Review

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Review

The Neural Mechanisms of Charles Bonnet Syndrome

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Abstract

Charles Bonnet Syndrome (CBS) describes the experience of visual hallucinations in individuals with visual impairments who are otherwise cognitively and neurophysiologically healthy. CBS remains underrecognized and is poorly understood, with limited knowledge of its underlying mechanisms. This review examines the neurobiological basis of CBS, discussing neuroimaging, neurophysiological, structural, and biochemical perspectives. The review identifies evidence on the roles of neural compensation and cortical hyperexcitability in the emergence of visual hallucinations following visual deprivation. Despite methodological heterogeneity, local changes are observed alongside brain-wide alterations in cortico-cortical connectivity within and beyond visual cortical areas, particularly in attentional networks. Evidence of CBS-specific structural changes remains limited, with observed differences largely attributable to visual deprivation. The review also examines neuroimaging, case studies, and computational work highlighting the potential roles of biochemical changes, particularly associated with the GABAergic system and acetylcholine. Finally, the review proposes future avenues leveraging advances in neuroimaging and deep neural network modelling to address gaps in the understanding of mechanisms and dynamics underlying hallucinatory and non-hallucinatory states in CBS patients.

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Introduction

Charles Bonnet Syndrome (CBS) describes the experience of visual hallucinations in patients with visual impairments who are otherwise cognitively and neurologically healthy (Eperjesi & Akbarali, 2004; Kester, 2009). These hallucinations are not triggered by visual stimulation. The exact mechanism remains unclear, although evidence suggests CBS develops after the onset of visual impairments (Adachi, 1996; Jones et al., 2025; Niazi et al., 2020; Peters et al., 2022; Subhi et al., 2021; Teunisse et al., 1996), making it a secondary condition to the visual impairment (Forte et al., 2025; Menon et al., 2003; Teunisse et al., 1996).

Unlike visual hallucinations associated with psychiatric conditions, the content of hallucinations itself does not often cause distress (Cox & Ffytche, 2014; Khan et al., 2008; Teunisse et al., 1996; Vukicevic & Fitzmaurice, 2008). The content of CBS visual hallucinations greatly varies, but is often categorised as either simple or complex (Menon et al., 2003). Simple visual hallucinations range from flashes of light, shapes, or color blobs, to geometric patterns (Ffytche et al., 1998; Lance, 1976; Scott et

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al., 2001; Vukicevic & Fitzmaurice, 2008), while complex form hallucinations commonly include people, faces (Brown & Murphy, 1992; Schultz et al., 1996; Teunisse et al., 1996), objects, scenes and buildings (Christoph et al., 2024; Jones et al., 2021; Kester, 2009; Schultz et al., 1996; Teunisse et al., 1996). The appearance of these hallucinations varies in perceived size—from miniaturised and normal-sized to larger-than-life (Menon et al., 2003)—and may include movement (Schultz et al., 1996). The content of the hallucinations also varies within individuals. In some cases, simple hallucinations can evolve into a more complex form (Menon et al., 2003; Teunisse et al., 1996). Unlike hallucinations caused by psychedelics, CBS hallucinations are not often seeded or developed from the current visual inputs (Preller & Vollenweider, 2018; Suzuki et al., 2017). They also do not always reflect a person's previous experiences or familiar content (Menon et al., 2003).

Individuals with low vision experiencing poor visual acuity and visual field loss (Forte et al., 2025; Potts, 2019), such as those with age-related macular degeneration and glaucoma, have a higher risk of developing CBS (Dhooge et al., 2023; Niazi et al., 2020; Peters et al., 2022). Among these patients, the estimated prevalence ranges from one to two in ten patients, likely affecting over 20 million people worldwide (Abbott et al., 2007; Christoph et al., 2025; Niazi et al., 2020; Subhi et al., 2021, 2022; Teunisse et al., 1995). CBS is not restricted to damage at the retinal level and can occur after lesions along the visual pathway (Freiman et al., 2004; Tobe, 2014), including occipital damage caused by stroke or other pathologies leading to hemianopia if unilateral, or cortical blindness if bilateral (Kölmel, 1985; Martínez-Sánchez & Bolívar, 2023; Symonds & Mackenzie, 1957; Voit et al., 2021). The visual field location of visual hallucinations is typically confined to degraded or damaged regions of the visual field (Lance, 1976; Martinelli et al., 2020; Menon et al., 2003). The duration of hallucinatory episodes varies among individuals; some experience permanent hallucinations, others have transient but recurring episodes. These episodes may last only seconds or minutes (Cox & Ffytche, 2014; Menon et al., 2003). Studies suggest that enhancing visual function, such as visual acuity, through spectacles or surgery may help reduce or eliminate hallucinations (Eperjesi & Akbarali, 2004; Voit et al., 2021; Yacoub & Ferrucci, 2011). Additional clinical observations (by one of the authors, GTP) further support the role of residual visual input in modulating hallucinatory activity. In cases of dual pathology, improvements to visual function can reduce or eliminated hallucinations. For example, in a patient with both glaucoma and cataract, restoration of visual acuity following cataract surgery led to remission of hallucinations. Similarly, in a glaucoma patient treated with topical pilocarpine, switching to medication that did not induce miosis relieved hallucinatory symptoms.

Monocular visual loss rarely produces hallucinations, and those that do occur are typically transient, presumably due to the stabilising influence of the preserved visual input. Consistent with this, a patient with sudden monocular near-blindness due to central retinal artery occlusion reported that hallucinations ceased after patching the damaged eye, thereby normalising the visual experience (Toosy et al., 2006). Hallucinations associated with hemianopia also differ from those seen in more generalised field loss or complete blindness (Lance, 1976). In hemianopia, they are usually brief and may disappear when the patient makes a saccade to inspect thes hallucinated region (Menon et al., 2003; Schultz & Melzack, 1991; Teunisse et al., 1996; Vaphiades et al., 1996). This pattern ssuggests that intact visual input from the unaffected eye or hemifield may help normalise activity in the visual cortex.

Studying Charles Bonnet Syndrome presents significant challenges due to the variability of patient experiences. The visual hallucinations associated with CBS can resemble those linked to psychiatric disorders and dementia, making accurate diagnosis and understanding of its true cause more difficult. These symptomatic similarities may also lead to social stigma (Scott et al., 2001; Teunisse et al., 1996; Unsalver et al., 2007), discouraging individuals from sharing their experiences. As a result, our knowledge of the neurobiological mechanisms behind CBS remains limited. In this review, we explore current evidence on the neurological underpinnings of CBS.

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Deafferentation and Hyperexcitability

One of the earliest explanations of CBS pathogenesis drew a parallel between visual hallucinations and phantom limb pain (Flor et al., 2006; Kuffler, 2018; Subedi & Grossberg, 2011), suggesting that both phenomena stem from the brain's response to sensory deprivation, though in different sensory areas (Vernon et al., 1961; Yuksel et al., 2004). This hypothesis, known as the perceptual release phenomenon (Schwartz & Vahgei, 1998), proposed that visual stimuli normally inhibit spontaneous cortical activity. When sensory input is lost, this suppression stops, leading to increased neuronal activity and causing the visual hallucinations (Cogan, 1973; McNamara et al., 1982). This theory also implicated disruptions of the brain's neurochemical regulation in the release phenomenon (Manford, 1998; Vukicevic & Fitzmaurice, 2008).

The theory of perceptual release was later reframed in terms of deafferentation (Burke, 2002). Deafferentation refers to the denervation of a population of neurons after sensory deprivation. Burke (2002) proposed that while some denervated neurons may deteriorate, others remain partially connected to nearby neurons. Without normal visual input, the remaining activity, no longer suppressed by incoming signals, results in disinhibition and overexcitation. This residual activity is likely essential, as CBS is generally absent in those born blind, potentially due to cortical reorganisation towards other sensory modalities (Menon et al., 2003).

Early neuroimaging studies also provided evidence of cortical overactivation linked to hallucinatory episodes in CBS. Functional magnetic resonance imaging (fMRI) showed an increased blood oxygen level-dependent (BOLD) response in the ventral visual cortex both before and during hallucinations (Ffytche et al., 1998). Complementary findings from single-photon emission computed tomography (SPECT) indicated cerebral hyperperfusion during hallucinations in CBS patients (Adachi, 1996). However, hyperperfusion was instead observed in the lateral temporal cortex, striatum, and thalamus (Adachi, 1996; Kazui et al., 2009). Collectively, these studies suggest increased neuronal activity during hallucinatory states. However, a key limitation of this early research was the absence of eye disease control comparisons (Adachi et al., 2000; Ffytche et al., 1998), making it difficult to determine whether some neural changes were specific to CBS or were instead a general consequence of visual impairment.

Comparative studies involving CBS patients and individuals with similar eye diseases but without hallucinations (hereafter referred to as eye disease controls) support the idea that deafferentation and cortical hyperexcitability underlie CBS. Converging evidence from fMRI studies shows a reduced cortical response to visual stimulation in CBS patients compared to eye disease controls, especially in the primary visual cortex and extrastriate areas such as V2 (daSilva Morgan et al., 2025; Ffytche et al., 1998). The decrease in cortical response during visual stimulation is thought to reflect higher levels of spontaneous activity at rest, such that incoming visual input causes a smaller relative increase in activation. In other words, the decreased stimulus-evoked activity may result from an already elevated baseline state in the visual cortex (Ffytche et al., 1998). Despite consistent results, it should be noted that while comparison groups were age- and visual acuity-matched, they were not matched for the extent and type of visual field defects. The visual stimuli used also differed (dynamic noise vs. checkerboard patterns), though stimuli were consistently presented within the central visual field region due to scanner bore constraints.

Interestingly, similar visual hallucinations have been observed in studies of prolonged blindfolding (Heron et al., 1956; Sireteanu et al., 2008). Despite having normal cognitive and visual function, blindfolded individuals reported simple visual hallucinations such as light spots and geometric patterns, which gradually became more complex after days of visual deprivation. In one of the studies, fMRI scans showed activation in the extrastriate regions during hallucinatory episodes (Sireteanu et al., 2008).

Additional neurophysiological evidence for hyperexcitability in CBS comes from a study using steady-state visually evoked potentials (SSVEPs) (Painter et al., 2018). Patients with age-related macular degeneration who experienced visual hallucinations showed increased SSVEP amplitude in response to peripheral visual stimulation compared to both non-hallucinating patients and visually

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healthy participants. Source localisation attributed this cortical hyperexcitability to early visual areas, mainly V2, and to a lesser degree, the primary visual cortex. By frequency-tagging the visual stimulation, the study isolated stimulus-driven hyperexcitability from endogenous baseline activity. This demonstrates that CBS also involves sensory-evoked hyperexcitability, distinct from changes to baseline activity reported in earlier neuroimaging studies. Moreover, these measurements were also taken outside of hallucinatory episodes, indicating that the observed hyperexcitability is not simply a result of active hallucinations but reflects inherent changes in cortical responsivity.

If hyperexcitability underlies CBS, inhibiting hyperexcited regions should conversely reduce the symptoms experienced. Indeed, repetitive inhibitory stimulation with transcranial direct current stimulation (tDCS) to the occipital region (Cathode Oz) has been shown to lower the frequency of visual hallucinations in CBS patients (daSilva Morgan et al., 2022). Although the inhibitory stimulation was not directly applied to regions typically associated with complex hallucinations, such as the ventral temporal cortex, inhibiting earlier regions, like V1 and V2, might indirectly attenuate hallucinations by decreasing feedforward excitatory signals to higher-level visual regions.

A study using transcranial magnetic stimulation (TMS) found a non-significant reduction in phosphene threshold among CBS patients compared to age-matched, eye disease controls (daSilva Morgan et al., 2025). Phosphenes are the illusory perceptions of light that can typically be induced by TMS. In TMS research, the minimum stimulation intensity needed to induce phosphenes—known as the phosphene threshold—is commonly used as a measure of cortical hyperexcitability (Gerwig et al., 2003; Mazzi et al., 2017). A lower threshold would thus indicate increased susceptibility to spontaneous visual activity. A previous TMS study indicated that even short periods of light deprivation can raise cortical excitability (Boroojerdi et al., 2000). Because all participants have visual impairments, this could account for the non-significant differences between CBS patients and the eye disease control group. However, the study also found a negative correlation between phosphene threshold and reported hallucination severity (daSilva Morgan et al., 2025), indicating that individuals with more severe visual hallucinations tend to have higher cortical excitability. This pattern is similar to prior findings in Lewy body dementia patients who experience hallucinations (Taylor et al., 2011).

Region-Specific Overactivation and Visual Hallucinatory Content

Several studies have noted interesting links between the phenomenological content of visual hallucinations in CBS patients and the brain's functional specialisation (Adachi et al., 2000; Ffytche et al., 1998; Martinelli et al., 2020; Santhouse et al., 2000). Ffytche et al. (1998) reported activity in the posterior fusiform gyrus (V4), a region involved in colour perception and constancy (Heywood et al., 1992; Pasupathy et al., 2020; Roe et al., 2012), in patients who experienced colour hallucinations. Similarly, the study reported activity in the mid-fusiform area, which is specialised for face and object recognition (Peelen & Downing, 2005; Pourtois et al., 2009; Weiner et al., 2014), in patients who hallucinated faces. Clustering analysis of CBS patients' reported hallucinatory content identified three main categories: scenes and figures, disembodied body parts, and palinopsia (recurrence of an image that has just been seen) (Santhouse et al., 2000). These categories were suggested to correspond with specific cortical regions along the visual pathway, such as the ventral temporal lobe (objects and landscapes), superior temporal sulcus (face processing), and visual parietal lobe (visual stability). This pattern indicates that hallucinations may arise from deafferentation and subsequently hyperexcitability in these specialised visual areas. Additional support for this notion comes from a lesion study. Martinelli et al. (2020) reported that visual hallucinations in post-stroke hemianopic patients occurred only when lesions impacted the primary visual cortex but spared extrastriate and occipitotemporal areas. This suggests that visual hallucinations may result from disruptions to cortico-cortical input between the primary visual cortex and subsequent areas in the visual pathway.

Further supporting evidence for the generation of hallucinations in the intact extrastriate cortex comes from interactions with the visuomotor system. One example is the disappearance of hallucinations with eye movements in hemianopic patients (Menon et al., 2003; Schultz & Melzack,

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1991; Teunisse et al., 1996; Vaphiades et al., 1996) mentioned previously. Another example is two patients who developed a persistent "landscape" type of visual hallucination occupying the entire visual field. These patients also developed periodic alternating nystagmus, and the hallucinations rotated following the direction and velocity of the slow phase of the nystagmus (Minakaran et al., 2019).

The Brain's Response to Visual Deprivation

While it is well-established that CBS hallucinations are associated with both deafferentation of the visual pathway and cortical hyperexcitability, the precise mechanism connecting these phenomena remains an open question. The increase in cortical excitability in the visual cortex can be explained in a few ways. This was initially characterised biochemically by two mechanisms: the increased neurotransmitter release from presynaptic neurons, driven by an increase in the size and number of vesicles, and heightened postsynaptic response following prolonged inactivity. Both changes align with the elevated spontaneous cortical activity observed in CBS patients.

Reichart et al. (2013) computationally described these changes as a homeostatic process, whereby the brain increases its activity in an attempt to compensate for degraded sensory input. The reduction in signals received from cortical neurons due to the lack of visual input encourages these neurons to stabilise their firing rate around the point at which they normally operate. This model offers a computational explanation of how deafferentation can lead to sustained hyperexcitability, providing a mechanistic understanding of the relationship between visual loss and the emergence of hallucinations in CBS.

The Role of Wider Brain Networks

Earlier findings suggested that broader brain networks, beyond the occipital visual cortex, may contribute to the generation of visual hallucinations (Adachi et al., 2000, p. 200). This hypothesis has since been supported by evidence implicating functional alterations in several brain networks, particularly the default mode network, the dorsal attention network, and the ventral attention network.

Indeed, several studies have demonstrated distributed patterns of activity associated with visual hallucinations in CBS (Ffytche, 2008; Hanoglu et al., 2019). Hallucinations induced by a series of bright light flashes (known as photic stimulation) led to changes in connectivity between the lateral geniculate nucleus (LGN) and cortical visual areas, observed using both EEG and fMRI measures (Ffytche, 2008) during hallucinations. Similarly, Hanoglu et al. (2019) reported that CBS patients with clinical eye diseases exhibited widespread hyper- and hypoactivity in the pons, cerebellum, frontal and parietal cortices, in addition to the visual cortex, when compared to eye-disease controls (Hanoglu et al., 2019, p. 20). Although these studies captured changes at different periods (during hallucinatory episodes, Ffytche, 2008, and at rest, Hanoglu et al., 2019), both suggest changes occurring in neural circuitry beyond ventral visual areas.

Consistent with these observations, resting-state fMRI data revealed both increased and decreased functional connectivity across multiple cortical networks, including the salience network, default mode network, and visual network (Kinakool et al., 2024). However, these results compared CBS patients with healthy age-matched controls rather than eye-disease controls. That said, a comparison between CBS patients and subjects with acquired blindness (identified as 'late blind' in Martial et al., 2019) still found an increase in brain connectivity between the precuneus and V2 (Martial et al., 2019), a common candidate area exhibiting cortical hyperexcitability in CBS patients (daSilva Morgan et al., 2025; Ffytche et al., 1998; Painter et al., 2018).

Differences in brain oscillatory activity have also been reported in CBS patients, especially those with complex visual hallucinations. Compared to eye-disease controls, CBS patients showed a reduction in occipital alpha power and an increase in occipital theta power (daSilva Morgan et al., 2025; Hanoglu et al., 2019). One interpretation of reduced alpha activity draws on its established role

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in inhibitory control—the suppression of distracting or irrelevant information—within the ventral visual cortex (Pfurtscheller, 2001; Thut et al., 2006; Zumer et al., 2014). The reduction of alpha power may therefore reflect diminished inhibition, contributing to the cortical hyperexcitability observed in CBS patients. From a different perspective, changes in alpha and theta oscillations can be linked to alterations in the attentional network (Fan et al., 2007; Keller et al., 2017).

Taken together, converging findings suggest changes in the brain's intracortical connectivity. Indeed, studies suggest that visual hallucinations in CBS and other conditions, such as Parkinson's disease and Lewy body dementia, are linked to dysfunction within and between attention-related networks (Graham et al., 2011, p. 201; Onofrj et al., 2013; Shine et al., 2014). According to the model of network dysfunction, visual hallucinations result from dysregulation between the default mode network, ventral attention network, and dorsal attention network (Collerton et al., 2023; Shine et al., 2014). In healthy individuals, the dorsal attention network is primarily involved in the top-down allocation of attention and short-term memory. It interacts with the ventral attentional network, which mediates bottom-up processing of salient sensory inputs, and with the default mode network, involved in self-referential thought and imagery. The dysregulation of connections among these networks prevents the dorsal attention network from controlling the abnormal connectivity between the ventral attentional network and the default mode network, leading to the emergence of false images and ambiguous percepts (Collerton et al., 2023; Shine et al., 2014).

Although various theories have attempted to explain hallucinations in CBS, from regional deafferentation to large-scale network dysfunction, a recent unifying framework offers an integrative perspective that recognises possible contributions from different models of visual hallucinations (Collerton et al., 2023). The framework suggests that in CBS deafferentation may reduce the quality of sensory input, causing increased reliance on internally generated predictions. When attentional control mechanisms fail to regulate the balance between top-down and bottom-up processing, hallucinations may arise as misinterpretations of spontaneous neural activity. The content of visual hallucinations may vary depending on the cortical region in which they occur. It is worth noting that while the framework recognises deafferentation as a primary contributor to visual hallucinations, it does not explicitly address the potential role of the subsequent cortical hyperexcitability. Nonetheless, it is plausible that the deafferented cortex becomes hyperexcitable, thereby increasing spontaneous neural activity. This generates spurious signals that subsequently produce non-veridical perceptions.

Structural Changes in CBS

There is limited evidence of structural changes in CBS patients. A single CBS case reported by Martial et al. (2019) showed reduced cortical thickness in associative and multimodal cortical regions, including the fusiform gyrus, medial temporal areas, and frontal cortices. These differences were observed between a CBS patient and individuals with acquired blindness. Differences in these areas, as well as in the primary visual cortex, were also noted when compared to healthy controls. The author highlighted that these findings were consistent with regions exhibiting atrophy identified earlier in SPECT studies (Adachi et al., 2000; Kazui et al., 2009). However, they are more likely related to visual loss itself rather than CBS specifically. Supporting this, (Firbank et al., 2022) report no structural differences between CBS patients and controls with eye disease. Conversely, alterations to occipital grey matter and widespread white matter changes were found when comparing CBS patients with healthy controls. This again suggests that the changes observed may reflect deafferentation following central vision loss, which has cortical representation in this region, rather than CBS-specific pathology. Indeed, such structural differences have previously been linked to visual impairments (Beer et al., 2020; Boucard et al., 2009; Nuzzi et al., 2020; Plank et al., 2011).

Outside the visual cortex, (Lawn & Ffytche, 2021) identified grey matter reductions in the cerebellum among individuals with CBS compared to eye-disease controls. Reductions were observed bilaterally in cerebellar modules VII, VIII, and IX. Interestingly, these lobules have previously been shown to play a role in the dorsal attentional network (Brissenden et al., 2016; Lawn

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& Ffytche, 2021; Stephen et al., 2018). This finding complements neurophysiological evidence indicating broader network involvement in the development of visual hallucinations in CBS. However, similar differences have also been reported in Parkinson's disease patients who experience visual hallucinations, implying that alterations in the dorsal attention network may be a general marker of visual hallucinations rather than a CBS-specific feature (Lawn & Ffytche, 2021).

Biochemical Changes

A seminal hypothesis by Burke (2002) proposed that biochemical changes following deafferentation may underlie visual hallucinations in CBS. Specifically, Burke suggested an increase in excitatory glutamatergic NMDA response and a decrease in inhibitory GABAergic response surrounding the deafferented cells. Supporting this hypothesis, many clinical case reports have documented the potential effectiveness of GABAergic medications such as gabapentin and pregabalin– traditionally used for neuropathic pain– in alleviating visual hallucinations in CBS (Cinar et al., 2011; Grüter et al., 2016; Paulig & Mentrup, 2001; Sawant & Bokdawala, 2013). These medications modulate the brain's GABAergic system by reducing activation by increasing inhibition, which lends further support to the notion that hyperexcitability may be a core feature of CBS neuropathogenesis.

While these observations hint at a potential role of GABAergic neurotransmission, it is important to note that these findings are based on case reports and cannot establish causation. When GABA and glutamate concentrations were compared between CBS patients and eye-disease controls using magnetic resonance spectroscopy, no significant differences were found, either in the early visual cortex or lateral occipital cortex (Bridge et al., 2024; Kinakool et al., 2024). Instead, the only difference found between the groups was a slow buildup of activity across the visual cortex prior to the hallucinatory episode, which is in line with early studies (Adachi et al., 2000; Ffytche, 2008). However, there may be neurotransmitter differences at a finer temporal or spatial scale than these studies could detect. Given that the measurements were averaged across time, Bridge et al. (2024) noted that changes to the neurotransmitters could have gone undetected if they were time-locked to a specific period, preceding or during visual hallucinations. Additionally, the spatial resolution of magnetic resonance spectroscopy is limited to centimetre-scale measurements, hindering the detection of tightly cortically localised differences between groups.

In addition to fast-acting neurotransmitters, slower-acting neuromodulators have also been implicated in CBS. There have been reports suggesting that selective serotonin reuptake inhibitors (SSRIs) are effective in treating CBS symptoms. While this suggests potential involvement of the serotonergic system (Jackson et al., 2008; Lang et al., 2007; Unsalver et al., 2007), no studies to date have systematically investigated serotonergic differences between CBS patients and controls. Acetylcholine has also been frequently discussed as a possible neuromodulator mediating the emergence of visual hallucinations in CBS. Typically, acetylcholine plays a role in memory, learning, attention and arousal (Mather, 2020; Perry et al., 1999). However, it has also been implicated in the development of visual hallucinations in many conditions, including drug-induced hallucinations, migraine aura, Parkinson's disease, and Lewy body dementia (Manford, 1998). Visual hallucinations in Lewy body dementia have been attributed to the imbalance between serotonin and acetylcholine, with an increase of serotonin and a marked reduction in the synthesis of acetylcholine (Cheng et al., 1991; Perry et al., 1990). Interestingly, reports have suggested fatigue and the state of drowsiness as risk factors for the emergence of visual hallucinations in CBS (Manford, 1998; Menon et al., 2003; Teunisse et al., 1998), with hallucinations more likely to occur during the state of low arousal, which is associated with low acetylcholine levels.

Furthermore, a computational simulation of acetylcholine in neural networks has suggested its contribution towards balancing bottom-up and top-down sensory signals (Reichert et al., 2013). When acetylcholine deficiency was simulated in the model, it led to an over-influence of top-down information, leading to visual hallucinations (Reichert et al., 2013). Fluctuations in acetylcholine levels within individuals over time may account for variability in the timing and onset of visual

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hallucinations in CBS. The link between acetylcholine and visual hallucinations in CBS also corresponds well with pharmacological findings, since anticholinergic medications frequently induce visual hallucinations (Das et al., 2020; Powell et al., 2020; Weil & Lees, 2021), whereas acetylcholinesterase inhibitors mitigate hallucinations in those with Parkinson's disease (Burn et al., 2006). In cases with CBS, acetylcholinesterase inhibitors have indeed been reported to alleviate visual hallucinations (Nguyen et al., 2013; Ukai et al., 2004).

Future Avenues in Neuroimaging

While accumulating neuroimaging evidence points to potential differences in cortical activity associated with CBS, there are many caveats that need to be considered. First, there is inconsistent use of control groups. Some studies use healthy controls, whereas others use eye-disease controls (daSilva Morgan et al., 2025; Ffytche et al., 1998; Painter et al., 2018). Second, there is variation in the use of regions of interest, with some confining their investigations to the visual cortices and others extending beyond. Third, there are differences in the observation windows—that is, whether the study examines group differences at rest, during visual stimulation, or during hallucinatory episodes. While there are studies that have examined the former two (Bridge et al., 2024; Hanoglu et al., 2019; Kinakool et al., 2024; Painter et al., 2018), there is only one case study that has explored within-individual differences in cortical activity by comparing periods of hallucination and remission. Although it can be difficult to time neuroimaging scans with unpredictable episodes of visual hallucinations, capturing transitions into and out of hallucination would help us understand the brain dynamics underlying the emergence of CBS.

Beyond comparing BOLD responses, brain dynamics in CBS could be examined through the lens of topographic maps. Neuroimaging methods, such as population receptive field mapping (pRF) (Dumoulin & Wandell, 2008), have previously been used to study cortical features of scotomas (Hummer et al., 2018) and visual field defects (Prabhakaran et al., 2021). They could similarly be employed to differentiate voxels encoding intact parts of the visual field from those receiving reduced or absent input. It would be interesting to explore this distinction during and outside the period of hallucinations. Typically, we would not expect blind-field areas to generate any neural responses, however, in CBS patients, responses might occur within these regions, particularly during visual hallucinations. Investigating where this blind-field activity takes place and relating it to the content of visual hallucinations could yield valuable insights.

While studies have previously examined resting state connectivity of those with CBS and controls (Bridge et al., 2024; Ffytche et al., 1998; Kinakool et al., 2024), and BOLD activation during hallucinatory episodes (Adachi et al., 2000; Ffytche et al., 1998; Hahamy et al., 2021; Kazui et al., 2009), these aspects have yet to be explored concurrently. Investigating changes in functional connectivity during visual hallucinations would provide insight into the dynamics and interactions between cortical areas. Techniques such as connective field analysis (Haak et al., 2013; Tangtartharakul et al., 2023) may assist in delineating functional connectivity of the blindfield areas, if they exist, to higher visual regions. Another recent method, laminar fMRI (Demirayak et al., 2022; Lawrence et al., 2019), is able to differentiate cortical activity driven by feedforward and feedback signals by measuring activity in specific cortical layers. Previous studies demonstrated the role of feedback connections in driving brain responses in parts of the cortex corresponding to the occluded visual field (Bennett et al., 2025; Morgan et al., 2016, 2019). Informed by these findings, laminar fMRI could potentially be applied to CBS patients to examine whether responses in cortical areas deprived of visual input are instead driven by other, higher, and intact visual areas.

Future Avenues in Computational Methods

Reichert et al. (2013) modelled the cortical mechanisms underlying Charles Bonnet Syndrome (CBS) using an early deep generative neural network known as a Deep Boltzmann Machine (DBM). The authors aimed to explore how cortical networks could produce such internally driven activity,

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which results in visual hallucinations. DBMs are hierarchical, probabilistic neural networks composed of multiple layers of bidirectionally connected stochastic units. These models learn to represent their training data by capturing its underlying probability distribution and can produce new samples by drawing from this distribution. Using this model, the authors simulated CBS by introducing a compensatory mechanism mimicking cortical homeostasis. That is, when the model received degraded visual input, it increased the gain of internal neuronal activity to match the average activation observed during training. This led to the spontaneous generation of internally driven visual patterns, analogous to hallucinations in CBS. The study further simulated the interplay between the compensatory mechanism and acetylcholine – a neurotransmitter hypothesised to modulate the balance between feedforward and feedback connections. Their model shows that less homeostatic adaptation was required for the emergence of hallucinations with decreased levels of acetylcholine. Conversely, hallucinations did not occur with increased levels of acetylcholine.

Modern deep neural network models have become widely used in studies of visual cortical processes (Doerig et al., 2023; Shah et al., 2024; Tuladhar et al., 2021) and in-silico modelling of neurodegenerative diseases (Moore et al., 2023, 2025; Shah et al., 2024; Tuladhar et al., 2021). They can offer new ways to advance simulations of CBS. Modern architectures, such as variational autoencoders, share similarities with DBMs but are capable of learning far more sophisticated visual features. Variational autoencoders (VAEs) are unsupervised generative models that encode sensory input into a probabilistic embedding space and can decode points in that space back into generated images. Similar to DBMs, variational autoencoders learn to approximate the underlying distribution of their training examples (Kingma & Welling, 2013). However, a major distinction of modern architectures, such as the variational autoencoder, is the use of convolutional neural networks as their backbone (Dong et al., 2017; Venkataraman, 2022). Such backbones better capture the biological processing of visual input, with receptive fields learning diverse spatially localised features of images (Erhan et al., 2009; Krizhevsky et al., 2012; Zeiler & Fergus, 2014). Models with a convolutional backbone inherently learn hierarchical representations, which can potentially be utilised to explore the correspondence between region-specific neural changes and the content of visual hallucinations. Furthermore, there are many variants of convolutional neural networks, some of which improve biological plausibility, for instance, recurrent models (Kietzmann et al., 2019; Spoerer et al., 2017, 2020). Another advantage of using modern deep neural networks is their scalability. The models can be trained on more naturalistic stimuli (i.e., higher-resolution colour images), thereby better capturing human visual experiences and enabling more realistic simulation of hallucination content. Overall, modern deep neural networks enable systematic manipulation of variables such as the damage site, severity, neural activation levels, and the directionality of neural connections – all of which may help explain the heterogeneity in CBS visual hallucinations.

Outstanding Questions

What neurobiological processes activate neuronal compensation post-deafferentation?

What are the links between region-level hyperexcitability and network-level connectivity changes, and are they underlaid by cascades of biochemical changes?

What underpins individual susceptibility to developing Charles Bonnet Syndrome?

Are hallucinations observed in CBS semiologically the same as those observed in sensory deprivation studies?

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If hyperexcitability and overactivity result from neural compensation to reduced sensory input, are sudden losses of visual input more likely to induce CBS due to phasic as opposed to gradual adaptation (Schultz & Melzack, 1991; Schwartz & Vahgei, 1998)?

Could there be a relationship between visual mental imagery (which also has high individual variability and involves top-down visual activation, (Cui et al., 2007; Dijkstra et al., 2019; Stokes et al., 2009)) and the propensity to develop CBS hallucinations?

Conclusion

Charles Bonnet Syndrome is a complex condition that poses challenges for both patients and researchers. The similarities in phenomenology between CBS and other hallucinatory conditions, such as psychosis and neurodegenerative diseases, can make it difficult for patients to disclose their experiences and for researchers to disentangle the mechanisms behind CBS.

Recent advances in neuroimaging have enriched the growing body of work exploring the neurobiological foundations of CBS, providing functional, structural, and biochemical insights. Although many neural features identified are not exclusive to CBS, they offer valuable understanding of key mechanisms in its development. Converging evidence suggests that cortical hyperexcitability, network dysfunction, and biochemical alterations contribute to the emergence of visual hallucinations following deprivation of visual input. Specifically, deafferentation may cause spontaneous overactivity in visual cortical areas, while larger brain networks fail to suppress or regulate this abnormal activity, allowing non-veridical perceptions to occur. At the neurophysiological level, these dysfunctions may be influenced by imbalances in various neurochemical levels.

While these findings suggest potential neural markers linked to CBS, it remains unclear why only some individuals develop the condition despite experiencing similar levels of visual impairment. This individual variability may stem from multifactorial influences, including genetic predisposition and age-related factors. While some conclusions and comparisons in earlier research were hindered by small sample sizes and inconsistent methodologies, recent studies have begun to address these gaps. Advances in neuroimaging now provide powerful tools to investigate the spatiotemporal dynamics of CBS more precisely.

Although many aspects of CBS are still unresolved, ongoing research and methodological innovation continue to enhance our understanding of this frequently under-recognised condition. With the integration of novel imaging and computational approaches, we are moving closer to identifying the key mechanisms responsible for visual hallucinations in CBS, ultimately leading to improved clinical recognition and treatment for those affected.

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