input in Patient A.P. compared to healthy controls. Figure 3.2 represents visual field defects in Patient A.P and one healthy control participant. Visual field data for participants are presented in Appendix G.

Figure 3.2.

Visual Field Plots of Retinal Sensitivity



Note. Illustration of retinal sensitivity thresholds in Patient A.P. (A. Left eye; B. Right eye) and one representative healthy control (C. Left eye; D. Right eye). On the left, 2D color maps representing retinal sensitivity threshold values. Colour scale represents approximately 10 dB range (white representing highest sensitivity and black representing absolute defects). On the right, sensitivity threshold values at test stimuli locations. Black squares represent absolute defects at test stimuli locations.

Glx Concentrations

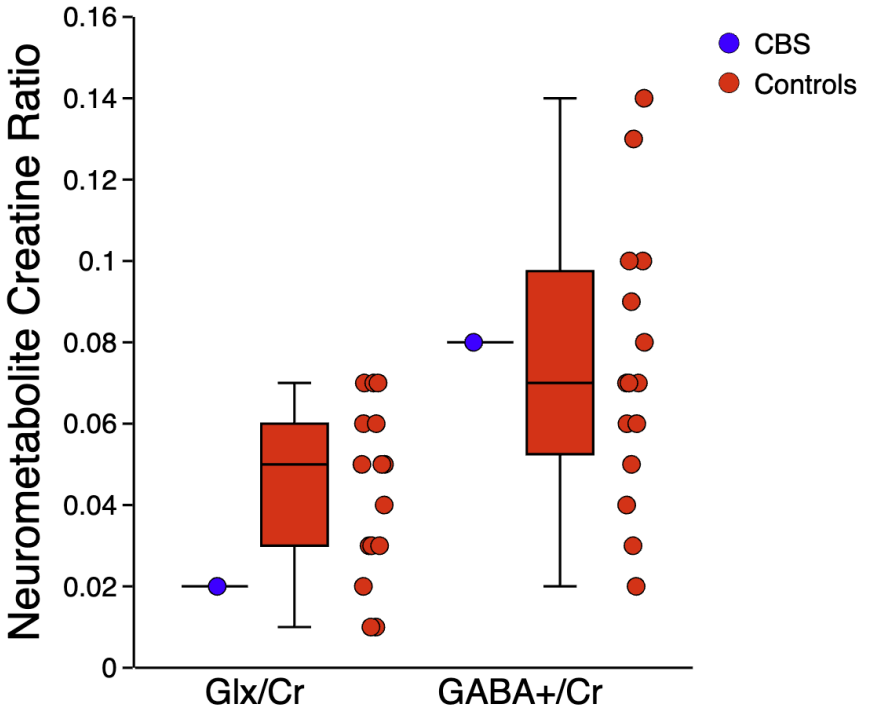
We compared Glx in reference to creatine (Glx/Cr) between Patient A.P. and healthy controls using the Crawford Howell *t*-test. There was no difference in Glx/w levels between Patient A.P. (Glx/Cr = 0.02) and healthy controls (mean (SD) = 0.04 (0.02), 95% CI = [0.03, 0.05]), $t(14) = -1.08$, $p = 0.298$, $z_{cc} = -1.11$.

GABA+ Concentrations

A Crawford-Howell *t*-test compared GABA+ in reference to creatine (GABA+/Cr) between Patient A.P. and healthy controls. There was no difference in GABA+/w levels between A.P. (GABA+/Cr = 0.08) and healthy controls (mean (SD) = 0.07 (0.03), 95% CI = [0.06, 0.08]), $t(14) = 0.17$, $p = 0.866$, $zcc = 0.17$. Figure 3.3 illustrates comparison of neurometabolite concentrations in Patient A.P. and the healthy control group.

Figure 3.3.

Comparison of Neurometabolite Concentrations



Note. Comparisons of neurometabolite concentrations in reference to creatine (Glx/Cr and GABA+/Cr) between Patient A.P. (blue) and healthy control group (orange). Glx = combined glutamate, glutamine, and glutathione; GABA+ = combined 3 methylene groups of gamma-aminobutyric acid.

Discussion

This study is the first to explore visual cortex glutamate and GABA concentrations in a single case study of a patient with CBS. Our findings show no changes in visual cortex Glx and GABA+ concentrations in our CBS participant, Patient A.P. compared to healthy, age-matched controls.

Prior studies found that glutamatergic signals in the visual cortex decline with advancing eye diseases, indicating that visual input loss is associated with decreased glutamate levels (Bang et al., 2023). Generally, participants who have their eyes open or view checkerboard visual stimuli show an increase in visual cortex glutamate (Bednařík et al., 2015, 2018; Betina Ip et al., 2017; Kurcyus et al., 2018), which implies that a lack of visual stimulation from vision loss may be associated with changes in baseline occipital glutamate levels. Regarding inhibitory mechanisms, reductions in occipital GABA have been linked to visual hallucinations in conditions such as Parkinson's disease and Lewy Body Dementia (Firbank et al., 2018; Khundakar et al., 2016) and this suggests that low GABA levels could be associated with the occurrence of visual hallucinations in other diseases. However, CBS hallucinations that are related to visual cortex deafferentation mechanisms likely differ from perceptual- attention deficit disorders such as Parkinson’s disease and Lewy Body Dementia which involve alpha-synuclein proteins (D’Antonio et al., 2022). The difference in pathophysiological mechanisms may explain the distinct neurochemical correlates in Patient A.P. who had similar Glx or GABA+ concentrations to healthy controls.

CBS hallucinations may not be associated with increased glutamate or reduced GABA-related inhibition in the visual cortex due to different mechanisms related to

vision loss. Unfortunately, there are no studies that investigated visual cortex neurometabolites in CBS so we cannot make cross-study comparisons. Moreover, this was a case study which makes it difficult to interpret or generalize the results. Patient A.P. did not experience any visual hallucinations during the scan and this could explain why there were no changes in neurometabolite concentrations. It is possible that neurometabolite concentrations may change during the occurrence of CBS visual hallucinations. The deafferentation theory posits that a disruption or reduction of afferent retinal input leads to an increased activation/ hyperexcitability in visual cortical regions thereby causing CBS visual hallucinations (Burke, 2002). One of the primary functions of V1 is to receive, integrate, and transmit visual information to V2, associative cortices, and higher order visual areas along the dorsal and ventral stream. It is thought that a dysfunction in early visual cortex (V1 and V2) prevents the transmission of visual stimuli to higher-order visual areas leading to endogenous activation, thereby causing complex visual hallucinations (Kazui et al., 2009). This was observed in CBS patients displaying increased activation in higher-order category selective regions such as activation in fusiform regions with face hallucinations or in colour area V4 with coloured hallucinations (ffytche et al., 1998). In this study, Patient A.P. experienced a variety of complex visual hallucinations such as scenes, faces, and objects. It is possible that hyperexcitability of visual areas involved in processing category selective stimuli (e.g., faces, objects) is associated with alterations in neurometabolite levels in these higher-order brain regions. As such, it is possible that neurometabolite (glutamate and GABA) alterations are not seen in early visual areas.

Considering both morphology and neurochemical correlates, there is an

intersection between brain tissue volume and neurometabolite concentrations. Brain neurometabolite levels are known to vary with tissue type; for instance, grey matter generally has twice the GABA concentration compared to white matter (Choi et al., 2007; Zhu et al., 2011). Our tissue correction method followed previous work that prevents underestimation of neurometabolite concentrations in grey and white matter by estimating a concentration ratio that assumes that neurometabolite levels in white matter are half of those in grey matter (Harris et al., 2015). In this study, a rigorous quality check was performed along three planes during voxel placement to ensure that the visual cortex voxel was placed correctly and minimized lipid or sinus contamination. It is also noteworthy to mention that CBS predominantly affects older adults and at the same time, ageing is characterized by cerebral atrophy, volume loss, ventricular enlargement, and sulci widening (Blinkouskaya et al., 2021). Moreover, CBS develops secondary to eye disease and age-related changes may be heightened by specific structural alterations that occur with vision loss (Blinkouskaya et al., 2021). Since older adults have higher GABA concentrations compared to younger adults (Pitchaimuthu et al., 2017), this further complicates interpretation of our findings due to a combined effect of ageing and possible neural alterations from vision loss. However, in this study our healthy control group was age-matched to the single patient to control for differences that may exist due to age. Moreover, A.P.’s history with anxiety and intermittent use of Lorazepam poses a challenge to this study. A.P. reported taking Lorazepam on occasion; sometimes quarter the dose once a week and other times 2-3 times a week. We could not monitor the exact history of medication intake and hence this could further complicate our interpretation of results.

In this study, there were no alterations to visual cortex glutamate and GABA concentrations in a case of CBS with AMD and ocular tuberculosis compared to healthy controls. CBS can occur due to a variety of mechanisms depending on etiology of vision loss (e.g., degenerative such as AMD, developmental such as retinitis pigmentosa, or cortical). It is possible that different mechanisms may be associated with distinct morphological and neurochemical alterations in the visual cortex depending on the vision loss etiology. Further, it could be that alterations to neurometabolites are seen in higher-order category selective visual regions rather than early visual areas.

Conclusion

This study demonstrates that compared to a group of healthy controls, Patient A.P. who developed CBS secondary to AMD and ocular tuberculosis had no alterations in visual cortex Glx and GABA+ concentrations. While acknowledging the limitations of a single case study, this research nonetheless is the first step to examine visual cortex excitatory (glutamate) and inhibitory (GABA) neurometabolite levels in CBS. Future investigations into the role of visual cortex neurometabolites in conjunction with eye diseases and their distinct cortical manifestations is warranted. Patient A.P. is a unique and rare case of CBS and future research should focus on different eye-disease etiologies and their possible association with neurochemical changes in the visual cortex. This will deepen our understanding of the neurochemical correlates associated with the underlying mechanisms behind visual hallucinatory experiences in CBS. Understanding neurochemical correlates related to vision loss in CBS could potentially help design personalized neuromodulation treatment protocols targeting specific brain regions that are affected by CBS mechanisms.

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CHAPTER IV

CHARLES BONNET SYNDROME HALLUCINATIONS ARE ASSOCIATED WITH VISUAL FUNCTION AND NOT PSYCHOSOCIAL HEALTH MEASURES

Kinakool, A. N., Moro, S. S., Sukhai, M. A., & Steeves, J. K. E. (2026). *Charles Bonnet Syndrome hallucinations are associated with visual function and not psychosocial health measures* [Manuscript in preparation]. Department of Psychology, York University

Abstract

Charles Bonnet Syndrome (CBS) is a condition involving complex visual hallucinations secondary to vision loss often from age-related visual impairment. CBS is more common in older adults but may occur at any age when visual input is reduced due to visual impairment. Public health measures aimed at reducing virus transmission during the COVID-19 pandemic contributed to the deterioration of psychosocial health in older adults. Specifically, older adults have experienced increased social isolation, loneliness, and reduced quality of life during the COVID-19 pandemic. Evidence suggests that CBS hallucinations were exacerbated by COVID-19 related social restrictions implying an association between psychosocial health measures and hallucinatory experiences. To explore this relationship, we examined psychosocial health measures including anxiety, loneliness, social isolation, physical activity, and quality of life during COVID-19 to assess whether they were associated with changes in the nature (vividness/ clarity) and frequency of CBS hallucinations. A self-administered online cross-sectional survey was administered to fifty-five individuals with CBS. Anxiety, loneliness, social isolation, quality of life, and physical activity were assessed. Fifty-three percent of participants reported “no-change” in frequency and eighty percent reported “no-change” in nature of hallucinations during the COVID-19 pandemic. Individuals who experienced a “change” (increase or decrease) in hallucination frequency during the COVID-19 pandemic were more likely to have poorer vision than those who experienced “no-change” in hallucination frequency. Further, this finding was driven by individuals who reported an increase in hallucination frequency during COVID-19 and reported poorer vision. There was no relationship between time since

hallucination onset and psychosocial health measures of anxiety, loneliness, social isolation, quality of life, and physical activity. Findings indicate that anxiety, loneliness, social isolation, quality of life, and physical activity were not related to changes in CBS hallucinations during the fifth wave of the COVID-19 pandemic in Canada. Only a minority of individuals showed an increase in the frequency of CBS hallucinations during the COVID-19 pandemic which may be related to the natural course of vision loss rather than an association with psychosocial health measures. These data support the notion that CBS hallucinations are associated with biological origins following vision loss rather than psychosocial health.

Charles Bonnet Syndrome (CBS) is a poorly understood, debilitating phenomenon where individuals experience complex visual hallucinations secondary to vision loss, often from diseases such as age-related macular degeneration, glaucoma, and cataracts (Burke, 2002). Individuals with CBS experience visual hallucinations in the form of images such as people, animals, landscapes, or patterns (Yacoub & Ferrucci, 2011). CBS hallucinations have been associated with hyperexcitability of the visual cortex, and other cortical and subcortical regions (Carpenter et al., 2019). Research shows that hallucination content is associated with topological activation of functionally specialized areas, i.e., activation of face processing network with face hallucinations and activation in color area (V4) of the fusiform gyrus with color hallucinations (ffytche et al., 1998). This hodotopic framework emphasizes that in CBS, the activation of functionally specialized areas and their connectivity to distant brain nodes forms brain- wide network alterations. Findings from neuroimaging studies also show morphological changes in occipital, temporal, parietal, and cerebellar regions (Adachi et al., 1994, 2000; Lawn & ffytche, 2021) further highlighting the neurophysiological changes associated with CBS.

CBS is more prevalent in older adults since it often occurs following age-related visual impairment (Menon et al., 2003). Older adults experienced adverse effects on their mental health measures such as stress, depression, affect, and well-being during the COVID-19 pandemic due to the implementation of public health safety measures such as social distancing and limitations on gatherings and travel (Gloster et al., 2020; Jones et al., 2021; Oldenburger et al., 2022). For instance, psychosocial health measures such as social isolation and loneliness measurably increased among older

adults during the pandemic, and this could contribute to a decreased quality of life (Donovan & Blazer, 2020; Jones et al., 2021; Lebrasseur et al., 2021).

The association between visual impairment and psychosocial health measures is also well-documented, with individuals experiencing vision loss reporting higher levels of anxiety, depression, and reduced quality of life (Almidani et al., 2024; Assi et al., 2021; Jones et al., 2018). In fact, there is an association between the duration of vision loss (how long a person has lived with vision loss) and psychosocial health. While one study found that shorter periods of visual loss are associated with higher distress (Williams et al., 1998), another found that psychological distress was 8 times higher in individuals who experienced vision loss for more than 2 years (Munaw & Tegegn, 2022). Individuals who have lived with vision loss for periods longer than 2 years, particularly those with bilateral vision loss, experience greater psychological distress (Munaw & Tegegn, 2022), and later-onset vision loss is linked to lower quality of life (Bonsaksen et al., 2025). Whether these findings extend to people who experience CBS remains an open question. Specifically, is the length of time a person has lived with visual hallucinations associated with their psychosocial health?

Since CBS is more prevalent among older adults and often develops secondary to visual impairment, it is possible that individuals with CBS also experienced adverse effects on their psychosocial health during the COVID-19 pandemic. In fact, psychosocial health measures may be associated with an exacerbation in CBS hallucinations during the COVID-19 pandemic; a survey conducted during the second wave of the COVID-19 pandemic in the United Kingdom found that loneliness was higher in older participants with CBS (Jones et al., 2021b). The authors also reported

that CBS hallucinations were exacerbated due to an increase in loneliness during the pandemic (Jones et al., 2021b). This highlights that COVID-related social restrictions may be associated with adverse effects on the psychosocial health of older adults with CBS (Jones et al., 2021b). Moreover, 47 percent of their participants believed that the lack of physical activity during the pandemic was responsible for the changes in their hallucination phenomenology (Jones et al., 2021b). Physical activity has been associated with improved quality of life and lower depression in older adults (Hao et al., 2024; Kiełtyka-Słowik et al., 2024; Li et al., 2024). However, it is unknown whether a lack of physical activity during the COVID-19 pandemic contributed to adverse effects on psychosocial health measures or changes in CBS hallucinations.

Jones and colleagues (2021b) found that 56% of CBS participants experienced an increase in the frequency of their hallucinations and 47% reported changes to the nature of their hallucinations (described as complex, troublesome, frightening, more vivid, intense, with abnormal features, e.g., people with two heads) during the COVID-19 pandemic lockdown (Jones et al., 2021b). This implies that COVID-19 related psychosocial health measures may be associated with changes in CBS hallucinations. While Jones and colleagues (2021b) recorded qualitative responses of CBS patients, further investigation using standardized and validated outcome measures is warranted. This study aimed to examine whether psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity were associated with changes in nature (vividness/ clarity) and frequency of CBS hallucinations during the COVID-19 pandemic. Further, the relationship between time since hallucination onset and psychosocial health measures was examined to determine whether how long a

person has lived with CBS hallucinations relates to their psychosocial health during the pandemic.

Materials and Methods

Participants

Fifty-five participants (mean age, 68 ± 17 years; 36 females) were recruited from the Canadian National Institute for the Blind Foundation CBS database and support groups. Data were collected between November 2021 to March 2022, during the fifth wave of the COVID-19 pandemic (Omicron variant) in Canada when social restrictions such as limited visitation in long term care, advisories to limit non-essential travel, limitations to number of people in social gatherings, and social distancing were in place (Oldenburger et al., 2022). Informed consent was obtained, and the study was approved by the York University Office of Research Ethics.

Study Design

A self-administered cross-sectional online survey was presented using Qualtrics (Qualtrics, Provo, Utah, USA). Ninety-five percent of participants completed the survey online and the remainder provided survey responses over the phone. All questionnaires were accessible for the visually impaired. Details of survey questions are presented in Appendix H.

Outcome measures

The survey included questions about demographic information, physical health, mental health, vision status, living conditions (alone or cohabitating), and the use of assistive devices. Moreover, the survey consisted of a battery of five standardized and validated questionnaires to assess anxiety, loneliness, social isolation, quality of life, and physical activity. Outcome measures included modified versions of the Generalized Anxiety Disorder-7 scale, a seven-item measure that assesses the severity of anxiety

(Wild et al., 2014) ; the DeJong Gierveld Loneliness Scale which assesses emotional and social loneliness (Gierveld & Tilburg, 2006); the Steptoe Social Isolation Index which assesses living conditions and degree of social isolation (Steptoe et al., 2013); and the World Health Organization quality of life - BREF scale which assesses the physical, psychological, social, and environmental domains of quality of life (Skevington et al., 2004). All modified questionnaires included a sentence asking participants to answer based on their experiences over the previous year during the COVID-19 pandemic. To improve accessibility, physical activity was assessed by modifying the International Physical Activity Questionnaire to include close-ended questions about participants' level of physical activity during the COVID-19 pandemic (Craig et al., 2003). Details of questionnaires are presented in Appendix H.

Statistical Analysis

Participant reports about the change in nature and frequency of visual hallucinations during COVID-19 restrictions were recorded. The data were sorted into two groups – those who experienced a "change" (increase or decrease) and those who experienced "no-change" in hallucination frequency during the COVID-19 pandemic. Comparison of psychosocial measures between these groups was examined using independent samples *t*-tests and Mann Whitney *U* tests. We further examined the comparison of psychosocial measures between those who experienced an "increase", "decrease", and "no-change" in hallucination frequency using One-way ANOVA and Kruskal Wallis tests. Further, a Chi-square test of independence assessed the association between subjective eyesight rating (excellent to very poor) and the "change" versus "no-change" in visual hallucination frequency to examine whether eyesight rating

was related to the change in visual hallucinations during the COVID-19 pandemic. To further examine this association, participants were divided into “increase”, “decrease”, and “no-change” in hallucination frequency during the COVID-19 pandemic. Finally, the relationship between time since hallucination onset (months) and psychosocial measures was examined to determine whether how long a person has lived with hallucinations was related to their psychosocial health.

Results

Participants reported a history of multiple vision-related diagnoses. Participant demographics and characteristics are presented in Table 4.1. Participant self-described hallucination characteristics are presented in Table 4.2.

Table 4.1.

Participant Demographic Information

		n (%)
Age (years)	> 70	27 (49)
	51 - 70	21 (38)
	30 - 50	5 (9)
	20 - 30	2 (4)
Sex	Men	19 (35)
	Women	36 (65)
Diagnosis*	Cataracts	32 (58)
	Macular degeneration	28 (49)
	Glaucoma	15 (27)
	Optic neuropathy	8 (15)
	Diabetic retinopathy	4 (7)
	Retinal tears	4 (7)
	Retinitis pigmentosa	2 (4)
	Macular telangiectasia	2 (4)
	Stargardt disease	2 (4)
	Occipital lobe stroke	1 (2)
Living arrangements	Cohabitating	34 (62)

	Alone	21 (38)
Ethnicity	White	54 (98)
	Indigenous	1 (2)
Use of visual assistive devices	Yes	50 (91)
	No	5 (9)
Did the participant receive CBS education from physician?	Yes	24 (44)
	No	27 (49)
	Not sure	4 (7)

Note. Data are presented as frequency (percentage). * All participants were diagnosed with a combination of these subcategories; CBS = Charles Bonnet Syndrome.

Table 4.2.

Hallucination Characteristics

		n (%)
Hallucination characteristics*	Patterns	33 (60)
	Figures	31 (56)
	Objects	29 (53)
	Animals	25 (45)
	Faces	17 (31)
	Other	24 (44)
Number of years since onset of hallucinations	< 5	28 (51)
	5 – 10	18 (33)
	11 – 15	3 (5)
	16 – 20	1 (2)
	> 20	3 (5)
	Not specified	2 (4)
Hallucination modality	Visual only	19 (35)
	Multisensory (visual and other hallucinations such as auditory, olfactory, and/or tactile)	36 (65)

Note. Hallucination characteristics as reported by participants. Data are presented as frequency (percentage). *Participants experienced a combination of these subcategories.

Hallucinatory Experiences during COVID-19

Eighty percent of participants reported no change (n = 44) and 20% (n = 11) reported a “change” in the nature of their hallucinations during COVID-19 pandemic restrictions. Specifically, 13% (n = 7) of participants reported a decrease and 7% (n = 4) reported an increase in the nature of hallucinations. Since the number of participants reporting a “change” in the nature of hallucinations was low, no further analyses were conducted due to the small sample size. With respect to frequency of hallucinations, 53% (n = 29) of participants reported “no- change” and 47% (n = 26) reported a “change” in the frequency of hallucinations during COVID- 19 pandemic restrictions. Specifically, 27% (n = 15) reported an increase and 20% (n = 11) reported a decrease in the frequency of hallucinations during COVID-19 restrictions.

Psychosocial Health Measures in Relation to Hallucination Frequency

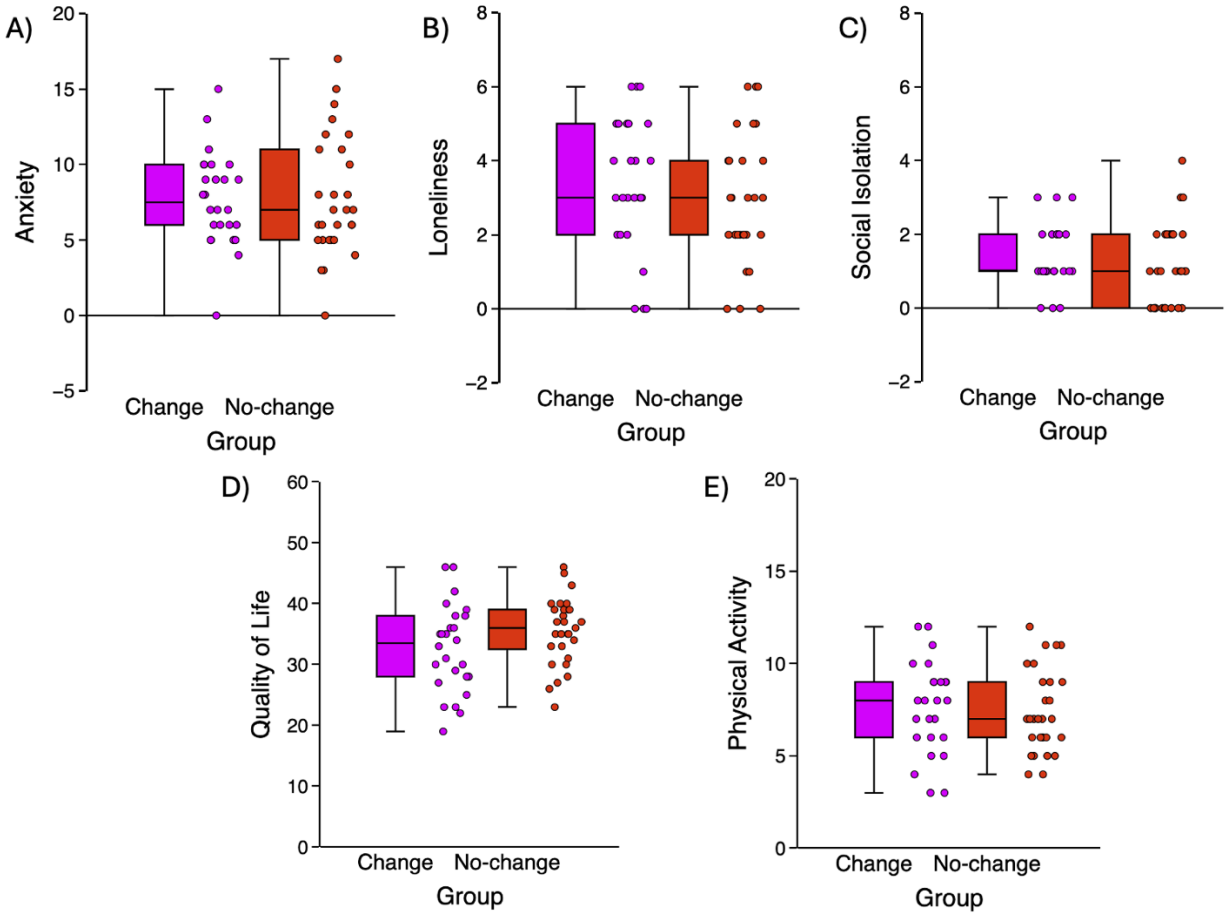
Anxiety, loneliness, social isolation, quality of life, and physical activity were compared in participants who reported experiencing a “change” and “no-change” in hallucination frequency during the COVID-19 pandemic restrictions using independent samples *t*-tests. The “change” group included both those who experienced an increase or decrease in frequency of hallucinations.

There was no difference in anxiety ($t(53) = 0.69$, $p = 0.945$, $d = 0.02$), loneliness ($t(53) = -0.93$, $p = 0.354$, $d = -0.25$), quality of life ($t(53) = 1.69$, $p = 0.096$, $d = 0.46$), and physical activity ($t(53) = -0.49$; $p = 0.624$, $d = -0.13$) in participants who experienced a “change” compared to “no-change” in hallucination frequency. Social isolation was not normally distributed for participants who experienced a “change” ($W = 0.86$, $p = 0.002$) and “no-change” ($W = 0.84$, $p = 0.001$) in hallucination frequency. A Mann Whitney *U*

test was conducted and there was no difference in social isolation for participants who experienced a “change” (Mdn = 1) compared to “no-change” (Mdn = 1) in hallucination frequency (U = 330; p = 0.410, r = -0.79). Figure 4.1 illustrates psychosocial measures for participants who experienced a “change” or “no-change” in hallucination frequency.

Figure 4.1.

Psychosocial Health as a Function of Hallucination Frequency Change

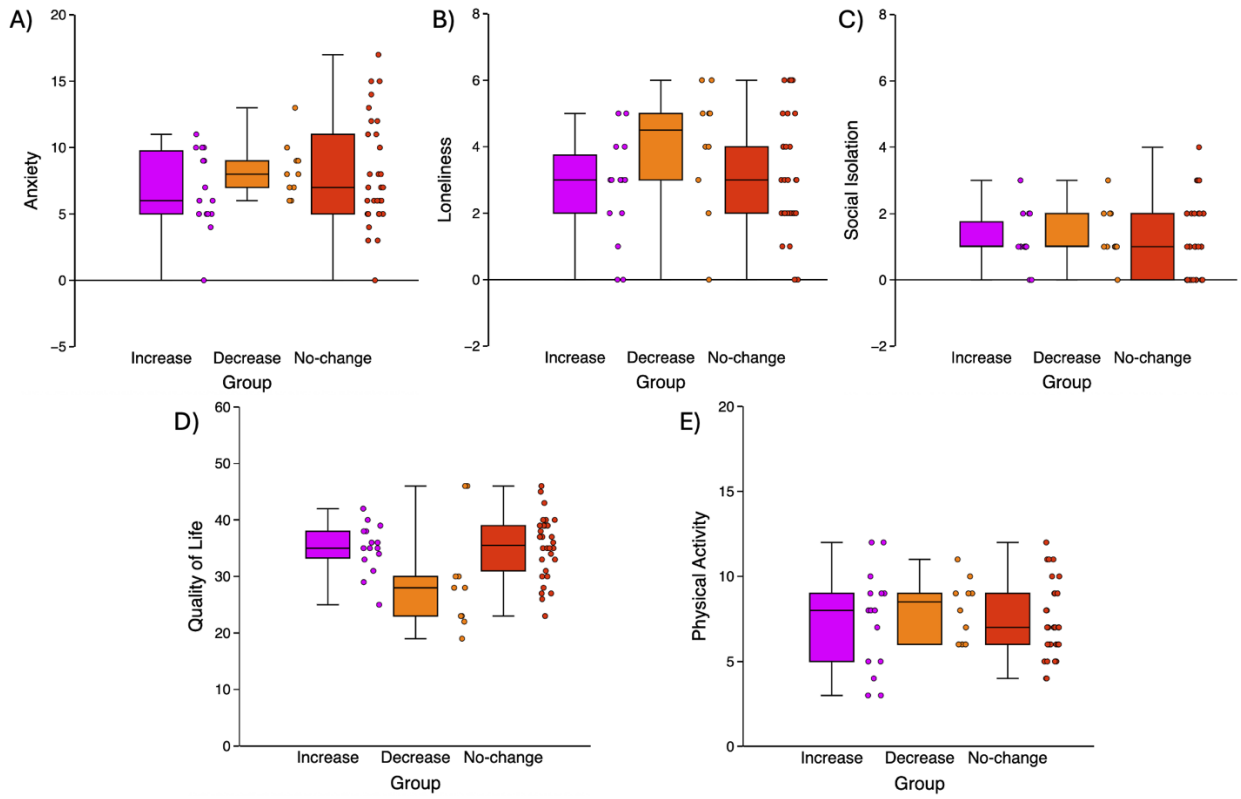


Note. Comparison of psychosocial health measures A) Anxiety, B) Loneliness, C) Social isolation, D) Quality of life, and E) Physical activity for participants who experienced a "change" (purple) and "no-change" (orange) in hallucination frequency during the COVID-19 pandemic restrictions.

To further examine “change” in hallucination frequency during the COVID-19 pandemic, we also examined difference in psychosocial factors between those who experienced and “increase”, “decrease”, and “no-change” in hallucination frequency. Kruskal Wallis test revealed no difference in loneliness (H (2) = 3.47, p = 0.176, ε^2 = 0.03), social isolation (H (2) = 0.45, p = 0.799, ε^2 = 0.00), and quality of life (H (2) = 5.59, p = 0.061, ε^2 = 0.06) between groups. Moreover, one-way ANOVA indicated no difference in anxiety (F (2, 52) = 0.73, p = 0.488, η^2 = 0.03) and physical activity (F (2, 52) = 0.37, p = 0.693, η^2 = 0.01) between those who experienced an “increase”, “decrease”, and “no-change” in hallucination frequency. Figure 4.2 illustrates psychosocial measures for participants who experienced an “increase”, “decrease”, and “no-change” in hallucination frequency.

Figure 4.2.

Psychological Health as a Function of Hallucination Frequency



Note. Comparison of psychosocial health measures A) Anxiety, B) Loneliness, C) Social isolation, D) Quality of life, and E) Physical activity for participants who experienced a "increase" (purple), "decrease" (yellow), and "no-change" (orange) in hallucination frequency during the COVID-19 pandemic restrictions.

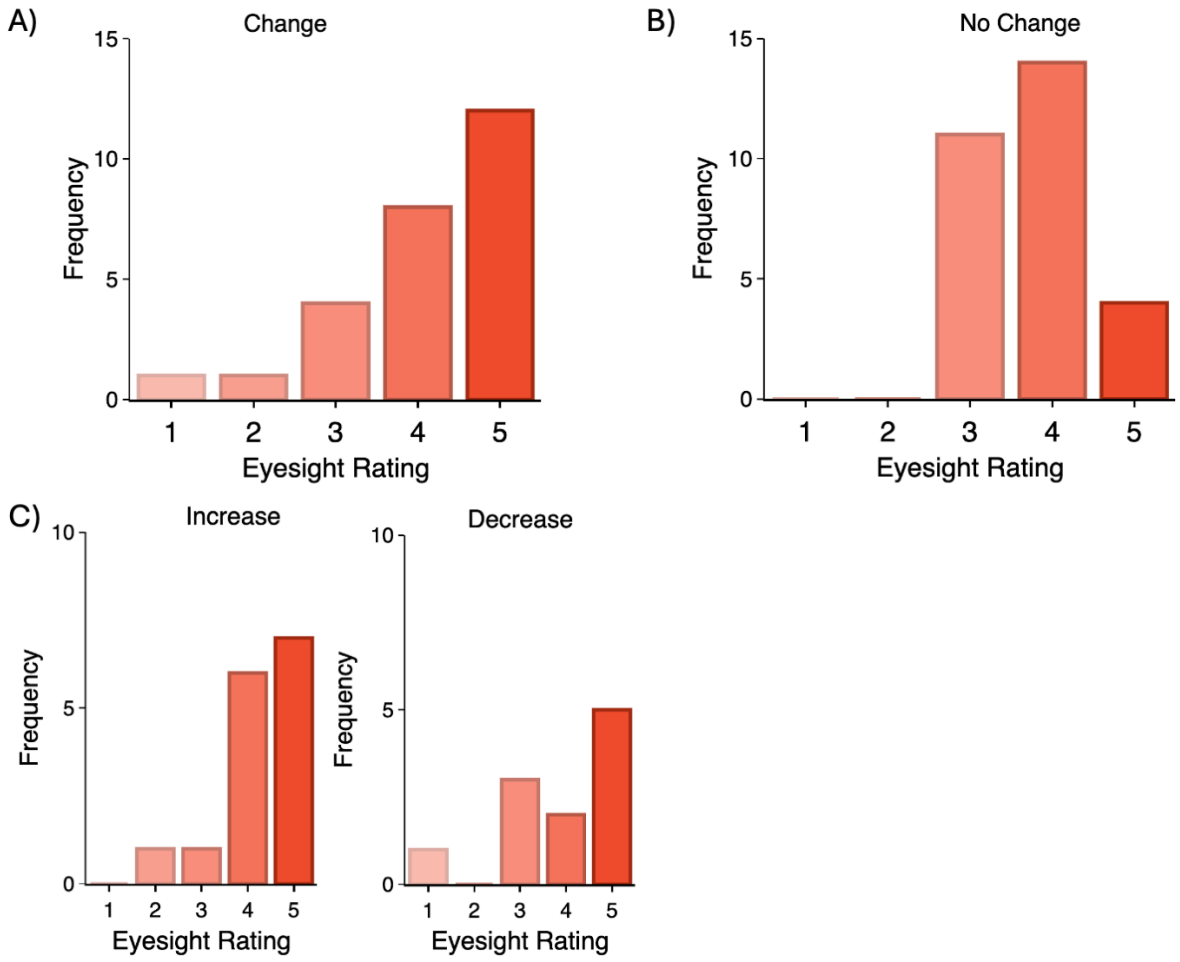
Hallucination Frequency in Relation to Visual Function

A chi-square test of independence was performed to examine the relationship between visual function as measured by self-reported eyesight using a Likert scale [1(excellent) to 5 (very poor)] and change in hallucination frequency ("change" versus "no-change") during the COVID-19 pandemic restrictions. Self-reported eyesight rating was associated with hallucination frequency change, χ^2 (4, N = 55) = 10.77, p = 0.029, V = 0.44, suggesting a medium effect size. Post hoc analyses using adjusted standardized residuals indicated that the frequency of participants who reported their eyesight as "very poor" (adjusted residual = 2.63, p < 0.01) was higher in the "change" group, and lower in the "no-change" (-2.63, p< 0.01) in hallucination frequency group.

The association between visual function and change in hallucination frequency was further explored by breaking down the "change" response to examine the subset of participants who reported "increase" and "decrease" in hallucination frequency during the COVID-19 pandemic. A chi-square test of independence was performed to examine the relationship between visual function and change in hallucination frequency ("increase", "decrease", and "no change") during the COVID- 19 pandemic restrictions. Self-reported eyesight rating was associated with hallucination frequency change, χ^2 (8, N = 55) = 17, p = 0.031, V = 0.40, suggesting a medium effect size. Post hoc analyses using adjusted standardized residuals showed that those who experienced an "increase" in hallucination frequency were less likely to rate their eyesight as "fair" (adjusted residual = -2.10, p < 0.05). Figure 4.3. illustrates the frequency distribution of eyesight rating for hallucination frequency during the COVID-19 pandemic restrictions.

Figure 4.3.

Frequency Distribution of Eyesight Rating



Note. Visual function as measured by self-reported eyesight using a Likert scale [1(excellent) to 5 (very poor)] and hallucination frequency during the COVID-19 pandemic restrictions. A) “Change”, B) “No-change”, and C) “Increase” and “Decrease” in hallucination frequency groups during the COVID-19 pandemic restrictions.

Time since Hallucination Onset

Time since hallucination onset represents the number of months that a person has lived with CBS hallucinations. The relationship between time since hallucination onset and psychosocial measures were examined. Spearman correlation analyses showed no relation between time since hallucination onset and anxiety, $r_s(53) = -0.09$, $p = 0.517$, 95% CI [-0.35, 0.18], loneliness, $r_s(53) = -0.05$, $p = 0.716$, 95% CI [-0.31, 0.22], social isolation, $r_s(53) = -0.20$, $p = 0.146$, 95% CI [-0.44, 0.07], quality of life, $r_s(53) = 0.16$, $p = 0.239$, 95% CI [-0.11, 0.41], and physical activity, $r_s(53) = -0.24$, $p = 0.083$, 95% CI [-0.48, 0.03].

Discussion

The current study investigated whether psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity were associated with changes in the nature and frequency of CBS visual hallucinations during the COVID-19 pandemic. Eighty percent of participants reported “no-change” in the nature of their hallucinations and 53% reported “no-change” in the frequency of hallucinations. Only 7% experienced an increase and 13% experienced a decrease in the nature of hallucinations during the COVID-19 pandemic. Twenty-seven percent of participants experienced an increase and 20% experienced a decrease in frequency of CBS hallucinations during COVID-19. Psychosocial health measures including anxiety, loneliness, social isolation, quality of life, and physical activity did not differ between those who experienced a “change” (increase or decrease) versus “no-change” in hallucination frequency during the COVID-19 pandemic. Moreover, self-reported eyesight rating of participants was associated with change in hallucination frequency. Specifically, the frequency of people with “very poor” vision was higher in the “change” (increase or decrease) compared to the “no-change” in hallucination frequency group. Further, those who reported an increase in hallucination frequency during the COVID-19 pandemic restrictions less frequently rated their eyesight as “fair”. Finally, time since hallucination onset was not associated with psychosocial health measures of anxiety, loneliness, social isolation, quality of life, and physical activity.

In this study, 80% of participants reported “no-change” in the nature of hallucinations, and 53% reported “no-change” in the frequency of visual hallucinations during COVID-19. A recent study by Jones and colleagues (2021b) reported an

exacerbation of CBS hallucinations during the COVID- 19 pandemic where 56% of participants reported an increase in hallucination frequency (Jones et al., 2021b). In the current study, 15 out of 55 participants reported an increase in hallucination frequency. Further, Jones and colleagues (2021b) reported an association between loneliness and change in the nature of hallucinations (Jones et al., 2021b). It is noteworthy to mention that Jones and colleagues (2021b)'s data were collected during the first COVID-19 national lockdown (June – July 2020) in the United Kingdom. During the lockdown, people were required to stay indoors and leave only for essential shopping or medical needs, and non-essential retail and leisure establishments were closed (Jarvis et al., 2021). The current study data were collected during the fifth wave (Omicron variant; November 2021 – March 2022) of the COVID-19 pandemic in Canada. While the government of Canada implemented a phased approach to ease public health restrictions, some mandates were still in place including limited visitation in long term care, advisories to limit non-essential travel, limitations to number of people in social gatherings, and social distancing (Oldenburger et al., 2022). Despite the public health measures and restrictions, this study found that the majority of participants did not experience a change in their CBS hallucinatory experiences. However, the difference in data collection periods could explain the differences in results. It is possible that since the current study data was collected at a later phase of the COVID-19 pandemic, participants may have adapted to the COVID-19 restrictions.

Social distancing during the COVID-19 pandemic increased social isolation and loneliness of the ageing population (Donovan & Blazer, 2020). Older adults have experienced adverse effects related to COVID-19 restrictions which contributed to a

decreased quality of life during the COVID-19 pandemic (Lebrasseur et al., 2021). However, our data do not indicate a relationship between psychosocial health and the change (increase or decrease) of CBS hallucinations during the COVID-19 pandemic. Psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity did not differ in individuals who experienced “change” versus those who experience “no-change” in hallucination frequency. It is possible that hallucinatory experiences changed over time due to potential age-related deterioration of vision rather than psychosocial health. Our findings show that more individuals reported that their vision was “very poor” in the “no-change” in hallucination frequency group, while fewer individuals reported “very poor” vision in the “change” in hallucination frequency group. This may indicate that change in hallucinations during COVID-19 pandemic may have been driven by visual function rather than psychosocial implications of the COVID-19 pandemic restrictions. This is supported by recent findings showing that psychosocial health measures such as anxiety, depression, and loneliness were not associated with CBS hallucinations in younger adults during the COVID-19 pandemic (Walker et al., 2024). Moreover, by further exploring CBS hallucinations over time, this study found no relation between time since hallucination onset and psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity. This indicates that how long a person has lived with CBS hallucinations is not associated with their psychosocial health status. This is contrary to evidence showing that late-onset vision loss is associated with decreased quality of life, and longer periods of bilateral visual loss (> 2 years) are associated with higher psychological distress (Bonsaksen et al., 2025; Munaw & Tegegn, 2022; Williams et al.,

1998).

The findings of the current study support the notion that changes in CBS hallucinations during the COVID-19 pandemic restrictions are associated with physiological changes related to vision loss rather than psychosocial health measures related to the COVID-19 pandemic.

Conclusion

Overall, this study shows that COVID-19 related psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity are not associated with changes (increase or decrease) in frequency of CBS hallucinations. In addition, time since hallucination onset was not associated with psychosocial health measures indicating that how long a person has lived with hallucinations does not relate to their psychosocial health. Visual function was associated with changes in hallucination frequency highlighting that CBS hallucinations are associated with physiological changes related to visual function rather than psychosocial correlates.

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CHAPTER V

GENERAL DISCUSSION

This dissertation investigated functional connectivity, morphology, neurochemical, and psychosocial correlates of the visual hallucinatory experiences in Charles Bonnet Syndrome (CBS). I sought to expand our understanding of the mechanisms involved in CBS visual hallucinations that occur following vision loss. In a case of CBS (Patient A.P.) secondary to age-related macular degeneration (AMD) and a history of ocular tuberculosis, I asked whether CBS showed altered functional connectivity between resting-state brain networks and morphological changes in brain tissue volume and cortical thickness. Moreover, in Patient A.P., I sought to examine visual cortex neurochemical correlates which have never been previously explored in CBS. Finally, to expand our understanding of both the physiological and psychosocial correlates, I explored whether psychosocial health measures and visual status during the COVID-19 pandemic restrictions were associated with changes in the nature (vividness/ clarity) and frequency of hallucinations in a group of individuals with CBS. I also sought to investigate whether time since hallucination onset was associated with psychosocial health measures. Overall, throughout the 3 experimental chapters presented in this dissertation, I demonstrate that compared to healthy controls, a case of CBS secondary to AMD and a history of ocular tuberculosis (Patient A.P.) exhibits unique functional connectivity between brain-wide networks but no morphological changes. Moreover, there were no alterations in visual cortex neurochemical correlates in Patient A.P. compared to healthy controls. Finally, change in hallucination frequency and time since hallucination onset were not associated with psychosocial health measures during the COVID-19 pandemic. In contrast, vision status was associated with changes in CBS hallucinations highlighting that physiological rather than psychosocial

correlates may be associated with changes in CBS hallucinations during the COVID-19 pandemic restrictions.

Summary

Chapter II

Chapter II investigated functional connectivity between resting-state brain networks and morphology in a CBS patient (Patient A.P.) compared to healthy controls.

The first part of this experiment explored functional connectivity between visual seed regions (occipital pole, cuneus, and lingual gyrus), and targets within the default-mode network (precuneus and posterior cingulate cortex), dorsal attention network (intraparietal sulcus), salience network (supramarginal gyrus and thalamus), and ventral visual stream (temporo-occipital fusiform cortex, inferior lateral occipital cortex, temporo-occipital inferior temporal gyrus, anterior and posterior parahippocampal gyrus). The dorsal attention network is a task-positive network that performs top-down modulation of perceptual visual processing while the default mode network is a task-negative network that deactivates during goal-directed tasks (Shine et al., 2011). It has been shown that visual hallucinations may arise when there is a disruption in this antagonistic relationship where there is a failure of modulation by the dorsal attention network and an overreliance on the default mode network (Shine et al., 2014). Therefore, I hypothesized that CBS would be associated with increased negative connectivity between early visual areas and default mode network nodes demonstrating network-level disruptions in functional connectivity. Specifically, a lack of visual input to early visual areas may be associated with increased activation of the default mode network, a hyperexcitability secondary to deafferentation of retinal input and a lack of

visual processing (Burge et al., 2016). Moreover, I predicted an increase in positive connectivity between visual areas and dorsal attention network (task-positive network). It is plausible that a lack or reduction of visual input (and hence decreased activation of visual areas) will be associated with a decreased activation in dorsal attention network which activates during perceptual visual processing. In line with my hypothesis, in Patient A.P. the left and right occipital poles showed increased negative connectivity with nodes in the default mode network (posterior cingulate cortex and precuneus). This stronger negative coupling with visual areas could indicate greater engagement of internally directed default mode network processes, thereby leading to the formation of visual hallucinations (Shine et al. 2011, 2014). This also aligns with reports from central vision loss showing increased negative connectivity between areas representing deafferented central visual fields and default mode network nodes (Sabbah et al., 2017) and supports the idea that central visual field loss is associated with default mode – visual anti-coupling. Notably, this direction of functional connectivity differs from findings in retinitis pigmentosa (early-onset, peripheral), where positive connectivity has been observed between visual areas and the default mode network (Martial et al., 2019). Taken together, A.P.'s results fit a deafferentation account in which vision loss is associated with hyperexcitability in default mode network nodes at rest, highlighting network-level mechanisms associated with CBS in late-onset central vision loss.

ffytche and colleagues (1998) previously showed that CBS is associated with the topological activation in specific brain areas that correspond to the visual percept of the hallucination (such as activation of fusiform cortex with face hallucinations or activation in colour area (V4) of the fusiform gyrus with colour hallucinations). This hodotopic

framework emphasizes functional-node level mechanisms linking hallucination content and activation of functionally specialized areas along the ventral visual stream. I predicted that in CBS secondary to central vision loss (AMD) visual areas would elicit altered (increased negative) functional connectivity with functionally specialized areas in the ventral visual stream.

In this study, there was a trend toward increased negative connectivity between the left lingual gyrus and inferior lateral occipital cortex which involves object recognition (Biederman, 1987; Mullin & Steeves, 2011). This connectivity pattern aligns with A.P.'s hallucinations of objects (e.g., cars) and further highlights an alteration between visual areas and category selective regions along the ventral visual stream. This demonstrates that a decrease in activation in visual areas from vision loss was associated with increased activation in specialized areas that elicit activity based on the type of visual hallucinations experienced by Patient A.P. Moreover, the right cuneal cortex displayed an increased positive connectivity with the right thalamus in Patient A.P. compared to healthy controls. The altered thalamo-cortical functional connectivity is in line with previous work showing disrupted thalamic circuitry in central vision late blindness and CBS (Adachi et al., 2000; Firbank et al., 2022; Sabbah et al., 2017). These results support the theory that visual deprivation disrupts early visual areas (V1 and V2) through thalamo-cortical connectivity, prevents transmission to higher-order visual regions, and may be associated with endogenous activation of specialized areas along the ventral visual stream (such as areas of object recognition in Patient A.P.) that produce complex visual hallucinations (Kazui et al., 2009).

The second part of the experiment measured global brain tissue volume changes

in Patient A.P. compared to healthy controls. I hypothesized that CBS would be associated with decreased global grey matter volume and cortical thickness of visual areas. There were no changes in grey matter, white matter, or total intracranial volume in Patient A.P. compared to the age-matched healthy control group. Previous neuroimaging studies showed inconsistent results in morphological alterations in CBS possibly due to differences in blindness etiologies and their distinct morphological manifestations depending on the mechanisms of vision loss. For instance, while a case study of CBS with retinitis pigmentosa showed decreased grey matter volume and cortical thickness in visual areas (Martial et al., 2019), other studies showed that CBS secondary to cataracts and glaucoma was not associated with morphological changes in primary (V1) and secondary (V2) visual areas (Adachi et al., 2000). Retinitis pigmentosa causes blindness in early adolescence and most people become legally blind by the age of 40 years (Kamde & Anjankar, 2023). However, eye diseases such as AMD are more common in older adults, after the age of 60 years (Vyawahare & Shinde, 2022). It is possible that the differences in mechanisms of vision loss - etiology, age of onset, and visual field locus (central vs. peripheral) - explain the differences in morphological findings across studies. Perhaps, vision loss that occurs early in life during critical periods of visual system development may demonstrate different morphological changes compared to vision loss that occurs in late adulthood, after the visual system is fully mature.

Taken together, these results suggest deafferentation-driven reorganization in Patient A.P. who developed CBS secondary to AMD and had a history of ocular tuberculosis. Loss of central visual input was associated with altered visual brain

excitability and altered network-level coupling at rest evident through increased negative connectivity with default mode network nodes, and increased thalamo-cortical coupling. Moreover, the activation of functionally specialized areas that correspond to the visual percept of hallucinations (e.g., activation of face processing network with face hallucinations) with the deactivation of visual areas indicates that the loss of visual input in CBS could be associated with increased endogenous activation of these functionally specialized areas to elicit hallucinatory images (Kazui et al., 2009). Central field representations show preferential connectivity with ventral visual stream regions (e.g., fusiform – face, lateral occipital – objects), whereas peripheral-field representations are associated with motion-selective areas (MT/ MT+) (Sabbah et al., 2017). Notably, the difference in direction of functional connectivity supports the view that visual field locus (central vs. peripheral) and timing (early vs. late onset) of vision loss drive the direction of functional connectivity between visual areas and category-selective functional nodes. There were no grey matter, white matter, total intracranial volume, and cortical thickness differences between Patient A.P. and group of healthy controls which indicates that the visual hallucinations are not associated with global morphological alterations in the brain or cortical thickness changes in visual areas unlike morphological changes observed in early-onset peripheral visual field loss (retinitis pigmentosa) (Martial et al., 2019). These findings highlight the importance of considering vision loss etiology, visual field defects (central vs. peripheral), and the timing of vision loss (early vs. late-onset) when investigating functional connectivity and morphological alterations in CBS.

Chapter III

Chapter III continued to investigate neurochemical correlates of CBS by

quantifying the concentrations of glutamate and GABA, the primary excitatory and inhibitory neurometabolites in the brain, respectively. The deafferentation theory posits that a disruption in visual input and hyperexcitability in visual regions plays a role in CBS visual hallucinations (Burke, 2002). I hypothesized that this hyperexcitability in CBS (Patient A.P.) would be associated with increased visual cortex Glx demonstrating increased visual cortex activation related to glutamate. I also hypothesized a decrease in visual cortex GABA+, demonstrating an imbalance in inhibitory mechanisms related to GABA. This experiment found no differences in visual cortex Glx and GABA+ concentrations between Patient A.P. and healthy control group, indicating that the visual hallucinatory experiences in CBS following AMD and ocular tuberculosis may extend beyond the excitatory or inhibitory effects of glutamate and GABA.

Taken together, these results expand upon the evidence found in Chapter II. The increased negative connectivity between visual areas and functionally specialized areas in the ventral stream could explain why there were no local changes in Glx and GABA+ levels in the visual cortex. This implies that neurometabolite alterations may not be evident in the visual cortex but may present in other regions of resting-state brain networks. This supports that the brain functions along many inter-connected networks and visual hallucinatory experiences due to vision loss may be a consequence of alterations in the neurochemistry of higher-order brain regions rather than early visual areas.

Chapter IV

Chapter IV investigated whether psychosocial health measures during the COVID-19 pandemic restrictions such as anxiety, loneliness, social isolation, quality of

life, and physical activity were associated with changes in nature (vividness/ clarity) and frequency of CBS hallucinations in a group of individuals with CBS. I also examined whether time since hallucinations onset (how long a person has lived with hallucinations) was associated with psychosocial measures. Further, I explored the association between vision status (self-reported eyesight rating) and changes in hallucination frequency during the COVID-19 pandemic.

CBS has been associated with physiological changes in the brain's functional connectivity and morphology and theories, such as the deafferentation theory, suggest that visual deprivation leads to deafferentation of visual areas thereby causing visual hallucinations (Burke, 2002). While physiological mechanisms have been implicated in CBS, it has been suggested that psychosocial health measures may exacerbate the visual hallucinatory experiences in CBS (Jones et al., 2021b). Jones and colleagues (2021b) reported an exacerbation of CBS hallucinations during the COVID-19 pandemic. Public health measures including extended periods of lockdowns were previously associated with increased social isolation and decreased quality of life in older adults (Lebrasseur et al., 2021). If psychosocial health contributes to CBS hallucinations, it is possible that COVID-19 related social restrictions exacerbated visual hallucinations in CBS. I predicted that CBS hallucinations would be associated with visual status and that time since hallucination onset (how long a person lived with hallucinations) may be related to psychosocial health. Despite previous evidence showing adverse effects of COVID-19 on psychosocial health (Gloster et al., 2020), this study found that 80% of participants reported "no-change" in the nature and 53% reported "no-change" in frequency of hallucinations during the COVID-19 pandemic.

Change in hallucination frequency during COVID-19 was not associated with psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity. Moreover, time since hallucination onset, which represents how long a person has lived with CBS hallucinations, was not associated with psychosocial health measures. In contrast, self-reported eyesight rating was associated with changes in hallucination frequency during the COVID-19 pandemic. Specifically, the frequency of participants who reported their eyesight as “very poor” was higher in participants who reported experiencing changes in their hallucination frequency compared to those who did not report experiencing changes in their hallucination frequency. This was driven by those who reported poor vision and an “increase” in hallucination frequency during COVID-19 restrictions. This further confirms that CBS arises from physiological mechanisms related to vision loss and is not influenced by psychosocial health.

Overall, my neuroimaging and psychosocial data have enabled further exploration of the functional connectivity, morphological, and neurochemical correlates in a single case of CBS (Patient A.P.) following AMD and a history of ocular tuberculosis and psychosocial correlates in a group of individuals with CBS. The role of two over-arching elements: mechanisms related to etiology of vision loss and CBS diagnostic criteria should be considered during the global interpretation of these results.

Pathophysiological Mechanisms and Etiology of Vision Loss

CBS is a rare condition that is highly under-reported, but greater attention has been brought to it following its inclusion in the WHO ICD-11 classification in June 2019 (Jones et al., 2021). Researchers have attempted to understand the mechanisms involved in CBS by proposing theories related to the consequences of vision loss.

The deafferentation theory posits that a disruption of sensory visual input due to the destruction of nerve fibers or ocular pathology leads to hyperexcitability of the deafferented areas of the visual cortex (Burke, 2002; Kester, 2009; Rovner, 2006; Schadlu et al., 2009). Factors such as the release of presynaptic neurotransmitters either through an increase in neurotransmitter vesicles, an increase in postsynaptic neurotransmitter receptors due to prolonged inactivity, or changes in the amount of GABA and glutamatergic N-Methyl-D-Aspartic acid (NMDA) within the synapse may increase the intensity of response and facilitate hyperexcitability of neurons, thereby leading to the generation of these phantom visual hallucinations (Burke, 2002). It has also been proposed that visual disruption may facilitate neuroplastic mechanisms through the sprouting of new axons and reorganization of receptive fields in the deafferented area (Tan et al., 2006). This could lead to neuronal hypersensitivity, and typical stimuli that would not otherwise elicit a response could now generate visual hallucinations from the remaining small amounts of retinal stimulation. Similarly, the perceptual release theory states that due to the interruption of sensory input to visual brain areas, there is an “unmasking” of nerve impulses that would otherwise be inhibited by higher cortical regions (Crumbliss et al., 2008; Kester, 2009; Menon et al., 2003; Schadlu et al., 2009; Vukicevic & Fitzmaurice, 2008). In other words, the disinhibition of

neuronal activity in visual association cortices elicits “release hallucinations” from cortical activity that was previously inhibited. Finally, the neuromatrix theory proposes that there are complex global neuronal networks that generate sensory phantoms or neuro-signatures which subserve genetically determined substrates that possess affective and cognitive attributes based on previous sensory experiences (Melzack, 1990; Menon et al., 2003). However, while some individuals see hallucinations of people they know from their past (Diana et al., 2021), Teunisse and colleagues (1996) showed that 77% of their CBS participants did not detect a personal relevance to the images they see. Due to the complexity of CBS and a myriad of eye diseases that may cause it, it is still unclear what mechanisms govern the occurrence of these visual hallucinations. Earlier research from ffytche and colleagues (1998) also showed that the content of hallucinations in CBS is closely linked to activation in specific brain areas. This hodotopic framework emphasizes that hallucination content is based on the topological activation of functionally specialized areas (e.g., activation of fusiform face area with face hallucinations, or colour area (V4) of the fusiform gyrus with colour hallucinations) (ffytche et al., 1998). The connectivity of these category selective areas with large-scale networks may lead to long-term network alterations.

Collerton and colleagues (2005) first sparked a debate surrounding visual hallucinatory mechanisms when they proposed the Perception and Attention Deficit Model. This model attempted to explain the mechanisms governing visual hallucinations based on phenomenology (Collerton et al., 2005) and has since been heavily debated and challenged. Catani and ffytche (2005) challenged the model by stating that there is a dichotomy in theoretical models that explain visual hallucinatory syndromes and

suggested that both phenomenology and etiology should be considered when attempting to explain the mechanisms underlying visual hallucinations (Catani & ffytche, 2005). The complexity of CBS suggests that phenomenology alone cannot fully explain its mechanisms, highlighting the importance of considering etiology as well.

When considering the phenomenology of visual hallucinations, some syndromes share common hallucinatory manifestations but there are also clear differences based on etiology. For example, while both CBS and Parkinson's disease patients experience recurrent complex visual hallucinations of people, animals, or objects, CBS does not feature extracampine hallucinations (such as the sensation of a presence) or passage hallucinations (brief visual experience of a figure or person passing in the peripheral visual field), which are common in schizophrenia and Parkinson's disease (Llorca et al., 2016; Waters et al., 2014). This suggests that phenomenology alone does not explain the underlying mechanisms because some hallucinatory experiences are present in both neurological and eye-related conditions. There is also considerable variability in the occurrence of simple versus complex hallucinations across conditions. Simple hallucinations are more common in sensory deprivation and eye disease (Leporé et al., 2010; Santhouse et al., 2000; Scott et al., 2001; Sörös et al., 2003; Teunisse et al., 1996; Vaphiades et al., 1996), while complex hallucinations dominate in perception and attention-deficit disorders, such as Lewy Body Dementia, Alzheimer's, and Parkinson's disease (Aarsland et al., 2001; Ballard et al., 2001; Barnes & David, 2001; Fenelon et al., 2000; Holroyd et al., 2001; Murgatroyd & Prettyman, 2001; Santhouse et al., 2000).

Even within the scope of sensory deprivation from eye diseases, individuals with CBS exhibit diverse hallucinatory experiences. Not all individuals with CBS experience

simple hallucinations and many report both simple and complex hallucinations (Firbank et al., 2022; Jones & Moosajee, 2021; Piarulli et al., 2021; Vacchiano et al., 2019). This variability reinforces the notion that a singular pathophysiological explanation is insufficient to describe the mechanisms of visual hallucinations, and that etiology may also play a key role. This is seen in ffytche's work which supported the view that both phenomenology and etiology must be considered to fully understand the mechanisms behind visual hallucinations, particularly in eye disease and sensory deprivation (ffytche et al., 1998). Therefore, ffytche proposed that we can no longer use a unitary model to explain the occurrence of visual hallucinations (ffytche, 2008). He suggested a two-syndrome model where one (as seen in visual deprivation and eye-disease) describes visual hallucinations with preserved insight and without delusions, and another (as in perception and attention deficit syndromes) where hallucinations are more often multi-sensory and may be accompanied by delusions and lack of insight.

Building on ffytche's two-syndrome model, depending on the etiology of eye-disease, functional connectivity dysfunctions and morphological alterations may manifest differently. For instance, a CBS case following retinitis pigmentosa demonstrated dysfunctional resting-state connectivity patterns between occipital fusiform and nodes of the default mode network, and in the salience network and clusters in middle temporal and medial frontal regions (Martial et al., 2019). In Chapter II, Patient A.P. who developed CBS following AMD and had a history of ocular tuberculosis showed thalamo-cortical disruptions along with distinct functional connectivity patterns between visual areas and functionally specialized regions in the ventral visual stream, as well as altered connectivity with the default mode network.

Moreover, I found no changes in grey matter volume, white matter volume, intracranial volume, and cortical thickness in Patient A.P. compared to controls, but this was not seen in an 85 year old with CBS secondary to retinitis pigmentosa who instead showed decreased grey matter volume and cortical thickness in visual brain regions (Martial et al., 2019).

This raises many questions; do functional connectivity patterns and morphological changes depend on the etiology of eye disease that causes CBS, locus of visual field loss (central versus peripheral), or developmental factors associated with the age of onset of vision loss? In other words, does this indicate that pathophysiological mechanisms associated with different eye-diseases determine the resting-state functional connectivity alterations and morphological changes in CBS? If a patient with CBS secondary to retinitis pigmentosa (early-onset, peripheral vision loss) shows dysfunctional activation patterns between the visual cortex and resting-state networks, will a person with CBS secondary to AMD (late-onset, central vision loss) show the same functional connectivity patterns? If their connectivity and morphological alterations differ, do we need to reconsider the notion that CBS stems from a unitary pathophysiological mechanism?

CBS diagnostic criteria

The CBS diagnostic criteria were introduced in the 1990s when Teunisse and colleagues (1996) proposed five diagnostic criteria to confirm whether a CBS diagnosis can be made. The criteria included:

1. At least one complex visual hallucination that occurred within the past 4 weeks.
2. A period between the first and last hallucination exceeding 4 weeks.

3. Full or partial retention of insight about the unreal nature of the hallucinations.
4. An absence of hallucinations in other sensory modalities.
5. An absence of delusions.

These diagnostic criteria, however, have brought forth many nuances to CBS diagnosis and sparked an ongoing debate about their applicability. There is a controversy about the notion that a CBS diagnosis can only be made if the hallucinations are purely visual. Several CBS case reports have reported hallucinations across other sensory modalities, including hearing, touch, and smell (Arun et al., 2013; Kukstas, 2019; Sarkar et al., 2017). In fact, disruption to sensory input across other sensory modalities is associated with similar hallucinatory manifestations. For instance, auditory hallucinations, also known as musical ear syndrome, have been reported in people with deafness (Griffiths, 2000), and cortical hyperexcitability and how it relates to the deafferentation theory is thought to be a shared mechanism involving both auditory and CBS visual hallucinations (Yuksel et al., 2004). This led authors to propose a Charles Bonnet PLUS Syndrome, where visual hallucinations are accompanied by other multisensory experiences and raised questions about the need to revisit the applications of the CBS diagnostic criteria to explore other differential diagnoses or disorders that may coincide with vision loss in CBS (Satgunam et al., 2019). In chapters II and III, Patient A.P. experienced visual hallucinations alone and his hallucination characteristics aligned with the CBS diagnostic criteria. In chapter IV, however, out of 55 participants 65% reported experiencing multisensory hallucinations including auditory, olfactory, and tactile. We attempted to record a detailed medical history of the participants to control for other differential diagnoses. Our findings align with three previous case-reports

showing multisensory hallucinations in CBS participants (Arun et al., 2013; Diana et al., 2021; Sarkar et al., 2017). Multisensory experiences are well-documented and are known to occur when there is a disruption to afferent sensory input and can be associated with cross-modal plasticity in auditory (Moro et al., 2020; Moro & Steeves, 2018), tactile (Weisser et al., 2005), and olfactory systems (Gubernick et al., 2014). This is consistent with the possibility that CBS hallucinatory experiences may involve other sensory modalities, in addition to vision, and may be associated with structural and functional reorganization of non-visual brain regions. This further highlights that we may need to revisit the CBS diagnostic criteria and possibly revise it to include those with CBS multisensory hallucinations. If studies strictly follow the current CBS diagnostic criteria despite reports of multisensory hallucinations, individuals with multisensory CBS hallucinations will not be included and that will amplify the lack of awareness about CBS and specifically the occurrence of multisensory hallucinations.

Another diagnostic criterion that poses a challenge is the retention of full or partial insight in CBS. Retention of insight indicates that a person is aware that the visual hallucinations are not real. While some studies solely included CBS participants with full insight (awareness that hallucinations are not real) (Chen & Liu, 2011; Hou & Zhang, 2012; Jackson et al., 2011; Leandro et al., 2017; Nesher et al., 2001; Tan et al., 2004), many others included participants with full or partial insight (partial awareness that hallucinations are not real) (for review see (Hamedani & Pelak, 2019)). It is noteworthy to mention that patients with some neurological disorders such as early dementia may have partial insight of the nature of their hallucinations, and this further complicates the decision to make a CBS diagnosis. In fact, Russell and colleagues

(2018) found that in 12 CBS patients and 10 age-matched healthy older adults, despite not having dementia upon initial assessment, all participants reported at least one “dementia-associated” hallucination upon follow-up. They also reported that even among those with normal insight, 6 out of 7 had cognitive abnormalities, and one patient with normal cognition developed dementia months later (Russell & Burns, 2014). Due to the increased likelihood of multiple coinciding pathologies in the elderly population, this could hinder the diagnosis of CBS and further fuels the debate on whether complex visual hallucinations should be divided into subgroups depending on phenomenology (content and subjective experience of hallucinations) and etiology of vision loss (Catani & ffytche, 2005), or whether we must consider a common phenomenology irrespective of vision loss etiology (Collerton et al., 2005). Since CBS predominantly occurs in the elderly and neurological and cognitive decline progresses with age, it is important to recognize that CBS is multi-faceted, and a careful examination of possible differential diagnoses must be implemented using an inter-disciplinary approach for effective diagnosis and management.

Limitations

The methods for each experiment in this dissertation were carefully planned based on previously published methods. Some unavoidable limitations are discussed in the following sections.

Etiology of Vision Loss and Interpretation of Results

In line with the phenomenology versus etiology debate, the co-occurrence of multiple eye pathologies in CBS further complicates the understanding of functional, morphological, and neurochemical correlates related to visual hallucinations. In Chapters II and III, Patient A.P. developed CBS secondary to AMD and had a history of ocular tuberculosis and it is unclear how the functional connectivity, morphological, and neurochemical findings are separately related to his diagnoses. It is unknown whether Patient A.P. would have shown the same functional connectivity, morphological, or neurochemical findings if he only had AMD without other coinciding eye pathologies.

Chapter II is the first study to explore resting-state functional connectivity in a CBS case secondary to AMD and ocular tuberculosis and Chapter III is the first study to investigate visual cortex Glx and GABA+ levels in CBS. However, since these were case studies, the results cannot be generalized. Patient A.P. first started experiencing vision loss when he was diagnosed with AMD. He was diagnosed with ocular tuberculosis 2 years later and was treated. Ocular tuberculosis is rare and affects less than 1% of the United States population (Alvarez et al., 2009). There is a lack of uniformity in diagnostic criteria, and it is unknown whether it’s rare prevalence is due to the fact that it presents as other conditions such as papilledema, papillitis, or neuroretinitis (Albert et al., 2016). It has been reported that 90% of cases remain

asymptomatic, and early detection and administration of steroidal treatment can reverse negative outcomes (Sridharan & Biswas, 2007). However, in rare cases, ocular tuberculosis may lead to retinal tears and scarring if not treated in a timely manner. Without baseline data, it is unknown whether there were neural alterations in Patient A.P. secondary to ocular tuberculosis and this makes it difficult to parse out the neural alterations that occurred from AMD versus ocular tuberculosis.

Additionally, it was not possible to know the type of AMD in Patient A.P. A.P reported not being on any medication/treatment for the AMD. AMD can be broadly categorized into dry or wet AMD. Dry AMD occurs when drusen, an extracellular material accumulates on the retina and causes the death of light-sensitive cells (Ambati & Fowler, 2012). Wet AMD occurs when new immature blood vessels grow into the retina, allowing blood and fluid accumulation. Dry AMD could progress to wet AMD, and the disease follows a progression from early-stage AMD to intermediate and finally late-stage AMD. Within AMD, there are different stages of disease progression which may afford distinct functional connectivity and morphological changes (Ambati & Fowler, 2012). There are no studies that compared functional connectivity, morphology, or neurochemical correlates in CBS participants with wet and dry AMD.

Recruitment and Sample Size

As is typical with studying rare patient groups and older adults with no health contraindications, we faced difficulties with recruiting participants that met the eligibility criteria for the MRI scanner. Participants in Chapters II and III were between 65 to 85 years of age, and many had contraindications related to MR scanning such as cardiac pacemakers, cochlear implants, and metal implants that led to their exclusion. An a

priori power analysis using G*Power 3.1 indicated that, under assumptions of a one-sample mean test, effect size $d = 0.8$ (large), $\alpha = 0.05$, and power $(1 – \beta) = 0.80$, a sample size of $n = 15$ would provide an 80% probability of detecting the hypothesized effect, if present. For chapter IV, power analysis was based on an independent samples *t*-test, effect size of $d = 0.8$ (large), $\alpha = 0.05$, and power $(1 – \beta) = 0.80$. A sample size of $n = 52$ (26 in each group) would provide an 80% probability of detecting the hypothesized effect. In Chapter II, I analyzed data from one CBS patient (Patient A.P.) and a group of 25 age-matched healthy controls. Chapter III included Patient A.P., and 15 healthy age-matched healthy controls. In Chapter IV, I recruited 55 individuals with CBS who completed an online survey during the COVID-19 pandemic restrictions and there was no direct communication with the participants. To ensure eligibility, I formulated a questionnaire that included standardized outcome measures as well as other questions about the participants' demographics, hallucinatory experiences, ocular, and medical history. Participant responses were thoroughly reviewed and catch-questions were included to ensure response reliability.

Despite having access to a large database with CBS patients who were willing to participate, some patients had difficulty travelling a long distance to participate in study chapters II and III. Recruitment was done through advertisements circulated in the Canadian National Institute for the Blind (CNIB) Foundation support groups, CBS Awareness Day (CNIB), York University Retirees Association, community centres, retirement homes, and through word of mouth. Recruitment efforts also extended to principal investigators of Human Connectome Project affiliated studies.

Eye-Disease Control Participants

A critical limitation of this study is the absence of an eye-disease control group comprising individuals with AMD but without visual hallucinations. As CBS often occurs secondary to ocular pathology such as AMD, the lack of a control group with similar neuro-ophthalmological characteristics but without hallucinations prevents us from distinguishing which brain changes are related to visual deprivation alone and which are specific to the emergence of CBS hallucinations. Without this comparison, we cannot determine whether the functional connectivity, morphology, or neurochemical correlates observed in our CBS participant are due to vision loss, or whether they reflect distinct neurophysiological mechanisms underlying hallucination susceptibility. Prior studies suggest that retinal degeneration alone is associated with structural and functional changes in the visual system depending on the region of visual field loss (Burge et al., 2016; Sabbah et al., 2017). Some of the changes from vision loss may overlap with findings in CBS. Thus, the inclusion of a non-hallucinating AMD control group would be essential for dissociating general effects of AMD-related visual deprivation from those specifically contributing to the development of hallucinations. Future studies should prioritize carefully matched clinical control groups to isolate the neurophysiological correlates unique to CBS.

Although the inclusion of an eye-disease control group would strengthen inferences about hallucination-specific mechanisms, the absence of such a group has not precluded impactful discoveries in previous work. Several CBS neuroimaging studies were conducted without including low-vision or eye-disease control groups. For instance, an event-related study design during the occurrence of hallucinatory episodes

showed content-specific activation in ventral visual regions (e.g., activation of fusiform gyrus with face hallucinations) (ffytche et al., 1998). The study showed hallucinations corresponding with specific patterns of ventral visual activation that are not accounted for by visual deprivation alone. Only CBS patients were scanned, and no eye-disease controls were included (ffytche et al., 1998). Similarly, another study examined cortical responses to peripheral visual stimuli and found enhanced visual cortical excitability in CBS participants compared to sighted controls (Painter et al., 2018). Results revealed that in a task-based fMRI design, there was visual cortex hyperexcitability in response to peripheral visual stimulation compared to sighted controls supporting the theory on hyperexcitability of visual areas in CBS (Burke, 2002). Similar to our study, the study by Painter and colleagues (2018) included only a healthy control group and no eye-disease controls. Additionally, in a recent fMRI study conducted by Hahamy and colleagues (2021), sighted and eye-disease control groups were included. The study found that only CBS participants showed a gradual build-up of spontaneous activity in early visual areas (V1 – V4) and the fusiform face area prior to hallucination onset. This activation pattern was not observed in both the healthy and eye-disease controls, indicating a unique neural signature of CBS hallucinations that is not simply a by-product of vision loss or blindness.

Together, these studies support the notion that CBS is associated with distinct functional and neurophysiological patterns beyond those observed in vision loss alone. Nonetheless, the current study acknowledges this limitation and emphasizes the importance of including carefully matched eye-disease controls in future investigations. Despite the clear benefits of including an AMD control group without hallucinations,

several barriers limited our ability to recruit participants. Although multiple individuals with eye disease were screened for inclusion, many did not meet the eligibility criteria due to contraindications for MRI such as metal implants, pacemakers, or cochlear implants. Furthermore, practical challenges such as advanced age, reduced mobility, and travel difficulties – common in individuals with profound vision loss – made participation in a demanding neuroimaging study infeasible for many potential candidates. As such, recruiting patient groups without MRI contraindications or mobility limitations remains a formidable challenge.

To overcome these barriers, a range of recruitment strategies were employed. These included outreach via advertisements distributed through the Canadian National Institute for the Blind (CNIB) Foundation support groups, promotion at CNIB's CBS Awareness Day events, targeted emails to the York University Retirees Association, community centres, and retirement homes, as well as word-of-mouth referrals. Although access to a large CNIB database of individuals with visual impairment was secured, eligibility screening consistently revealed that candidates did not meet the inclusion criteria required for MRI studies. These challenges underscore the broader difficulty of recruiting clinical control groups with complex medical or mobility limitations.

In parallel with local recruitment efforts, we also explored the possibility of leveraging open-access neuroimaging datasets. However, no open datasets currently exist that include resting-state fMRI from individuals with AMD. While several studies have investigated brain function in AMD using fMRI, such as Xiao et al. (2022) and Liu et al. (2022), none of these datasets have been made publicly available.

Future research

There are many possible directions in which the experiments in this dissertation could be developed. Three directions will contribute evidence to answer emerging questions including: phenomenology versus etiology, multisensory hallucinations, and non-invasive brain stimulation.

Phenomenology versus Etiology

It is important to recognize that CBS is a multi-faceted condition that shares commonalities with some neurological conditions. As previously discussed, simple hallucinations are more common in eye disease, but complex hallucinations can coincide with simple hallucinations in CBS (Firbank et al., 2022; Jones & Moosajee, 2021; Piarulli et al., 2021; Vacchiano et al., 2019). While simple and complex hallucinations involve the similar mechanisms, they are associated with hyperexcitability of early visual and higher-order visual areas, respectively (Zhuzhuni et al., 2018). This implies that functional connectivity patterns could differ in those who experience simple hallucinations alone, compared to those who experience both simple and complex hallucinations. The lack of uniformity in including patients regardless of the phenomenology of visual hallucinations makes cross-study comparisons difficult.

Regarding the etiology of vision loss, several studies collapse CBS patients into one group despite the variation in vision loss etiologies (Doeller et al., 2021; Hahamy et al., 2021; Jones & Moosajee, 2021; Karagöl, 2021; Russell et al., 2018; Teunisse et al., 1996). Studies have shown that depending on the type of eye disease, distinct visual system alterations can occur (Chan et al., 2021; Ferreira et al., 2017; Marc et al., 2007; Stein et al., 2021; Zhang et al., 2019). Even within a single etiology (e.g., AMD), there

are different stages of disease progression which may afford distinct functional connectivity and morphological changes (Ambati & Fowler, 2012). Loss of vision due to inherited eye-diseases such as retinitis pigmentosa, which manifests in early adolescence, may lead to unique functional connectivity patterns and morphological changes depending on the locus of vision loss (central vs. peripheral) and age at vision loss in relation to visual development and plasticity (Kamde & Anjankar, 2023; Martial et al., 2019). Especially in the aging population, multiple eye diseases may coincide, and this further complicates the interpretation of results making it nearly impossible to parse structural, functional, and neurochemical changes associated with each eye disease. Future studies should attempt to divide participants into groups based on etiology and phenomenology to distinguish between the distinct manifestations of CBS. Moreover, the chronicity of CBS (how long a person lived with vision loss), and how that may affect cortical processing and function must be considered when conducting future research.

Multisensory Hallucinations

The current CBS diagnostic criteria exclude those who experience multisensory hallucinations. However, several case reports have discussed CBS Plus syndrome and showed that multisensory hallucinations may be present in CBS even in the absence of other conditions that may affect regions involving multisensory integration (Arun et al., 2013; Diana et al., 2021; Sarkar et al., 2017). In chapter IV, 65% of the participants reported multisensory hallucinations despite the absence of non-visual disorders. In older patients who may have visual and auditory deficits, mechanisms involving cross-modal plasticity and multisensory integration may be at play (Sinnett et al., 2008). This could affect the functional connectivity patterns and long-term cross-modal plasticity

between brain regions associated with auditory and multisensory (audiovisual) processing. Due to the multi-faceted nature of CBS, future research should explore the possibility of co-occurrence of hallucinations across visual and other sensory modalities when planning methodologies.

Non-Invasive Brain Stimulation

Currently, there are no known treatments for CBS, and pharmacological interventions and mitigation techniques are not always effective (Menon et al., 2003; Piarulli et al., 2021; Schultz et al., 1996; Vitorovic & Biller, 2013; Vukicevic & Fitzmaurice, 2008). Non-invasive brain stimulation techniques such as cathodal transcranial direct current stimulation (ctDCS), 1 Hz repetitive transcranial magnetic stimulation (rTMS), and continuous theta burst stimulation (cTBS) have shown promising results in mitigating and/ or eliminating CBS hallucinations. These techniques elicit inhibitory effects through long-term depression synaptic effects, increasing resting membrane potentials, making neuron depolarization difficult, and thereby reducing neuronal excitability (Huang et al., 2011; Peng et al., 2018; Yamada & Sumiyoshi, 2021). In a group of 16 CBS participants with CBS visual hallucinations following AMD, ctDCS reduced the frequency of hallucinations especially in patients who had greater occipital hyperexcitability before the treatment (daSilva Morgan et al., 2022). 1 Hz rTMS to the occipital cortex also led to the complete cessation of visual hallucinations in a case with CBS following ischemic visual cortex injury (Merabet et al., 2003). Similarly, another CBS patient with ischemic occipital cortex damage showed a normalization of resting-state functional connectivity patterns and complete cessation of hallucinations following occipital cTBS delivered 5 times a day for 4 consecutive days but the visual

hallucinations returned to baseline levels after a few weeks (Bodén et al., 2021). These results show that non-invasive brain stimulation techniques may be promising to mitigate or completely alleviate CBS visual hallucinations. By exploring hyperexcitability and functional connectivity patterns in CBS, these non-invasive brain stimulation techniques can be tailored to target specific regions of hyperexcitability to restore presumed neuronal excitability imbalances in the brain. When formulating treatment protocols however, it is important to account for differences in hyperexcitability and functional connectivity patterns depending on the etiology of vision loss in CBS. Future research should focus on exploring appropriate stimulation protocols and dosage parameters for the treatment of CBS.

Conclusion

My dissertation explored cortical mechanisms in a rare group of individuals who experience visual hallucinations secondary to vision loss. Through 3 experimental studies, I investigated resting-state functional connectivity of brain networks and how they may be associated with the visual hallucinatory experiences in a single-case (Patient A.P.) who developed CBS following AMD and had a history of ocular tuberculosis. I also examined brain tissue volume and cortical thickness as well as excitatory (Glx) and inhibitory (GABA) neurometabolite levels within the visual cortex in Patient A.P. Finally, I examined the role of psychosocial health measures such as anxiety, loneliness, social isolation, quality of life, and physical activity on the visual hallucinatory experiences in a group of 55 CBS participants. I have shown that in Patient A.P. who had a history of AMD and ocular tuberculosis, there were functional-node level alterations in resting-state functional connectivity between early visual areas and ventral stream functionally specialized areas that process complex visual percepts. I also found dysfunctional thalamo-cortical connectivity associated with deafferentation-driven hyperexcitability, as well as network-level functional connectivity alterations between early visual areas and the default-mode network demonstrating an overreliance on internally directed visual processing. Moreover, I found that in Patient A.P., visual cortex Glx and GABA levels did not differ compared to age-matched healthy controls. This indicates that the excitatory (glutamatergic) and inhibitory (GABAergic) mechanisms may not be at play in the visual cortex and may instead extend to higher-order specialized areas of visual processing. Finally, I found that self-reported vision status rather than psychosocial health measures such as anxiety, loneliness, social

isolation, quality of life, and physical activity were associated with changes in the frequency of CBS hallucinations during the COVID-19 pandemic. Moreover, time since hallucination onset which represents how long a person has lived with hallucinations was not related to psychosocial health.

Taken together, these results contribute to evidence that individuals with CBS undergo morphological cortical changes as well as network and functional-node level alterations that shape how brain regions communicate to perform functions. Perhaps, depending on the etiology and timing of vision loss, the brain undergoes reorganization in structure and functional connectivity as an adaptation to the lack of sensory input. This information can lead us to better understand the neuroplastic changes related to visual hallucinations from vision loss by considering functional, morphological, neurochemical, and psychosocial correlates. Overall, the results presented in this dissertation from Patient A.P. who developed CBS following AMD and had a history of ocular tuberculosis, and a group of CBS participants helps us understand how cortical adaptations following vision loss may lead to visual hallucinations. Understanding the mechanisms of CBS can not only help introduce treatment protocols to mitigate and/ or eliminate CBS hallucinations but also promote awareness and education about the condition.

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APPENDIX A: Copyright Permissions

Figure A.1.

Figure retrieved from:

Kelly, K. R., McKetton, L., Schneider, K. A., Gallie, B. L., & Steeves, J. K. E. (2014). Altered anterior visual system development following early monocular enucleation. *NeuroImage: Clinical*, 4, 72-81.

APPENDIX B: Patient A.P. Assessment Form General Information

- General health history (physical/ mental): Hypertension; carotid artery surgery; Got COVID in March.
- Ocular history: Macular degeneration (2011); TB in macula (2013); Cataracts removal (2018)
- Mobility (Ambulatory/ non-ambulatory): Ambulatory; has some balance issues (uses cane)
- Assistive devices used for vision: Reading glasses; 40” monitor; uses large lit keyboard
- How would you rate your eyesight with assistive devices?

  1 – Excellent 5 – Very Poor

Table B.1.

Visual Hallucinations Questionnaire – Exclusion Criteria

1. Do you have any visual problem? E.g., cataracts, glaucoma, diabetic retinopathy, macular degeneration or any other cause of visual loss?	Macular degeneration; TB in macula (2013); Cataracts removal (2018)
2. Do you suffer from any medical or psychiatric conditions? E.g., migraine, Parkinson’s disease, Alzheimer’s disease, Lewy body dementia, schizophrenia, narcolepsy, psychotic depression and mania, epilepsy, stroke, delirium tremens, or any other conditions?	hypertension; carotid artery surgery; COVID in March. Exclude if psychiatric conditions

3.	When did you lose your vision?	2011 (when AMD had started)
4.	When did the visual images begin? (year)	April 2020
5.	Please list your medications	Blood pressure medication Statins Acid reflux medication (proton pump inhibitors) Exclude if: anxiety/antidepressants, medication that lowers seizure thresholds: TCAs, CPZ, clozapine, amphetamines, gancyclovir, ritonavir, cocaine, MDMA, ketamine, PCP; w/d from EtOH, benzos, barbiturates; Mild risk with most SSRIs, SNRIs, FGAs and SGAs, Li, some abx
6.	Have you had any previous treatment for the visual images, including mediation? If so, was it successful and how long was it successful for?	☐ Yes, describe: ■ No
7.	Did the onset of the visual images occur at the same time as any change in medication, or did a change in medication change the appearance of the images?	N/A Exclude if hallucinations brought on by medication
8.	Do you experience visual aura with migraines, or are the visual images associated with migraine?	No Exclude if associated with migraine
9.	Please check the appropriate box if you have any of the following:	YES NO Any metal in your cranium ☐ ■ Increased intracranial pressure ☐ ■ Pregnant or possibly pregnant ☐ ■

Heart disease	☐	■
85 % occluded in the past before carotid surgery		
Cardiac pacemaker or intracardiac lines	☐	■
Medication pump	☐	■
Tricyclic-antidepressants	☐	■
Neuroleptic	☐	■
Epileptic	☐	■
History of epilepsy or other seizure disorders	☐	■
Family history of epilepsy or other seizure disorders	☐	■
Fainting spells or syncope	☐	■
Hearing problems or ringing in your ears	☐	■
Cochlear implants	☐	■
Implanted neurostimulator	☐	■
Medication infusion device	☐	■
Spinal cord surgery	☐	■
Spinal or ventricular derivations	☐	■
Any medication that significantly lowers seizure threshold	☐	■
History of head trauma	☐	■
History of brain surgery	☐	■

10. Is there any previous history of medical conditions that are not mentioned or history of drug abuse?	No Exclude if previous history of drug abuse
11. When did you begin to notice difficulties in seeing?	When were you diagnosed? 2011 (TB in L macula) When did you lose your vision? 2011 (vision started deteriorating) Onset of hallucinations? April 2020
12. Are the visual images	☐ Simple (e.g., flashes of light, zig zags, lightning bolts) ■ Complex (e.g., a scene with people, animals etc.)? ☐ Coloured; which colours _____ ☐ Black or white ☐ 2D image ■ 3D image (has depth) Description: 2 halos in different rainbow colours spinning; green faces; trees twinkle and lattice structures in the sky; comic images; figures; keeps him awake; person next to him faces not clear; cars while crossing street; tiger coming down the stairs

13. Do you experience any other hallucinations (e.g., auditory, olfactory, tactile)?	☐ Auditory ☐ Olfactory ☐ Tactile ☐ Gustatory ☐ N/A Description: No
14. Please describe the visual loss; is there a fog, dark or black, bright, etc.?	Description: Floaters; Foggy unless he goes closer to object
15. Have you noticed any difficulty in seeing colours? E.g., are the colours as bright as they used to be? Can you see all colours (yellow, green, red, blue)?	Description: Colours are duller because of the MD
16. Can you recognize faces, or pictures of faces? E.g., do you have difficulty differentiating whether a person is a stranger or a family member?	Description: No Exclude if prosopagnosia (only if relates to medical history – stroke, dementia, etc.)
17. Can you recognize objects, or pictures of objects? Do you have trouble recognizing what objects are?	Description: No Exclude if agnosia (only if relates to medical history)
18. When did you last see these images?	Halos (2 days ago); February
19. Are you still seeing these images	Yes Exclude if no longer seeing images
20. How often do you see the visual images?	Several times a week
21. When you see these images, for how long do you see them?	Seconds to hours

22. Do the visual images interfere with your vision; if yes, how? For example, do the images like cars, people, come in the way of your vision?	Yes, people on the street and cars (not since February 2023)
23. How do the visual images make you feel?	■ Irritable ☐ Frightened ☐ Anxious ☐ Indifferent ☐ Other
24. Where in the visual field do you notice the visual difficulties? E.g., do you have difficulty seeing to the left or right?	☐ Left ☐ Right ■ Center; can see more in periphery ☐ Top ☐ Bottom Exclude if hemineglect (only if relates to medical history, e.g., stroke)
25. Do the visual images involve the full area of your visual field or a part of your visual field?	■ Full visual field ☐ Part of visual field
26. If visual images involve part of the visual field, where do you see them?	☐ Right ☐ Left ☐ Top ☐ Bottom ☐ Center ■ All around visual field

27. <Follow up to Q25> Do you see the images where you have reduced/no vision, or in the area where you have vision?	☐ Area of reduced/ no vision ☐ Area where you have vision ☐ Not sure Description: Throughout the visual field
28. Do the images	■ Appear/ disappear gradually ☐ Suddenly appear/ disappear ☐ Sometimes gradual & sometimes sudden Description:
29. Are the images you see	☐ Still ■ Moving Description:
30. If images are moving, do they move in	☐ Same direction ■ Different directions ☐ Both same and different directions ☐ Not sure Which direction; describe:
31. Do these visual experiences feel real to you (e.g., if they are objects, do they exist in the real world)? How do you know the images are real/not real? Do you think the images are real (They may feel real, but they do know they are not)	☐ Real ■ Unreal Description: Images feel real, but he knows they are not real. Exclude if thinks images are real
32. How do you know the images are not real?	Description: Uses logic
33. If images are objects, do they exist in the real world?	Description: Yes

34. Are the images that you see "normal"?	■ Normal size ☐ Smaller than normal ☐ Larger than normal ☐ Distorted ☐ Change shape/ colour ☐ Have strange characteristics (e.g., they fly) Description: Some images are smaller
35. When do you see the images?	■ Morning ☐ Night ☐ Same time of day ☐ Different times of day Description:
36. Where (e.g., at home only, while gardening) do you notice these images?	Description: No specific place
37. Under which lighting conditions do you experience the visual images?	■ Day/ bright light conditions ☐ Night/ dark or dim conditions ☐ Images not dependent on light conditions Description: If out on a bright day, starts seeing halos
38. Can you trigger or start these visual images?	☐ Yes, how – describe: ■ No; tries to ignore them but cannot exactly stop them
39. Does any specific factor trigger your hallucinations?	☐ Yes, describe: ■ No; Not sure but no precise link between anxiety and hallucinations

40. Can you stop or reduce these images E.g., when you look to the right or to the left, up or down, do the images disappear? If you blink, do the images disappear?	☐ Yes, describe: <is it some of the time, most of the time> ■ No He tries to look away or ignore the images, but they reappear.
41. Are these images triggered by sound (e.g., speech, music, etc.)?	☐ Yes, describe: ■ No ☐ Not sure
42. Do you see these images with	■ Eyes open; using eye mask helps the images disappear ☐ Eyes closed ☐ Both with eyes open and closed
43. If you close one eye do you still see them?	■ Yes ☐ No Describe: Tried in the past but he can still see the images even when he closes one eye. Exclude if they say one eye
44. Have you encountered these images before, prior to vision loss (e.g., if you see people, are they people you know or saw on TV; have you seen them in a dream)?	☐ Yes, describe: ■ No
45. Do the images interact with you?	☐ Yes, describe: ■ No
46. Do you live alone?	☐ Yes ■ No; lives with wife

47. Have you told anyone about your visual experiences?	■ Yes, who: Doctor, family ▭ No
48. Is there any other information that you feel may be important?	
49. Can you try to draw what you are seeing or have seen? (Please use the back page if you need more space).	

Note. Screening form for CBS participant Patient A.P.

Table B.2.

Visual Hallucinations Rating Scale

The following structured interview is designed to elicit specific details regarding different dimensions of hallucinations. When asking questions, the interview is designed to rate the patient's experiences over the last week for the majority of items. Rate the patient's response based on what they believe at the time of interview or the last time the patient experienced them

NUMBER OF IMAGES	
How many different images have you seen over the last week?	☐ One ☐ Two ☐ Three ■ >Three
Types of images	☐ Patterns ■ Faces ■ Objects ■ Animals ☐ Figures ☐ Other Description:
FREQUENCY	
How often do you experience images? e.g., every day, all day long etc.	☐ Images not present or present less than once a week (specify frequency if present): ☐ Images occur at least once a week ■ Images occur several times a week but less than once a day.

	☐ Images occur daily. ☐ Images occur continuously or almost continually, i.e., stop only for a few seconds or minutes.
DURATION	
When you see the Images, how long do they last, e.g. a few seconds, minutes, hours, all day long?	☐ Images not present. ■ Images last for a few seconds. ☐ Images last for several minutes. ■ Images last for at least one hour. ☐ Images last for hours at a time.
SIZE	
When you see the images, how much of the visual field do they involve?	☐ No images present. ☐ <¼ of visual field. ☐ ¼ of visual field. ☐ ¾ of visual field. ☐ Half of visual field. ■ Full visual field.
DISTINCTNESS	
How vivid are your images? Are they more distinct than real images, about the same, or less distinct?	☐ Images not present. ■ Less distinct than real images. ☐ About the same as real images. ☐ More distinct than real images. ☐ Extremely vivid, overpower real images.
ORIGIN OF IMAGES	

What do you think causes these images? Where do you think these images come from?	☐ Images not present. ■ Images are not real. ☐ Less than 50% conviction that images are real. ☐ 50% or more conviction (but less than 100%) that images are real. ☐ Images are completely real (100% conviction).

DISTRESS BY ALL IMAGE CONTENT

How distressing are the images to your quality of life, whether they are negative or not?	☐ Images not distressing at all. ☐ Images occasionally cause distress, majority of the time are not distressing. ■ Equal amounts of distress and non-distress. ☐ Majority of images are distressing. ☐ Images are always distressing.

AMOUNT OF NEGATIVE CONTENT IN IMAGES

Are your images unpleasant or represent negative things? How much of the time are the images unpleasant?	■ No unpleasant content. ☐ Occasional unpleasant content. ☐ Minority of image content is unpleasant or negative (less than 50%) ☐ Majority of image content is unpleasant or negative (more than 50%) ☐ All of image content is unpleasant or negative.
Can you give me some examples of unpleasant images?	Describe: N/A

DISTRESS BY NEGATIVE CONTENT

When images are distressing, how distressing or unpleasant are they? - Do they cause you minimal, moderate, severe distress?	☐ Images not distressing at all or no distressing images. ☐ Images occasionally distressing. ■ Images are distressing to a moderate degree. ☐ Images are very distressing, although patient could feel worse. ☐ Images are always distressing.
DISRUPTION TO QUALITY OF LIFE CAUSED BY IMAGES	
How much disruption do the images cause to your life? The disruption refers to your work or ability to perform daily activities, interference with your relationships with friends and/or family or looking after yourself (e.g., bathing, eating, etc.)	☐ No disruption to life ☐ Minimal amount of disruption to life ■ Moderate amount of disruption to life ☐ Severe disruption of life ☐ Complete disruption of life
CONTROLLABILITY OF IMAGES	
Do you think you have any control over the images? Can you dismiss or bring on your images?	☐ Complete control over images; can always bring on or dismiss them at will. ☐ Have some control over images on the majority of occasions. ☐ Have some control over images approximately half of the time. ☐ Have some control over images but only occasionally. Experience images that are uncontrollable majority of the time. ■ No control over when images and cannot dismiss or bring them on at all.

Note. Rating of characteristics associated with visual hallucinations.

Table B.3.

North-East Visual Hallucinations Interview (NEVHI)

Section 1: Screening of visual hallucinations and the assessment of the hallucination phenomenology

Some people see things that other people cannot see. Please respond with "yes" or "no"

	Yes	No	Simple/Complex	Description
1. Do you feel like your eyes ever play tricks on you?	X		Complex	
2. Have you ever seen something (or things) that other people could not see?	X		Complex	
3. Have you ever had visual hallucinations?	X		Complex	
4. Have you ever had other visual experiences?	X		Complex	

Section 2: The temporal aspects of hallucinations

The following questions are about the visual hallucinations that you have described.

1. When did your hallucinations start?	A week ago	A month ago	Several months ago	1 year ago	**More than a year ago**
2. How long do your hallucinations usually last?	Up to 1 minute	**1 min to 1 hour**	1 hour to 2 hours	2 hours but less than all the time	All the time

3. When was your last hallucination?	Within the last 24 hours	2- 6 days ago	**1 – 4 weeks ago**	1 – 11 months ago	1 year or longer
4. How often have you had hallucinations during the last month?	Daily	Weekly	Every Fortnight	**Only once during last month**	Never

Section 3: Emotions, cognitions, and behaviours associated with recurrent visual hallucinations during the last month.

For the following questions please respond with ‘never (0)’, ‘seldom (1)’, ‘quite often (2)’, ‘very often (3)’, or ‘always (4)’

	Never 0	Seldom 1	Quite often 2	Very often 3	Always 4
1. How often were your hallucinations nice?				X	
2. How often were your hallucinations pleasant?				X	
3. How often were your hallucinations irritating?					X
4. How often were your hallucinations frightening?	X				
5. How often could you control the start of your hallucinations?	X				
6. How often could you control the end of your hallucinations?		X			

7. How often could you control the content of your hallucinations?		X		
8. Whilst you were experiencing hallucinations, how often have you been aware that you were experiencing a hallucination?				X
9. Whilst you were experiencing the hallucinations, how often did you act them out?	X			

Note. Hallucination phenomenology, temporal dynamics, emotional, cognitive, and behavioural aspects of visual hallucinations.

Table B.4.

Hallucinations Subsection of Specific Psychotic Experiences Questionnaire (SPEQ)

Answer the following questions based on your experiences with hallucinations over the past month:

	Not at all	Rarely	Once a month	Once a week	Several times a week	Daily
1. Hear noises or sounds when there is nothing about to explain them?	**0**	1	2	3	4	5
2. Feel that someone is touching you, but when you look nobody is there?	**0**	1	2	3	4	5
3. Hear sounds or music that people near you don't hear?	**0**	1	2	3	4	5
4. Detect smells which don't seem to come from your surroundings?	**0**	1	2	3	4	5
5. See things that other people cannot?	0	1	2	3	**4**	5
6. See shapes, lights, or colours even though there is nothing really there?	0	1	2	3	**4**	5
7. Experience unusual burning sensations or	**0**	1	2	3	4	5

other strange feelings in or on your body that can't be explained?						
8. Hear voices commenting on what you're thinking or doing?	**0**	1	2	3	4	5
9. Notice smells or odours that people next to you seem unaware of?	**0**	1	2	3	4	5
			SPEQ Score: ___8____			

Note. Frequency of multimodal hallucinations including visual, auditory, olfactory, and tactile.

Table B.5.

Hallucinations subsection of Neuropsychiatric Inventory (NPI)

Does the patient have hallucinations such as seeing false visions or hearing false 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 has abnormal experiences of sounds or visions.

- ■ Yes (if yes, please proceed to subsections)
- ☐ No (if no, please proceed to next screening question)
- ☐ N/A

1. Does the patient describe hearing voices or act as if he/ she hears voices?	☐ YES ■ NO **Frequency:** 1. Rarely – less than once per week 2. Sometimes – about once per week 3. Often – several times per week but less than everyday 4. Very often – once or more per day **Severity:** 1. Mild – hallucinations are present but harmless and cause little distress for the patient 2. Moderate – hallucinations are distressing and are disruptive for the patient. 3. Severe – hallucinations are very disruptive and are a major source of behavioural disturbance. PRN medications may be required to control them.

	Distress: How emotionally distressing do you find this behaviour? 0. Not at all 1. Minimally (almost no change in work routine) 2. Mildly (almost no change in work routine but a little time rebudgeting required) 3. Moderately (disrupts work routine, requires time budgeting) 4. Severely (disruptive, upsetting to staff and other residents, major time infringement) 5. Very severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)
2. Does the patient talk to people who are not there?	☐ YES ■ NO **Frequency:** 1. Rarely – less than once per week 2. Sometimes – about once per week 3. Often – several times per week but less than everyday 4. Very often – once or more per day **Severity:** 1. Mild – hallucinations are present but harmless and cause little distress for the patient 2. Moderate – hallucinations are distressing and are disruptive for the patient. 3. Severe – hallucinations are very disruptive and are a major of behavioural disturbance. PRN medications may be required to control them. **Distress:** How emotionally distressing do you find this behaviour? 0. Not at all

	1. Minimally (almost no change in work routine) 2. Mildly (almost no change in work routine but a little time rebudgeting required) 3. Moderately (disrupts work routine, requires time budgeting) 4. Severely (disruptive, upsetting to staff and other residents, major time infringement) 5. Very severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)
3. Does he/ she describe seeing things not seen by others or behave as if he/she is seeing things not seen by others (people, animals, lights, etc.)?	■ YES ☐ NO **Frequency:** ■ 1. Rarely – less than once per week ☐ 2. Sometimes – about once per week ☐ 3. Often – several times per week but less than everyday ☐ 4. Very often – once or more per day **Severity:** ☐ 1. Mild – hallucinations are present but harmless and cause little distress for the patient ■ 2. Moderate – hallucinations are distressing and are disruptive for the patient. ☐ 3. Severe – hallucinations are very disruptive and are a major source of behavioural disturbance. PRN medications may be required to control them. **Distress:** How emotionally distressing do you find this behaviour? ☐ 0. Not at all ■ 1. Minimally (almost no change in work routine) ☐ 2. Mildly (almost no change in work routine but a

	little time rebudgeting required) ☐ 3. Moderately (disrupts work routine, requires time budgeting) ☐ 4. Severely (disruptive, upsetting to staff and other residents, major time infringement) ☐ 5. Very severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)
4. Does he/ she report smelling odours not smelled by others?	☐ YES ■ NO **Frequency:** 1. Rarely – less than once per week 2. Sometimes – about once per week 3. Often – several times per week but less than everyday 4. Very often – once or more per day **Severity:** 1. Mild – hallucinations are present but harmless and cause little distress for the patient 2. Moderate – hallucinations are distressing and are disruptive for the patient. 3. Severe – hallucinations are very disruptive and are a major source of behavioural disturbance. PRN medications may be required to control them. **Distress:** How emotionally distressing do you find this behaviour? 0. Not at all 1. Minimally (almost no change in work routine) 2. Mildly (almost no change in work routine but a little time rebudgeting required) 3. Moderately (disrupts work routine, requires time budgeting)

	4. Severely (disruptive, upsetting to staff and other residents, major time infringement) 5. Very severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)
5. Does he/ she describe feeling things on his/ her skin or otherwise appear to be feeling things crawling or touching him/ her?	☐ YES ■ NO **Frequency:** 1. Rarely – less than once per week 2. Sometimes – about once per week 3. Often – several times per week but less than everyday 4. Very often – once or more per day **Severity:** 1. Mild – hallucinations are present but harmless and cause little distress for the patient 2. Moderate – hallucinations are distressing and are disruptive for the patient. 3. Severe – hallucinations are very disruptive and are a major of behavioural disturbance. PRN medications may be required to control them. **Distress:** How emotionally distressing do you find this behaviour? 0. Not at all 1. Minimally (almost no change in work routine) 2. Mildly (almost no change in work routine but a little time rebudgeting required) 3. Moderately (disrupts work routine, requires time budgeting) 4. Severely (disruptive, upsetting to staff and other residents, major time infringement) 5. Very severely or Extremely (very disruptive, major

	source of distress for staff and other residents, requires time usually devoted to other residents or activities)
6. Does he/ she describe tastes that are without any known cause?	☐ YES ■ NO **Frequency:** 1. Rarely – less than once per week 2. Sometimes – about once per week 3. Often – several times per week but less than everyday 4. Very often – once or more per day **Severity:** 1. Mild – hallucinations are present but harmless and cause little distress for the patient 2. Moderate – hallucinations are distressing and are disruptive for the patient. 3. Severe – hallucinations are very disruptive and are a major source of behavioural disturbance. PRN medications may be required to control them. **Distress:** How emotionally distressing do you find this behaviour? 0. Not at all 1. Minimally (almost no change in work routine) 2. Mildly (almost no change in work routine but a little time rebudgeting required) 3. Moderately (disrupts work routine, requires time budgeting) 4. Severely (disruptive, upsetting to staff and other residents, major time infringement) 5. Very severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

7. Does he/ she describe any other unusual sensory experiences?	☐ YES ■ NO **Frequency:** 1. Rarely – less than once per week 2. Sometimes – about once per week 3. Often – several times per week but less than everyday 4. Very often – once or more per day **Severity:** 1. Mild – hallucinations are present but harmless and cause little distress for the patient 2. Moderate – hallucinations are distressing and are disruptive for the patient. 3. Severe – hallucinations are very disruptive and are a major source of behavioural disturbance. PRN medications may be required to control them. **Distress:** How emotionally distressing do you find this behaviour? 0. Not at all 1. Minimally (almost no change in work routine) 2. Mildly (almost no change in work routine but a little time rebudgeting required) 3. Moderately (disrupts work routine, requires time budgeting) 4. Severely (disruptive, upsetting to staff and other residents, major time infringement) 5. Very severely or Extremely (very disruptive, major source of distress for staff and other residents, requires time usually devoted to other residents or activities)

NPI (hallucinations) Score: Frequency____1____ Severity____2____
Distress____1____

Total Score: ____4____

Note. Neuropsychiatric evaluation of visual hallucinatory experiences.

Table B.6.

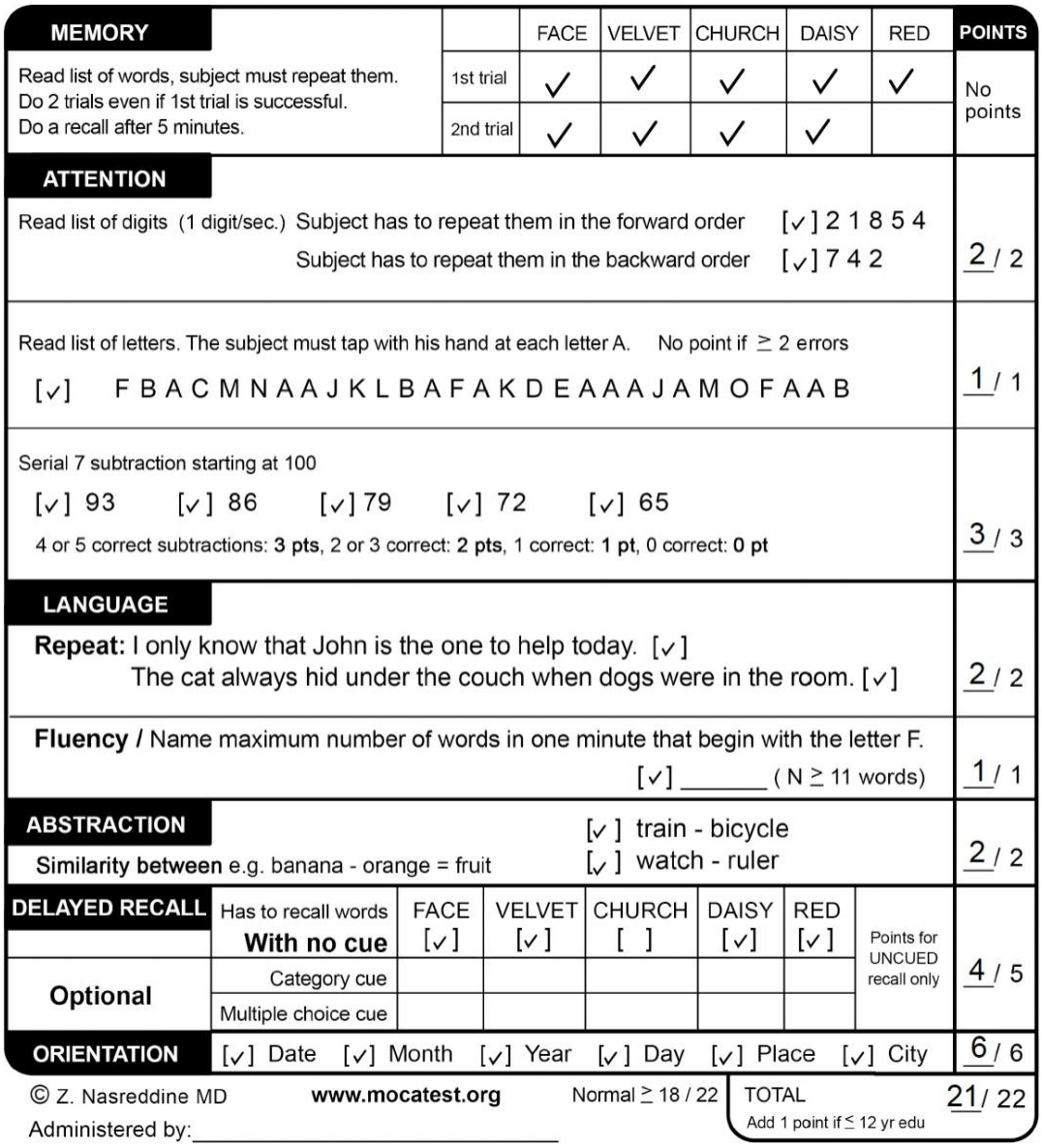
Waterloo Handedness Questionnaire

	Left always	Left usually	Equal	Right usually	Right always
1. Draw	-2	-1	0	1	**2**
2. Write	-2	-1	0	1	**2**
3. Hammer	-2	-1	0	1	**2**
4. Use a pencil rubber	-2	-1	0	1	**2**
5. Use a toothbrush	-2	-1	0	1	**2**
6. Hold a sewing needle	-2	-1	0	1	**2**
7. Cut bread with a knife	-2	-1	0	1	**2**
8. Swing a tennis racket	-2	-1	0	1	**2**
9. Throw a ball	-2	-1	0	1	**2**
10. Shave with a razor	-2	-1	0	1	**2**
11. Strike a match	-2	-1	0	1	**2**
12. Use a fly swatter	-2	-1	0	1	**2**
13. Use tweezers	-2	-1	0	1	**2**
14. Roll a marble	-2	-1	0	1	**2**
15. Use a comb	-2	-1	0	1	**2**
WHQ Score: ___30____	Group Classification: ___R____			Overall Classification: _Right-handed_	

Note. Evaluation of hand-dominance based on activities.

Figure B.1.

Montreal Cognitive Assessment (MoCA) – Blind



MEMORY		FACE	VELVET	CHURCH	DAISY	RED	POINTS
Read list of words, subject must repeat them. Do 2 trials even if 1st trial is successful. Do a recall after 5 minutes.	1st trial	✓	✓	✓	✓	✓	No points
	2nd trial	✓	✓	✓	✓		

ATTENTION

Read list of digits (1 digit/sec.) Subject has to repeat them in the forward order [✓] 2 1 8 5 4

Subject has to repeat them in the backward order [✓] 7 4 2 — 2 / 2

Read list of letters. The subject must tap with his hand at each letter A. No point if ≥ 2 errors

[✓] F B A C M N A A J K L B A F A K D E A A A J A M O F A A B — 1 / 1

Serial 7 subtraction starting at 100

[✓] 93 [✓] 86 [✓] 79 [✓] 72 [✓] 65

4 or 5 correct subtractions: **3 pts**, 2 or 3 correct: **2 pts**, 1 correct: **1 pt**, 0 correct: **0 pt** — 3 / 3

LANGUAGE

Repeat: I only know that John is the one to help today. [✓]

The cat always hid under the couch when dogs were in the room. [✓] — 2 / 2

Fluency / Name maximum number of words in one minute that begin with the letter F.

[✓] _____ (N ≥ 11 words) — 1 / 1

ABSTRACTION

Similarity between e.g. banana - orange = fruit

[✓] train - bicycle

[✓] watch - ruler — 2 / 2

DELAYED RECALL	Has to recall words	FACE	VELVET	CHURCH	DAISY	RED	Points for UNCUED recall only	POINTS
	With no cue	[✓]	[✓]	[ ]	[✓]	[✓]		
Optional	Category cue							4 / 5
	Multiple choice cue							

ORIENTATION [✓] Date [✓] Month [✓] Year [✓] Day [✓] Place [✓] City — 6 / 6

© Z. Nasreddine MD **www.mocatest.org** Normal ≥ 18 / 22

TOTAL 21 / 22

Add 1 point if ≤ 12 yr edu

Administered by:_____

Note. Evaluation of cognitive functioning for Patient A.P. MoCA-Blind version is used to accommodate for vision loss.

APPENDIX C: Healthy Control Assessment General Information

- General health history (physical/ mental):
- Ocular history:
- Mobility (Ambulatory/ Non-ambulatory):
- Assistive devices used for vision:
- How would you rate your eyesight with assistive devices?

1 – Excellent 5 – Poor

Table C.1.

Medical Screening and Exclusion

Any of the following?	**Yes**	**No**
1. Any metal in your cranium		
2. Increased intracranial pressure		
3. Pregnant or possibly pregnant		
4. Heart disease		
5. Cardiac pacemaker or intracardiac lines		
6. Implanted medication pump		
7. Tricyclic-antidepressants		
8. neuroleptic		

9. epileptic	
10. Family history of epilepsy or other seizure disorders	
11. Fainting spells or syncope	
12. Hearing problems or ringing in your ears	
13. Cochlear implants	
14. Implanted neurostimulator	
15. Medication infusion device	
16. Spinal cord surgery	
17. Spinal or ventricular derivations	
18. Any medication that significantly lowers seizure threshold	
19. History of head trauma	
20. History of brain surgery	

EXCLUSION	**Yes (Exclude)**	**No**
1. Do you see visual images that do not exist in reality (visual hallucinations)		
2. Psychiatric conditions (e.g., Depression)		

3. Any neurological conditions (Parkinson's disease, Alzheimer's disease, Lewy body dementia, schizophrenia, narcolepsy, psychotic depression and mania, epilepsy, stroke, delirium tremens, or any other conditions)

4. Hx of drug abuse

Researcher notes:

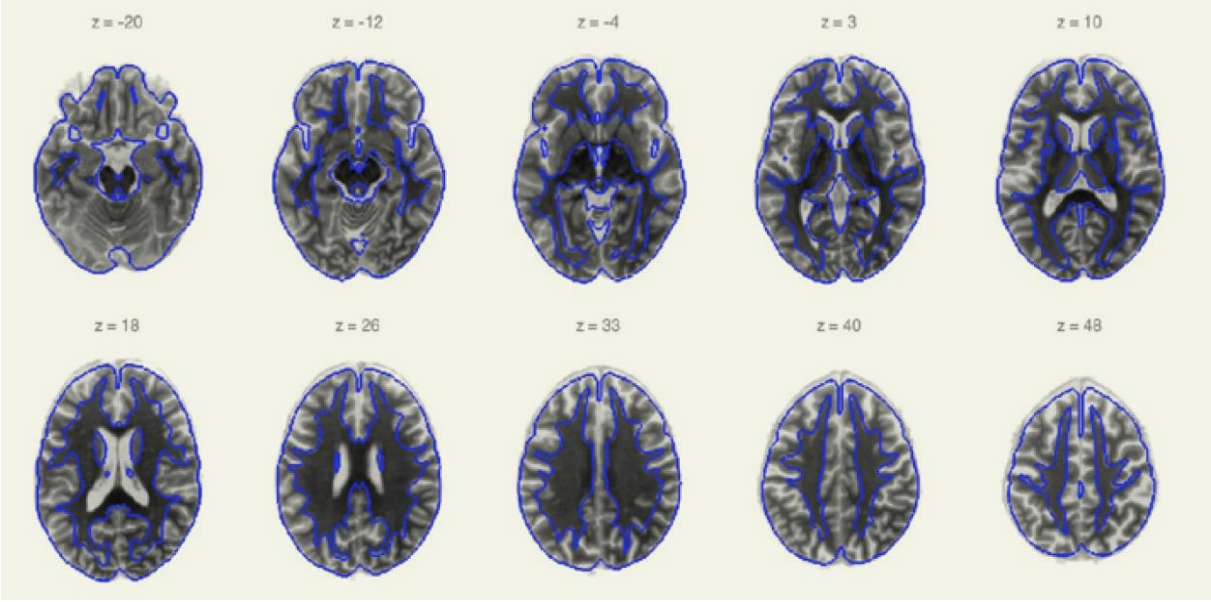
Medications:

APPENDIX D: Resting-state Quality Control of Preprocessed and Denoised Data

Covariates were evaluated based on automated quality control measures like maximum global signal change, mean global signal change, maximum motion, and mean motion. Visual quality control was conducted by inspecting normalized structural and functional data overlaid onto probability maps from MNI-space template (Figure D.1.). Similarly, segmentation of grey matter, white matter, and CSF, and plots of structural grey matter masks onto functional data were inspected to visualize the similarity between the grey matter mask and the reference MNI-space template. After denoising, carpet plots comparing data before and after denoising and signals from outliers, subject motion, and global signal change were inspected for each subject.

Figure D.1.

Quality Assessment of Normalized Data



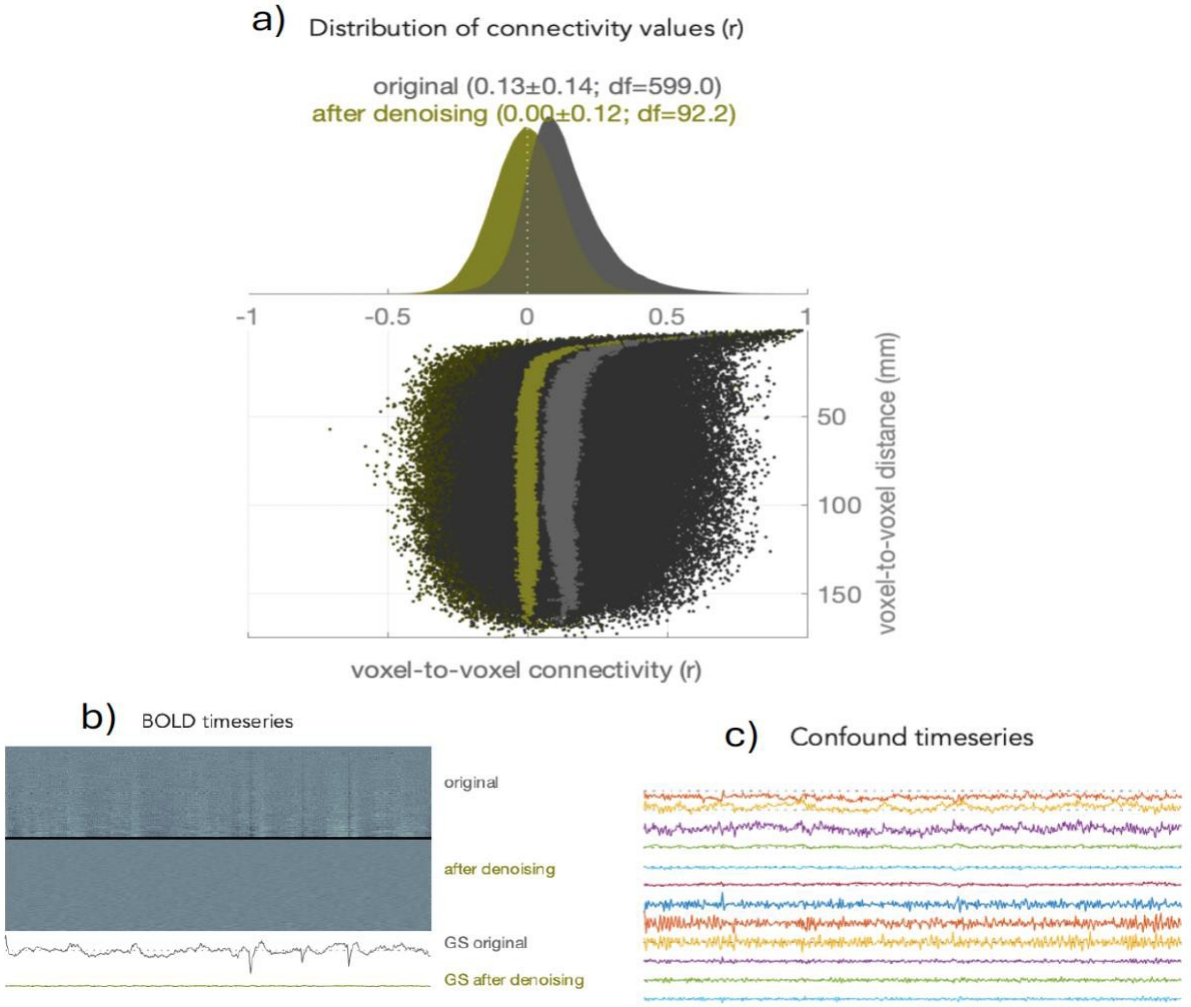
Note. Quality assessment of normalization of structural data onto outlines of MNI tissue probability map template.

The Global signal timeseries changes were also inspected through quality control

plots along with voxel-to-voxel connectivity to ensure that skewness in distribution of connectivity values is centered and normalized after temporal band-pass filtering. The distribution of connectivity plot displayed the correlation coefficients of BOLD time series from random voxels prior to and after regressing temporal confounding factors (Whitfield-Gabrieli & Nieto-Castanon, 2012). Under the first-level covariates quality control timeseries, framewise displacement was also examined. Framewise displacement represents a composite measure of motion along 3 translational and 3 rotational parameters (Morfini et al., 2023). Secondary to framewise displacement measures, volumes that have been scrubbed due to motion were removed from the analysis. All 12 potential noise components accounted for in the denoising pipeline were visualized after applying the filtering to remove frequencies below 0.008 Hz or above 0.09 Hz (Figure D.2).

Figure D.2.

Global Signal Timeseries

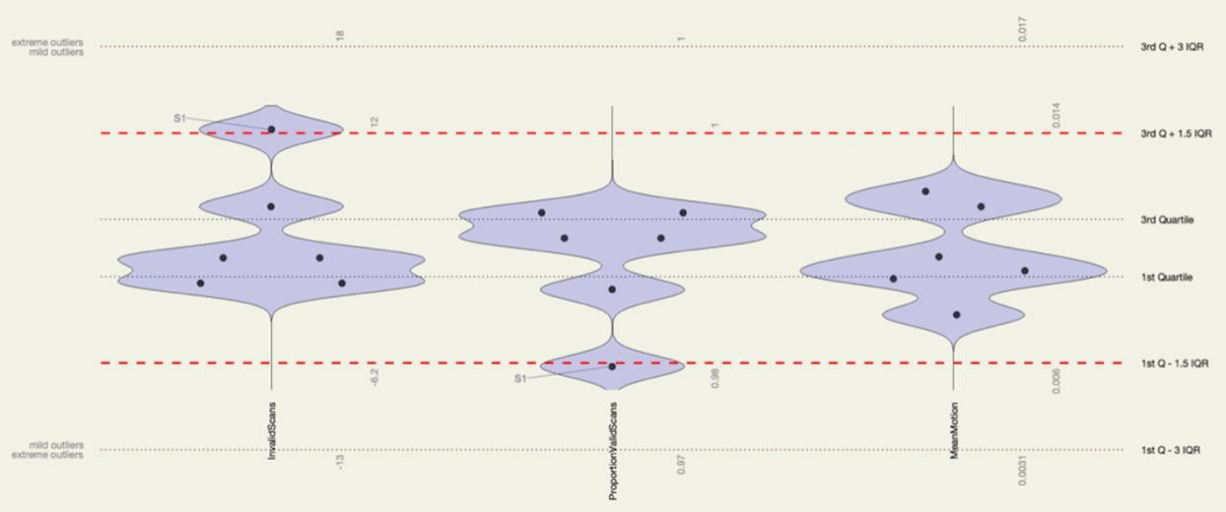


Note. a) Plot depicting the distribution of global signal (GS) timeseries changes of voxel-to-voxel functional connectivity values before (grey) and after (green) denoising; b) Carpet plot of BOLD signal traces and artifact detection tool (ART) timeseries representing BOLD global signal changes (z) after denoising; c) Twelve noise components visualized after temporal band-pass filtering.

An automated quality control plot also helped visualize extreme values that were above the threshold Q3 + 3 IQR or below Q1 – 3 IQR, where Q1 and Q3 are the first and third quartiles of the distribution of connectivity values and IQR represents inter-quartile range. Invalid and valid scans which illustrate the number of run-specific outlier scans were inspected to check the overall quality of the data for each participant (Figure D.3.).

Figure D.3.

Quality Control of Outliers



Note. Quality control plot for subjects representing extreme values and invalid scans, valid scans and mean motion within the threshold Q3 + 3 IQR or below Q1 – 3 IQR; Q1= first quartile, Q3=third quartile, IQR=inter-quartile range of the distribution of connectivity values.

Appendix E: Resting-state seed-based connectivity

Table E.1.

Comparison of Functional Connectivity of Occipital Poles to Target Regions

		Crawford-Howell t-test				
Seed	**Target**	**t(24)**	**Difference (A.P. – control mean)**	**z_{cc}**	**p-unc**	**p-FDR**
L-OP	L-Supramarginal gyrus	-1.20	-0.26	-1.23	0.241	0.273
	R-Supramarginal gyrus	-1.12	-0.26	-1.15	0.273	0.273
L-OP	L-Anterior parahippocampal	0.4	0.07	0.41	0.693	0.816
	R-Anterior parahippocampal	0.60	0.11	0.61	0.553	0.816
	L-Posterior parahippocampal	0.45	0.08	0.46	0.659	0.816
	R-Posterior parahippocampal	-0.24	-0.04	-0.24	0.816	0.816
L-OP	L-thalamus	0.62	0.12	0.63	0.545	0.956
	R-thalamus	-0.06	-0.01	-0.06	0.956	0.956
L-OP	Posterior cingulate cortex	-2.61	-0.56	-2.66	**0.015***	**0.016***

	Precuneus	-2.60	-0.55	-2.65	**0.016***	**0.016***
L-OP	L-Intraparietal sulcus	-1.49	-0.33	-1.52	0.149	0.299
	R-Intraparietal sulcus	0.54	0.10	0.55	0.596	0.596
L-OP	L-temporo-occipital fusiform	-1.02	-0.31	-1.04	0.317	0.644
	R-temporo-occipital fusiform	-1.09	-0.31	-1.11	0.286	0.644
	L-Temporo-occipital ITG	-0.90	-0.21	-0.92	0.376	0.644
	R-temporo-occipital ITG	0.47	0.07	0.48	0.644	0.644
	L-inferior lateral occipital cortex	-0.58	-0.14	-0.59	0.570	0.644
	R-inferior lateral occipital cortex	-0.72	-0.22	-0.74	0.478	0.644
R-OP	L-Supramarginal gyrus	-0.86	-0.16	-0.88	0.397	0.436
	R-Supramarginal gyrus	-0.79	-0.19	-0.81	0.436	0.436
R-OP	L-Anterior parahippocampal	0.52	0.09	0.53	0.607	0.916

	R-Anterior parahippocampal	0.04	0.01	0.04	0.969	0.916
	L-Posterior parahippocampal	0.41	0.08	0.42	0.687	0.916
	R-Posterior parahippocampal	-0.67	-0.11	-0.68	0.510	0.916
R-OP	L-thalamus	0.79	0.12	0.81	0.436	0.829
	R-thalamus	0.22	0.03	0.22	0.829	0.829
R-OP	Posterior cingulate cortex	-2.52	-0.59	-2.57	**0.019***	**0.020***
	Precuneus	-2.50	-0.58	-2.55	**0.020***	**0.020***
R-OP	L-Intraparietal sulcus	-1.34	-0.32	-1.37	0.193	0.354
	R-Intraparietal sulcus	0.95	0.21	0.97	0.354	0.354
R-OP	L-temporo-occipital fusiform	-1.07	-0.28	-1.09	0.296	0.528
	R-temporo-occipital fusiform	-1.57	-0.42	-1.60	0.131	0.528
	L-Temporo-occipital ITG	-1.15	-0.18	-1.17	0.263	0.528
	R-temporo-occipital ITG	-0.02	-0.01	-0.03	0.981	0.981
	L-inferior lateral occipital cortex	0.95	0.19	0.97	0.352	0.528

R-inferior lateral occipital cortex	0.03	0.01	0.03	0.976	0.981

Note. Comparisons of functional connectivity between occipital poles and target brain regions for Patient A.P. compared to healthy using a Crawford-Howell *t*-test. L = left; R = right; OP = occipital pole; ITG = temporo-occipital inferior temporal gyrus.

*Significance is set to *p*-uncorrected (*p*-unc) < 0.05; *p*-FDR < 0.05

Table E.2.

Comparisons of Functional Connectivity of Cuneal Cortex to Target Regions

		Crawford-Howell t-test				
Seed	**Target**	**t(24)**	**Difference (A.P. – control mean)**	**z_{cc}**	**p-unc**	**p-FDR**
L-CC	L-Supramarginal gyrus	0.30	0.06	0.30	0.768	0.987
	R-Supramarginal gyrus	0.02	0.00	0.02	0.987	0.987
L-CC	L-Anterior parahippocampal	0.75	0.12	0.46	0.462	0.706
	R-Anterior parahippocampal	0.41	0.06	0.69	0.686	0.706
	L-Posterior parahippocampal	-1.25	-0.17	0.22	0.223	0.706
	R-Posterior parahippocampal	-0.38	-0.06	0.71	0.706	0.706
L-CC	L-thalamus	1.52	0.32	1.55	0.141	0.141
	R-thalamus	1.55	0.36	1.58	0.134	0.141
L-CC	Posterior cingulate cortex	-0.58	-0.19	-0.59	0.570	0.570

	Precuneus	-0.60	-0.20	-0.61	0.556	0.570
L-CC	L-Intraparietal sulcus	0.30	0.07	0.31	0.765	0.799
	R-Intraparietal sulcus	-0.26	-0.06	-0.26	0.799	0.799
L-CC	L-temporo-occipital fusiform	-1.16	-0.19	-1.19	0.256	0.384
	R-temporo-occipital fusiform	-1.90	-0.41	-1.94	0.070	0.264
	L-Temporo-occipital ITG	0.01	0.00	0.01	0.989	0.989
	R-temporo-occipital ITG	-0.76	-0.15	-0.78	0.453	0.543
	L-inferior lateral occipital cortex	-1.75	-0.36	-1.79	0.093	0.264
	R-inferior lateral occipital cortex	-1.56	-0.37	-1.59	0.132	0.264
R-CC	L-Supramarginal gyrus	1.18	0.26	1.20	0.251	0.251
	R-Supramarginal gyrus	1.40	0.18	1.43	0.175	0.251
R-CC	L-Anterior parahippocampal	-0.52	-0.08	-0.53	0.606	0.778

	R-Anterior parahippocampal	0.29	0.04	0.29	0.778	0.778
	L-Posterior parahippocampal	-0.84	-0.13	-0.86	0.410	0.778
	R-Posterior parahippocampal	-0.36	-0.06	-0.37	0.720	0.778
R-CC	L-thalamus	1.63	0.33	1.66	0.117	0.117
	R-thalamus	2.67	0.52	2.72	**0.013**	**0.027***
R-CC	Posterior cingulate cortex	0.10	0.03	0.10	0.921	0.983
	Precuneus	0.12	0.01	0.02	0.983	0.983
R-CC	L-Intraparietal sulcus	1.04	0.25	1.06	0.309	0.617
	R-Intraparietal sulcus	-0.13	-0.03	-0.14	0.894	0.894
R-CC	L-temporo-occipital fusiform	-0.38	-0.07	-0.39	0.709	0.945
	R-temporo-occipital fusiform	-1.25	-0.30	-1.27	0.224	0.492
	L-Temporo-occipital ITG	0.07	0.01	0.07	0.945	0.945
	R-temporo-	-0.22	-0.68	-0.23	0.826	0.945

occipital ITG					
L-inferior lateral occipital cortex	-1.19	-0.24	-1.21	0.246	0.492
R-inferior lateral occipital cortex	-1.24	-0.29	-1.26	0.229	0.492

Note. Comparison of functional connectivity between cuneal cortices and target brain regions for Patient A.P. compared to healthy using a Crawford-Howell *t*-test. L = left; R = right; CC = cuneal cortex; ITG = temporo-occipital inferior temporal gyrus.

*Significance is set to *p*-uncorrected (*p*-unc) < 0.05; *p*-FDR < 0.05

Table E.3.

Comparisons of Functional Connectivity of Lingual Gyrus to Target Regions

		Crawford-Howell t-test				
Seed	**Target**	**t(24)**	**Difference (A.P. – control mean)**	**z_{cc}**	**p-unc**	**p-FDR**
L-LG	L-Supramarginal gyrus	0.37	0.08	0.38	0.713	0.882
	R-Supramarginal gyrus	-0.15	-0.04	-0.15	0.882	0.882
L-LG	L-Anterior parahippocampal	0.16	0.02	0.17	0.873	0.900
	R-Anterior parahippocampal	-0.53	-0.10	-0.54	0.602	0.900
	L-Posterior parahippocampal	0.13	0.02	0.13	0.900	0.900
	R-Posterior	-0.39	-0.07	-0.40	0.702	0.900

	parahippocampal					
L-LG	L-thalamus	0.45	0.10	0.46	0.654	0.781
	R-thalamus	-0.28	-0.07	-0.29	0.781	0.781
L-LG	Posterior cingulate cortex	-1.41	-0.42	-1.44	0.170	0.170
	Precuneus	-1.57	-0.48	-1.60	0.130	0.170
L-LG	L-Intraparietal sulcus	0.66	0.17	0.67	0.516	0.807
	R-Intraparietal sulcus	0.25	0.05	0.25	0.807	0.807
L-LG	L-temporo-occipital fusiform	-0.85	-0.12	-0.87	0.402	0.482
	R-temporo-occipital fusiform	-2.35	-0.54	-2.40	0.027	0.081
	L-Temporo-occipital ITG	0.43	0.09	0.44	0.672	0.672
	R-temporo-	-1.14	-0.23	-1.16	0.265	0.397

	occipital ITG					
	L-inf. Lateral occipital cortex	-2.04	-0.41	-2.08	0.052	0.104
	R-inf. Lateral occipital cortex	-2.87	-0.55	-2.93	0.010	0.050
R-LG	L-Supramarginal gyrus	1.25	0.28	1.28	0.223	0.447
	R-Supramarginal gyrus	0.59	0.13	0.60	0.563	0.563
R-LG	L-Anterior parahippocampal	0.71	0.12	0.73	0.484	0.964
	R-Anterior parahippocampal	-0.36	-0.06	-0.37	0.723	0.964
	L-Posterior parahippocampal	0.90	0.15	0.92	0.376	0.964
	R-Posterior parahippocampal	-0.05	-0.01	-0.05	0.964	0.964
R-LG	L-thalamus	0.70	0.13	0.71	0.494	0.712

	R-thalamus	0.37	0.08	0.38	0.712	0.712
R-LG	Posterior cingulate cortex	-0.38	-0.10	-0.39	0.705	0.705
	Precuneus	-0.60	-0.17	-0.61	0.556	0.705
R-LG	L-Intraparietal sulcus	1.29	0.31	1.31	0.211	0.422
	R-Intraparietal sulcus	0.19	0.04	0.19	0.854	0.854
R-LG	L-temporo-occipital fusiform	-0.85	-0.14	-0.87	0.403	0.483
	R-temporo-occipital fusiform	-2.06	-0.51	-2.10	0.051	0.199
	L-Temporo-occipital ITG	0.87	0.19	0.89	0.392	0.483
	R-temporo-occipital ITG	-0.60	-0.14	-0.61	0.556	0.556
	L-inf. Lateral occipital cortex	-1.68	-0.36	-1.71	0.106	0.212

R-inf. Lateral occipital cortex	-1.92	-0.42	-1.96	0.066	0.199

Note. Comparison of functional connectivity between lingual gyri and target brain regions for Patient A.P. compared to healthy using a Crawford-Howell *t*-test. L = left; R = right; LG = lingual gyrus; ITG = temporo-occipital inferior temporal gyrus. *Significance is set to *p*-uncorrected (*p*-unc) < 0.05; *p*-FDR < 0.05

Table E.4.

Cortical Thickness of Brain Regions

Region	Cortical thickness (mm)			Statistics		
	Patient A.P.	Healthy controls Mean ± SD	Healthy Controls 95% CI	*t*(24)	*p*	z_{cc}
R cuneus	1.78	1.85 ± 0.11	[1.81, 1.90]	-0.67	0.508	-0.685
L cuneus	1.86	1.78 ± 0.10	[1.73, 1.82]	0.79	0.436	0.809
R lingual	2.02	1.99 ± 0.12	[1.94, 2.04]	0.25	0.805	0.255
L lingual	1.87	1.91 ± 0.09	[1.87, 1.95]	0.41	0.682	-0.423
R fusiform	2.51	2.64 ± 0.10	[2.60, 2.68]	-1.23	0.229	-1.259
L fusiform	2.48	2.63 ± 0.08	[2.60, 2.66]	-1.83	0.080	-1.868
R ITG	2.67	2.70 ± 0.13	[2.65, 2.75]	-0.23	0.822	-0.231
L ITG	2.60	2.66 ± 0.13	[2.61, 2.72]	-0.48	0.635	-0.490
R LOC	2.10	2.09 ± 0.13	[2.04, 2.15]	0.05	0.963	0.048
L LOC	2.14	2.00 ± 0.11	[1.94, 2.03]	1.31	0.203	1.334

R PaHC	2.38	2.56 ± 0.23	[2.46, 2.65]	-0.75	0.463	-0.760
L PaHC	2.45	2.62 ± 0.20	[2.54, 2.70]	-0.83	0.416	-0.843
R PeriC	1.54	1.62 ± 0.15	[1.56, 1.69]	-0.57	0.577	-0.577
L PeriC	1.52	1.52 ± 0.12	[1.46, 1.57]	0.04	0.973	0.035
R precun	2.17	2.25 ± 0.10	[2.21, 2.29]	-0.79	0.438	-0.804
L precun	2.22	2.21 ± 0.12	[2.16, 2.25]	0.11	0.911	0.116

Note. Comparisons of cortical thickness (mm) for brain regions for Patient A.P. and healthy control group using Crawford Howell *t*-test. R = right; L = left; ITG = inferior temporal gyrus; LOC = lateral occipital cortex; PaHC = parahippocampal; PeriC = pericalcarine; Precun = precuneus.

Table E.5.

Volumetric Measures of Participants

Region	**Absolute volume (cm^3)**			**Statistics**		
	Patient A.P.	Healthy controls Mean ± SD	Healthy controls 95% CI	$t(24)$	p	z_{cc}
Grey matter	631	585.36 ± 61.01	[560.17, 610.55]	0.34	0.741	-0.342
White matter	452	472.60 ± 60.30	[447.71, 497.49]	0.73	0.470	0.748
Total intracranial volume	1608	1435.52 ± 156.80	[1370.80, 1500.24]	1.08	0.291	1.099

Note. Absolute grey matter, white matter, and total intracranial volume (cm^3) for Patient A.P. and healthy controls. *****Significance is set to $p < 0.05$.

APPENDIX F: Gannet Analysis

MRS data were analyzed using a linear combination model on Gannet (v3.3.1; Baltimore, Maryland, United States; https://www.GABA+MRS.com) (Edden et al., 2014) and SPM12 (statistical Parametric Mapping; Welcome Centre for Human Neuroimaging; London, United Kingdom; https://www.fil.ion.ucl.ac.uk/spm) which both run on MATLAB Version: 9.13 (R2022b) (MathWorks; Natick, Massachussets, United States; https://www.mathworks.com/products/matlab.html). Gannet performs batch analysis of edited difference spectrum double Gaussian fit on MRS data. Several Gannet modules were used to analyze the MRS data.

GannetLoad was first run for each subject using a script that calls on an array of files and yields a single output data structure. Several processing steps were performed including phase-array channel combination, exponential line broadening, Fourier transformation of time-resolve to frequency-domain spectra, frequency, and phase correction for removal of movement-related and scanner drift artifacts, time-averaging and outlier rejection based on 3 standard deviations from the mean frequency, phase, or area of FWHM. Outlier rejection was applied in a pairwise manner where rejection of one OFF scan led to the rejection of the subsequent ON scan to maintain balance in subtraction. Following GannetLoad, the GannetFit module which estimates GABA+ and Glx concentrations using uncorrected creatine (Cr) as an internal reference and both corrected and uncorrected water reference was used. This is done through non-linear least-squares spectra fitting. These estimates are produced relative to both water and creatine to make sure that the results hold irrespective of the reference and to ensure more robust interpretations. GannetFit then provided an output of a single Gaussian

peak for each of the GABA and Glx metabolites with a linear baseline. Further, the GannetCoregister and GannetSegment functionalities were run. A binary mask was created based on the voxel size, orientation and location using the anatomical T1-weighted image as a reference. Moreover, SPM segmentation was used to calculate fractions of grey matter (f_{GM}), white matter (f_{WM}), and cerebrospinal fluid (f_{CSF}) to help segment tissue fractions within the voxel. Finally, GannetQuantify used the signal estimates generated by GannetFit to quantify GABA and Glx by applying tissue specific relaxation and water visibility constants.

APPENDIX G: Visual Field Perimetry

Table G.1.

Visual Field Perimetry Measures of Participants

Participant	Mean retinal sensitivity (dB)	
	Right eye	Left eye
Patient A.P.	7.4	4.2
Sub-02	28	26.6
Sub-03	23.1	23.8
Sub-04	25.6	24.4
Sub-05	25.7	24.1
Sub-06	23	22
Sub-07	25.6	25.9

Note. Mean retinal sensitivity of left and right eye for Patient A.P. and healthy controls.

APPENDIX H: Psychosocial Questionnaire Demographic Information

- Date of Birth (DD/MM/YYYY):
- Age:
- What is your biological sex?
    - Male
    - Female
    - Other _____
    - Prefer not to say
- What is your ethnicity?
    - White
    - South Asian (e.g., Indian, Pakistani, Sri Lankan, etc.)
    - Chinese
    - Black
    - Filipino
    - Latin American
    - Arab
    - Southeast Asian (e.g., Vietnamese, Cambodian, Malaysian, etc.)
    - West Asian (e.g., Iranian, Afghan, etc.)

- Korean
- Japanese
- Other; please specify

- Do you identify as a member of indigenous communities (e.g., Métis, Inuit, etc.)?
  - Yes
  - No
- Is English your first language?
  - Yes
  - No
- How would you rate your English proficiency?
  - Not fluent in English
  - Can somewhat speak English
  - Conversational English speaker
  - Able to speak English above average
  - Bilingual speaker (able to speak English fluently)
- On a scale from 1 (Excellent) to 5 (Very Poor), how would you say your overall **physical health** is:
  - 1 - Excellent
  - 2
  - 3

- 4
- 5 – Very poor

- On a scale from 1 (Excellent) to 5 (Very Poor), how would you say your overall **mental health** is:
  - 1 - Excellent
  - 2
  - 3
  - 4
  - 5 – Very poor
- Do you use assistive devices to help with your vision?
  - Yes
  - No
- Which of the following assistive devices do you use to help you with your vision? Please select all that apply.
  - Eyeglasses or contact lenses
  - White cane or identification cane
  - Recording equipment or portable note-taking device
  - Magnifiers
  - Closed-circuit devices (e.g., CCTV)

- Large print reading materials
- Dark lined paper or dark ink pens
- Braille reading materials or manual Brailler
- A device with oversized buttons (e.g., remote control or telephone)
- Audio or described video for television programs
- Another aid or assistive device; please specify. _____

- At the present time, on a scale from 1 (Excellent) to 5 (Very Poor), would you say your eyesight (with assistive devices or visual aids, if you use them) is:
  - 1 - Excellent
  - 2
  - 3
  - 4
  - 5 – Very poor
- How much difficulty do you have with your daily living because of your vision?
  - No difficulty
  - Some difficulty
  - A lot of difficulty
  - Cannot do at all
- Do you currently, or have you previously had any of the following eye

conditions? Please select all that apply.

- Macular degeneration
- Glaucoma
- Diabetic retinopathy
- Scotoma
- Cataracts
- Occipital lobe stroke
- Other _____
- No, I have not previously experienced or currently have any of the above eye conditions

- Do you have other health conditions (e.g. diabetes, dementia, Parkinson's disease, etc.)? If yes, please indicate the health conditions in the space provided.
  - Yes
  - No
- Have you had a discussion with your doctor about Charles Bonnet Syndrome?
  - Yes
  - No
  - Not sure
- Have you been diagnosed with Charles Bonnet Syndrome?
  - Yes

- No
- Not sure

International Physical Activity Questionnaire - Modified

Please answer the following set of questions based on **the average level of your physical activity** during the past year amidst the COVID-19 pandemic.

1. Think about the time you spent **sitting** including time spent at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading, or sitting or lying down to watch television. **During the last year**, how much time did you spend sitting during a day? Please answer based on the average time you spend sitting.
   - 0% - 25% of the day
   - 25% - 50% of the day
   - 50% - 75% of the day
   - 75% - 100% of the day
2. Think about the time you spend **walking** during the week. This includes at work and at home, walking to travel from place to place, and any other walking that you might do solely for recreation, sport, exercise, or leisure. **During this past year**, how many days do you usually walk for at least 10 minutes at a time?
   - 0 days per week
   - 1 – 3 days per week
   - 4 – 7 days per week
3. **During the past year**, on how many days did you do moderate physical activities like gardening, cleaning, bicycling at a regular pace, swimming or other fitness

activities. Think only about those physical activities that you did for at least 10 minutes at a time. Do not include walking.

- 0 days per week
- 1 – 3 days per week
- 4 – 7 days per week

4. **During the past year**, on how many days did you do vigorous physical activities like heavy lifting, heavier garden or construction work, chopping woods, aerobics, jogging/running or fast bicycling? Think only about those physical activities that you did for at least 10 minutes at a time.
   - 0 days per week
   - 1 – 3 days per week
   - 4 – 7 days per week

Hallucinations

Hallucinations may be experienced by people with a variety of underlying neurological, visual, or auditory (hearing) issues. Hallucinations may be experienced in different ways, for example, the presence of visual images or flashes, noises, feeling as if you are being touched, or even the presence of different smells. They can last for a few seconds or persist for longer durations such as hours or days. The intensity (strength), frequency (amount or regularity), and type of hallucinations may vary greatly from one person to another. Often, a person may be aware that the hallucinations are only seen by them.

- Do you experience hallucinations? If yes, please explain in the provided space.
  - Yes

- No

- In which year did your hallucinations start? (YYYY)
- Are you currently on medications to treat the hallucinations?
  - Yes
  - No
- Have you had a change in dosage, stopped or started a new prescription of those medications during the PAST YEAR? If yes, please provide details in the space provided.
  - Yes
  - No
- What **types of visual hallucinations or images** have you been experiencing recently and within the PAST YEAR? Please pick all the options that apply.
  - Patterns
  - Faces
  - Figures
  - Animals
  - Objects
  - Flashes
  - Other

- NA

- What types of visual hallucinations or images did you previously experience **BEFORE the COVID-19 pandemic**? Please pick all the options that apply.
  - Patterns
  - Faces
  - Figures
  - Animals
  - Objects
  - Flashes
  - Other
  - NA

- **Currently and during the PAST YEAR**, how long does each hallucination last on average? Please pick the duration that best describes your typical hallucinations.
  - Seconds
  - Minutes
  - Hours
  - Days
  - Continuous
  - Other _____

- NA

- **BEFORE the COVID-19 pandemic**, how long did each hallucination last on average? Please pick the duration that best describes your typical past hallucinations.
  - Seconds
  - Minutes
  - Hours
  - Days
  - Continuous
  - Other _____
  - NA

- Did the frequency (the number of occurrences) of your hallucinations change **during the PAST YEAR**?
  - I am experiencing MORE hallucinations
  - I am experiencing LESS hallucinations
  - There has been NO CHANGE in the frequency of my hallucinations
- If you are experiencing MORE hallucinations, please indicate the option that best describes the level of increase in frequency **during the PAST YEAR**:
  - 0% - 25% increase
  - 25% - 50% increase

- 50% - 75% increase
- 75% - 100% increase

- If you are experiencing LESS hallucinations, please indicate the option that best describes the level of decrease in frequency **during the PAST YEAR**:
  - 0% - 25% decrease
  - 25% - 50% decrease
  - 50% - 75% decrease
  - 75% - 100% decrease
- Did the nature (vividness, clarity, intensity) of the hallucinations change **over the PAST YEAR**?
  - Yes
  - No
  - Not sure
  - NA

Specific Psychotic Experiences Questionnaire (SPEQ) – Modified

Please answer the following questions indicating your experiences with hallucinations. You may choose the answer that best explains your average experiences during the PAST YEAR.

- Hear noises or sounds when there is nothing about to explain them?
  - Not at all

- Rarely
- Once a month
- Once a week
- Several times a week
- Daily

- Feel that someone is touching you, but when you look nobody is there?Not at all
  - Rarely
  - Once a month
  - Once a week
  - Several times a week
  - Daily
- Hear sounds or music that people near you don’t hear?
  - Not at all
  - Rarely
  - Once a month
  - Once a week
  - Several times a week
  - Daily

- Detect smells which don’t seem to come from your surroundings?
  - Not at all
  - Rarely
  - Once a month
  - Once a week
  - Several times a week
  - Daily
- See things that other people cannot?
  - Not at all
  - Rarely
  - Once a month
  - Once a week
  - Several times a week
  - Daily
- See shapes, lights, or colours even though there is nothing really there?
  - Not at all
  - Rarely
  - Once a month

- Once a week
- Several times a week
- Daily

- Experience unusual burning sensations or other strange feelings in or on your body that can't be explained?
  - Not at all
  - Rarely
  - Once a month
  - Once a week
  - Several times a week
  - Daily
- Hear voices commenting on what you're thinking or doing?
  - Not at all
  - Rarely
  - Once a month
  - Once a week
  - Several times a week
  - Daily

- Notice smells or odours that people next to you seem unaware of?
  - Not at all
  - Rarely
  - Once a month
  - Once a week
  - Several times a week
  - Daily

World Health Organization Quality of Life – BREF Scale - Modified

Quality of life is a term that describes a person's well-being in relation to their environment and social context. It describes how a person feels about their physical health, psychological state, level of independence, social relationships, and life satisfaction.

- How would you rate your quality of life from 1 (Very poor) to 5 (Very good)?
  1- Very poor
  2- Poor
  3- Neither poor nor good
  4- Good
  5- Very good

Please answer the following questions based on your life situation and experiences with the ongoing COVID-19 pandemic over the PAST YEAR. Each question has five options

ranging from 1 (Very dissatisfied) to 5 (Very satisfied). You may pick only one answer per question.

- How satisfied are you with your sleep?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied
- How satisfied are you with your health?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied
- How satisfied are you with your ability to perform your daily living activities
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied

- Very satisfied

- How satisfied are you with your capacity for work?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied
- How satisfied are you with yourself?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied
- How satisfied are you with your personal relationships?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied

- Very satisfied

- How satisfied are you with your sex life?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied
- How satisfied are you with the support you get from your friends?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied
- How satisfied are you with the conditions of your living place?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied

- How satisfied are you with your access to health services?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied
- How satisfied are you with your mode of transportation?
  - Very dissatisfied
  - Dissatisfied
  - Neither satisfied nor dissatisfied
  - Satisfied
  - Very satisfied

Generalized Anxiety Disorder - 7 Scale - Modified

Considering the ongoing global situation with the COVID-19 pandemic, answer the following questions based on how you have felt **during the past year**. Each question has four options ranging from “Not at all” to “Nearly every day”. You may pick only one option per question.

- Feeling nervous, anxious, or on edge
  - Not at all
  - Several days

- More than half the days
- Nearly everyday

- Not being able to stop or control worrying
  - Not at all
  - Several days
  - More than half the days
  - Nearly everyday
- Worrying too much about different things
  - Not at all
  - Several days
  - More than half the days
  - Nearly everyday
- Trouble relaxing
  - Not at all
  - Several days
  - More than half the days
  - Nearly everyday
- Being so restless that it is hard to sit still
  - Not at all

- Several days
- More than half the days
- Nearly everyday

- Becoming easily annoyed or irritable
  - Not at all
  - Several days
  - More than half the days
  - Nearly everyday

- Feeling afraid, as if something awful might happen
  - Not at all
  - Several days
  - More than half the days
  - Nearly everyday

DeJong Gierveld Loneliness Scale - Modified

Considering the ongoing global situation with COVID-19, please answer the following questions based on how you have felt **during the PAST YEAR**. Each question has three options “Yes”, “More or less”, and “No”. You may only pick one option per question.

- I experience a general sense of emptiness
  - Yes

- More or less
- No

- I miss having people around me
  - Yes
  - More or less
  - No
- I often feel rejected
  - Yes
  - More or less
  - No
- There are plenty of people I can rely on when I have problems
  - Yes
  - More or less
  - No
- There are many people I can trust completely
  - Yes
  - More or less
  - No
- There are enough people I feel close to
  - Yes

- More or less
- No

Steptoe Social Isolation Index - Modified

Please answer the following questions based on your social circumstances over the past year during the COVID-19 pandemic. If the statement applies to your situation, please pick “Yes”, otherwise pick “No”.

- Are you married/ cohabitating?
- Do you contact your children (face-to-face, by telephone or writing/email) at least once a month? If you DO NOT have children please pick “No”.
  - Yes
  - No
- Do you contact other family (face-to-face, by telephone or writing/email) at least once a month? If you DO NOT have family please pick “No”.
  - Yes
  - No
- Do you contact your friends (face-to-face, by telephone or writing/email) at least once a month? If you DO NOT have friends please pick “No”.
  - Yes
  - No
- Do you participate in social clubs, resident groups, religious groups, or communities?

- Yes
- No