Deafferentation and Network Dysregulation Hypotheses in Charles Bonnet Syndrome (CBS) Mechanisms

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Abstract:
Charles Bonnet Syndrome (CBS) is a rare condition characterized by complex, persistent visual hallucinations (VH) in patients with normal cognitive function and vision impairment. At present, the cause of CBS remains unclear; there is evidence that deafferentation, hallucinations caused by a deprivation of visual stimuli, which propagates neural hyperactivity through cortical excitability, is considered a putative mechanism by which CBS arises. However, emerging research posits that the condition stems from changes in sensory and control neural networks. Studies have shown reorganization of functional connectivity among different systems, including the default mode network (DMN), salience network (SN), and visual network (VN) in CBS patients, modeling alterations in brain activity. By comparing various neural network models, this review evaluates the extent to which different hypotheses drive visual hallucinations in CBS patients. Therefore, we propose a multi-stage process which systematically combines the two hypotheses in order to clarify the underlying mechanisms behind CBS.

Introduction:

Charles Bonnet Syndrome (CBS) is a neurological condition in which patients with severe vision loss experience vivid, chronic visual hallucinations (VH), despite being otherwise mentally healthy (Russell 2014). VH can be symptomatologically categorized as simple or complex, ranging from flashes of light and geometric shapes to real-life figures and scenes (Martial 2019, Vacchiano 2019). Unlike hallucinations from psychiatric diseases such as Parkinson's, schizophrenia, and Alzheimer's, of whose patients undergo cerebral atrophy or physical injury in the brain, the ones present in CBS primarily occur in individuals with severe vision degeneration, not neural (Kinakool 2015). Therefore, CBS stands as a uniquely neurobiological case of VH, not associated with psychiatric illness or cognitive impairment. CBS appears in nearly 20% of those with a history of ocular pathology, including macular degeneration, cataracts, and glaucoma, and affects 47 million people worldwide (Kelson 2022, Christoph 2024). Even so, it goes unrecognized by more than half of clinicians who treat patients with this condition and the underlying pathophysiology of CBS is largely understudied (Kelson 2022).

Currently, two major models are used to explain the basic mechanisms of CBS. The bottom-up visual network model attributes CBS to deafferentation, or the lack of sensory input to the brain. Without typical amounts of input, the cortex becomes hyperexcitable, resulting in excessive reactions to the small amounts of stimuli it receives from the optic nerve; these assumptions lead to the formation of hallucinations (Kumral 2015, Spitzber 2025). This hyperexcitability can be modeled by an imbalance between excitatory and inhibitory neurotransmitters, glutamate and γ-aminobutyric acid (GABA), respectively. Glutamatergic neurotransmitters increase the likelihood of neuronal firing, amplifying activity in neuronal pathways, whereas inhibitory neurotransmitters suppress signal firing to prevent overstimulation (Andersen 2023). When this balance shifts towards excitation, the visual cortex becomes more prone to releasing hallucinations. This phenomenon, termed "phantom vision", is analogous to the studied

"phantom limb", in which the mind reports feelings of pain despite lacking afferent stimulation from the nervous system (Strong 2019). Alternatively, the top-down high-order networks attribute the mechanism to dysfunction in wide-scale brain connectivity. The networks in particular are the salience network (SN), which prioritizes relevant information signals, and default mode network (DMN), which monitors internal signals and suppresses external sensory information (Mohan 2016, Schimmelpfennig 2023). This hypothesis claims that when higher-order networks fail, hallucinations generated by lower-order networks are permitted to be passed from subconsciousness to consciousness.

While the deafferentation model remains the most widely accepted explanation, the precise neurobiological systems that drive hallucination generation and complexity are still unclear. No existing study provides a comprehensive understanding of which mechanism serves as the primary driver for CBS hallucinations, and functional magnetic resonance imaging (fMRI) studies have yielded inconsistent results regarding whether VH arise from visual networks or higher-order neural networks. Therefore, by synthesizing findings from multimodal neuroimaging, this review aims to clarify whether CBS hallucinations are driven primarily by hyperactivity in visual areas or by contributions from higher-order brain networks.

Methods:
We conducted a systematic search using PubMed and Google Scholar, employing several keywords and in combination, including Charles Bonnet Syndrome, visual network, deafferentation, default mode network, functional connectivity, fMRI. We included all studies published in the English language and within the last fifteen years that consisted of human subjects with Charles Bonnet syndrome diagnosis, tested a group of at least 1 CBS patient, used fMRI and/or other imaging to collect data, and examined at least 1 neural network. Our Exclusion criteria consisted of research published >15 years ago, non-human subjects, no neuroimaging, studies primarily focusing on other causes of hallucinations (like schizophrenia or Parkinson's).

We eventually included 18 studies from which 7 studies were prospective (all 7 of which were case controlled) and 11 studies were case studies.

Table 1: Synthesization of Quantitative Studies

Author/Year	N (CBS vs Control)	Methods	Networks Examined	Main Findings
daSilva Morgan et al. (2019)	19 CBS, 18 ED	fMRI, EEG, TMS	VN	CBS patients have less TBS thresholds, stronger in complex hallucinators, lower activity in CBS, multimodal
Martial et al. (2019)	1 CBS (RP), 14 ED, 26 healthy	fMRI	DMN, SN, VN	reorganization of brain processing in visual/salience networks, precuneus (DMN) showed higher connectivity in CBS

Hanoglu et al. (2022)	4 CBS, 3 ED, 15 healthy	fMRI	DMN	no difference in DMN (CBS+/CBS-), decreased connectivity in CBS- and controls vs CBS+
Kinakool et al. (2024)	1 CBS, 2+ healthy	fMRI	SN, DMN, VN	changes in connectivity (both increase + decrease) among the three networks (SN, DMN, VN)
Osorio et al. (2012)	1 CBS, 2+ ED, 2+ healthy	fMRI, VBM	VN, DMN	CBS has less cortical thickness than LB, CBS patients have abnormal visual network
Vacchiano et al. (2019)	1 CBS (Leber's Hereditary Optic Neuropathy)	fMRI	VN, auditory network	alterations occur in auditory and visual networks while resting, evidence of cross-modal plasticity in CBS
Kumral et al. (2015)	1 CBS (ischemic stroke, right occipital lobe infarction)	fMRI	VN	evidence of CBS coexisting with embolic event, supports dysregular neuronal network influence
Firbank et al. (2022)	16 CBS, 17 ED, 19 healthy	fMRI (DTI)	VN, DMN	reduced cortical thickness in occipital cortex, no significant change in white matter during VH, negative correlation between hippocampus volume and hallucination severity
Piarulli et al. (2021)	1 CBS (RP, no psychiatric history)	EEG, MRI	electrophysiological findings; no networks	reduced power in frontal areas, increased power in occipital/midline posterior regions
Spitzberg et al. (2025)	1 CBS (macular degeneration, glaucoma)	fMRI (TMS)	VN	reduced activity in lower parts of the visual network, hyperactive in higher parts. Used TMS to stimulate activity in lower parts.
Diana et al. (2021)	1 CBS (hyposmia, meningioma)	fMRI	VN, DMN	evidence of CBS coexisting with brain tumor, injury in brain
Bridge et al. (2024)	6 CBS, 6 non-CBS controls	fMRI, MRS	VN	no significant change in GABA+/glutamate concentrations in occipital

				regions in CBS compared to non-CBS
Kelson et al. (2022)	1 CBS (bilateral cataracts, mild cognitive impairment)	fMRI	VN	no evidence of acute infarction (physical injury in the brain) in occipital lobe to support development of CBS
Sawant and Bokdawala (2013)	1 CBS (metamorphopsia)	fMRI	VN	pregabalin, or reducing the activity of excitatory neurotransmitters, was effective in subduing complex VH
Cinar et al. (2011)	1 CBS (glaucoma, primary dementia)	fMRI, EEG	VN	pregabalin, or reducing the activity of excitatory neurotransmitters, gradually got rid of all VH
Kosman and Silbersweig (2017)	1 CBS (bilateral optic atrophy)	fMRI	DMN	VH is constructed under the influence of both excessive VN activity and lacking DMN activity
Jang et al. (2010)	1 CBS (glaucoma left eye)	fMRI, EEG, PET-CT	VN, DMN	burst-activity located in thalamocortical region, reduction of hypermetabolic region after treatment
Teruel et al. (2025)	1 CBS (diabetes-related blindness)	CT	did not specify	distinguished from psychiatric disorders, no evidence of organic degeneration.

Table 1: Data from 18 original studies were collected, in which at least 1 CBS patient was examined by neuroimaging. The amount *n* of CBS and control patients is specified, as well as the utilized modes of neuroimaging and examined neural networks (if any).

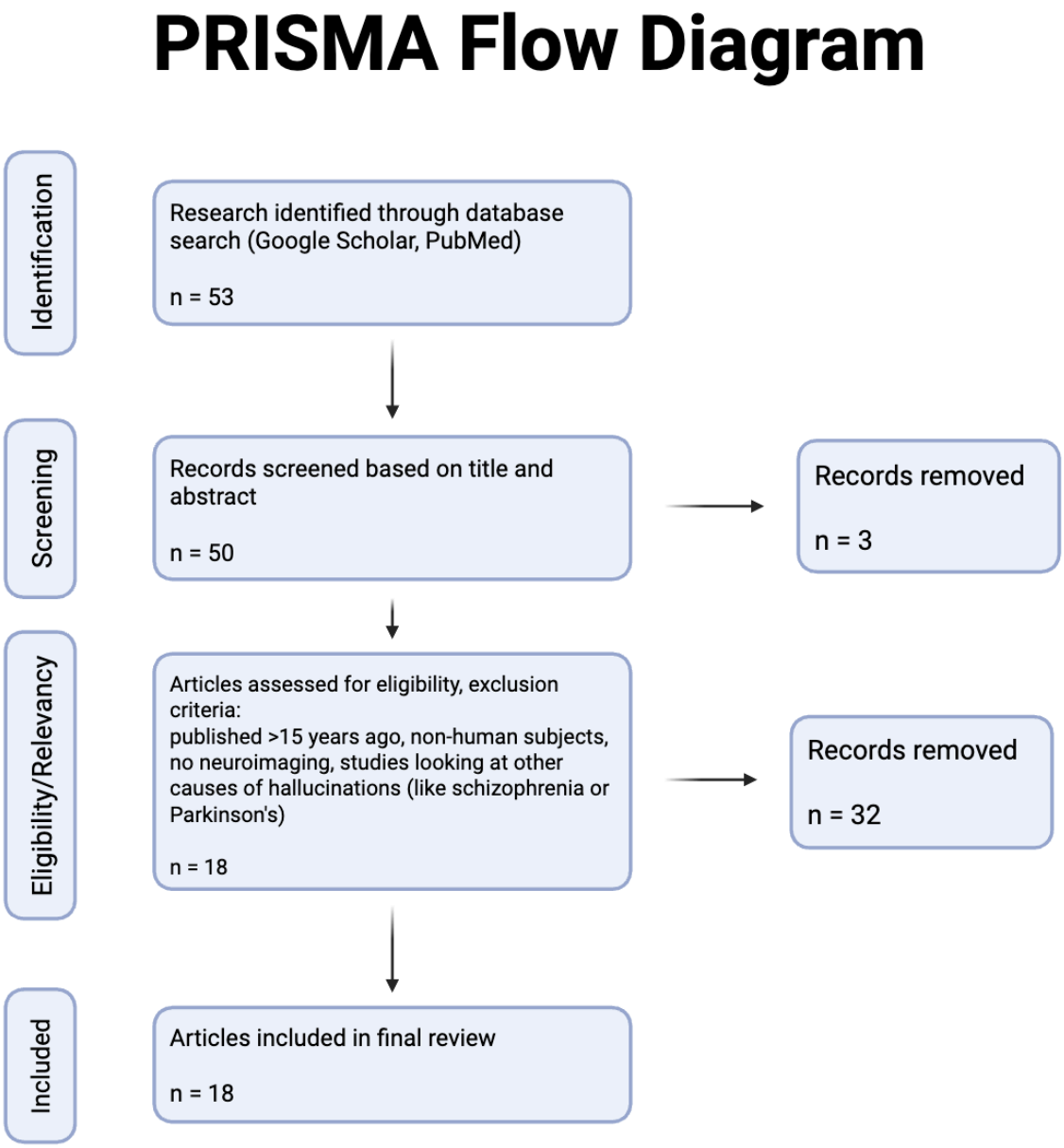


Figure 1: PRISMA flow diagram for inclusion/exclusion of studies. Figure 1 shows the selection and identification process of studies. The original database search resulted in 53 records from Google Scholar and PubMed. After records were screened based on relevancy, and if the title/abstract contained the keywords: deafferentation, default mode network, functional connectivity, fMRI, 50 records remain. Of these, 32 records were removed because they were published >15 years ago (n = 6), did not use neuroimaging (n = 24), or exclusively examined other causes of hallucinations (n = 2). 18 full-length papers are referenced in the table and left to be used in qualitative synthesis (see Table 1).

Results (see Table 1):

3.1.0: Bottom-up Mechanisms: The Deafferentation Hypothesis

The leading hypothesis for the bottom-up argument begins with deafferentation, the lack of sensory input. In healthy patients, vision and images are formed by a balance between external visual input from the VN and stored images from the DMN. However, since individuals with CBS are known to have moderate to severe vision loss, far less visual input is processed by the VN, thus causing an imbalance (Martial 2019). The VN is forced to compensate for the lack of external stimuli by firing off excessive amounts of signals, causing hyperexcitability in the visual cortex (Spitzberg 2025, Morgan 2025). This leads the visual cortex to generate “release hallucinations,” which are purely based on stored images and thus have no component of reality (Hamedani 2019). Several studies using resting-state fMRI (rs-fMRI) showed increased visual cortex activity in CBS patients compared to visually impaired control patients, both in the presence and absence of external visual stimuli (Martial 2019). Transient cortical activity, or spontaneous bursts, was also observed during VH, indicating breaches in inhibitory processes due to cortical excitation (Morgan 2025). A transition from tonic-firing, linear signal transmissions, to low-threshold burst-firing, nonlinear spikes in signal transmission, was also found in the thalamocortical region during a period of VH, indicating hyperexcitability between sensory and executive control regions (Jang 2011, Iavarone 2019, see Table 1). Furthermore, transcranial magnetic stimulation (TMS) observed cortical excitability when vision loss patients detected brief, phantom percepts of light (‘phosphenes’), indicating lowered phosphene thresholds (Spitzberg 2025). In other words, it takes less light to stimulate the visual cortex, indicating hyperexcitability in the occipital region.

3.1.1: Cortical thickness and Neuroplasticity

Structural MRI studies further support the deafferentation model by revealing variations in cortical thickness in brain regions associated with visual processing. To model brain tissue concentration in CBS patients, voxel-based morphometry (VBM) observed an average reduction of 0.9797mm in cortical thickness in visual processing regions, such as the fusiform gyrus, cuneus, and precalcarine cortex, when compared to non-hallucinating vision loss controls. (Martial 2019, see Figure 2b). These structural changes likely reflect compensatory neuroplasticity, adaptive reorganization in response to long-term visual deprivation. This reorganization may increase the likelihood of spontaneous firing in visual areas, predisposing these regions to hallucination generation (see Figure 2a). Beyond the occipital cortex, structural changes in memory related regions also correlate with hallucination severity. For example, decreased hippocampal volume, but not occipital volume, has been associated with more severe visual hallucinations in CBS (Firbank 2021). This places emphasis on the role which higher order associative systems, involved in memory and scene recognition, have in severe VH experiences.

3.1.2: Neurochemistry

The deafferentation model has been proposed to be supported by an imbalance between inhibitory (GABAergic) and excitatory (glutamatergic) neurochemicals in the occipital cortex of CBS patients. However, recent magnetic resonance spectroscopy (MRS) data show largely stable neurochemical levels when compared to vision loss controls, suggesting that neurochemical composition does not influence hallucination generation (Bridge 2024, Kinakool

2015). Multiple case reports found pregabalin, a drug which reduces the release of certain excitatory neurotransmitters, was effective in limiting complex VH experiences, such that VH were cleared completely within 2-15 days of pregabalin therapy (Cinar 2012, Sawant 2013). This suggests a change in the efficiency of inhibitory signaling, rather than a measurable change in chemical levels, is more closely related to the mechanism behind CBS. Visual deprivation induces homeostatic plasticity, in which neurons increase their responsiveness to compensate for reduced input. This process, often described as synaptic scaling, leads to functional disinhibition, where inhibitory circuits operate less effectively even without a drop in GABA concentration. As a result, glutamatergic signals can propagate more easily, creating a state of heightened cortical excitability. This neurochemical instability provides a mechanistic link between sensory deprivation and the spontaneous visual activity that initiates CBS hallucinations (Figure 2).

3.2.0: Top-down Mechanisms: Functional Connectivity

Conversely, the top-down hypothesis suggests that network dysconnectivity drives hallucinations in CBS patients. rs-fMRI studies show differences in functional connectivity between high-order neural networks in CBS patients. For example, decreased connectivity between regions of the DMN, prefrontal cortex, and visual cortex suggests a failure of control and thought suppression (Kinakool 2015, see Figure 3a). Increased connectivity between the temporo-occipital fusiform gyrus in the SN and regions in the visual network emphasizes the misattribution of generated images (Kinakool 2015, see Figure 3a). The SN puts aberrant importance and priority on spontaneous images, thus spearheading complex hallucinations. This argument posits that dysfunctions in brain connectivity in regions which are responsible for gating sensory and visual signals, particularly the DMN and SN, fail to inhibit the CBS hallucinations from reaching conscious awareness (Schimmelpfennig 2023, see Figure 3a).

3.2.1: EEG

Electroencephalography (EEG) studies reveal abnormalities in cortical oscillatory activity in CBS patients. Several studies report reduced alpha power (8-12 Hz) in the frontal lobe, in CBS subjects compared to visually impaired controls, critical absolute t-values being $|t| = 3.12$, $p = 0.05$ (Piarulli 2021). In healthy individuals, alpha oscillations are known to support inhibition of information processing in idle brain regions (Kinakool 2015, Morgan 2025) Reduced alpha power therefore suggests that higher-order networks and the frontal lobe fail to suppress the processing networks responsible for the conceptualization of hallucinations. This allows spontaneous occipital activity generated through deafferentation to propagate forward. Additionally, a recent study, which compared resting state conditions, observed a decrease in theta-delta band activity in midline frontal regions, while paralleled by an increase in strength of the same band in posteromedial cortical regions; critical absolute t-values being $|t| = 3.22$ for delta and $|t| = 3.13$ for theta, $p = 0.05$ (Piarulli 2021). This opposing pattern reflects large-scale neural network desynchronization. Slower bands, like theta-delta, coordinate communication across the entirety of the brain. The reduction of theta-delta band activity could suggest the decrease in top-down control, as they control the same regions. Alternatively, an increase in the posteromedial region could signify the increase in internal signal generation in the visual cortex (see Figure 3b).

3.3.0: Comparisons to other models

Although CBS is unique in arising from visual deprivation rather than psychiatric or neurodegenerative disease, it shares mechanistic features with other well-studied hallucination phenomena. In conditions like Parkinson's disease and Lewy Body Dementia, dysfunction in high-order networks is also present, suggesting that impaired higher order regulation may represent a general mechanism of hallucination susceptibility, regardless of the initiating cause (Mehraram 2022, Yao 2014). CBS also parallels a mechanism similar to the studied "phantom limb," as the brain uses stored percepts to elicit feelings of pain, despite no real stimuli (Jones 2025). In the phantom limb, the observed amputated patient experiences vivid sensations, including pain, in the amputated limb, despite the absence of sensory signals. Both phantom limb pain and CBS sensory deprivation leads to hyperexcitability in the corresponding cortical regions, resulting in spontaneous activity that is misinterpreted as a real percept.

Discussion:
This review evaluates whether VH in CBS arises primarily from bottom-up hyperexcitability or from top-down dysregulation. Across neuroimaging, neurochemistry and electrophysiology findings, evidence supports a combined multi-stage mechanism in which visual deafferentation generates unstable sensory signals, while large-scale network dysfunction determines whether those internally generated signals reach conscious awareness. Visual hyperexcitability in the neurons and synapses of the occipital cortex is an attempt at compensation for the lack of visual input from deafferented cells.

Severe visual loss diminishes afferent input to the occipital cortex, triggering homeostatic plasticity, a compensatory increase in neuronal sensitivity designed to restore baseline activity in the absence of incoming sensory information. MRS studies indicate that while absolute concentrations of GABA and glutamate often remain stable, the efficiency of inhibitory GABAergic signaling decreases, leading to functional disinhibition. This excitability aligns with synaptic scaling mechanisms and explains why CBS patients exhibit lower phosphene thresholds in TMS studies (Morgan 2025). Even minimal stimulation can trigger visual percepts, suggesting that the visual cortex enters an unstable, easily activated state.

Parallel evidence from fMRI data reinforce this model, demonstrating reduced grey matter and cortical thinning in visual regions, including the fusiform gyrus and cuneus. Such reorganization may heighten susceptibility to spontaneous firing of signals. The association between reduced hippocampal volume and hallucination severity further suggests that memory and scene construction systems may influence the richness and complexity of VH, supporting a contribution from both sensory and associative networks.

Although bottom up hyperexcitability may generate spontaneous visual activity, it does not fully explain why some visually impaired individuals hallucinate or why hallucinations vary in complexity. Top down mechanisms address this gap. When DMN regulation is weakened, spontaneous visual activity is more likely to be misinterpreted as real. At the same time, increased connectivity within the SN suggests that internally generated visual signals are assigned inappropriate importance. Therefore VH are assigned higher priority and have greater clearance. Hyperactive SN signaling may amplify spontaneous occipital activity propelling it towards awareness and contributing to the emergence of complex hallucinations. Electrophysiological data supports this interpretation. Decreased alpha amplitude suggests that higher order networks fail to gate the generated images or suppress irrelevant or noisy sensory signals from the VN from entering conscious awareness.

The lower level network, fueled by deafferentation and vision loss by ocular pathology, generates the signals through spontaneous neuron activations. Additional findings of altered theta-delta activity between frontal and posteromedial regions indicate impaired global coordination. Theta-delta abnormalities reflect a breakdown in long range neural coordination. Reduced frontal activity weakens top down suppression, while increased posteromedial activity amplifies internally generated imagery. This desynchronization prevents higher order networks from properly filtering, inhibiting, and contextualizing spontaneous visual signals, allowing them to manifest as hallucinations.

Vision loss in the patient leads to reduced sensory input. The deafferentation in the VN generates signals, which fuels the content of the VH. A dysfunction in high-order networks, DMN and SN, represent a failure of gating the image generations, allowing them to enter conscious perception and become hallucinations. Thus only a combined model can accurately present the full clinical explanation.

This mechanistic model is especially important to establish because many cases of CBS go undiagnosed by clinicians. This is largely due to both the lack of awareness about the condition, and the stigma surrounding the nature of hallucinations, making patients reluctant to confess the hallucinatory experiences in fear of being diagnosed with a psychotic or neurodegenerative disease. Its general prevalence is not to be ignored, as it was diagnosed in 20% of visually impaired patients, while 40% were recorded as not having told anyone about their VH experiences (Eriksen 2025). This further drives its necessity to be better understood.

It is difficult for the deafferentation hypothesis to explain why only some visually impaired people experience VH, suggesting that VH is also influenced by some coexisting factor. Further pursuits should consider multi-modal data collection to capture a fuller picture of VH in CBS.
These studies, however, face potential limitations. First, existing sample sizes are extremely small, The majority of records included in this paper is limited to case studies, with only one examined patient. Few studies utilize multi-modal imaging, like fMRI and EEG combined, so thus yield less precise data. Difficulties in standardization also appear, particularly in the severity of VH across CBS patients. Hallucination content varies significantly across individuals, whether simple or complex, and the concept of “vision loss” itself is not uniform due to the varying ocular pathologies that occur in CBS individuals.

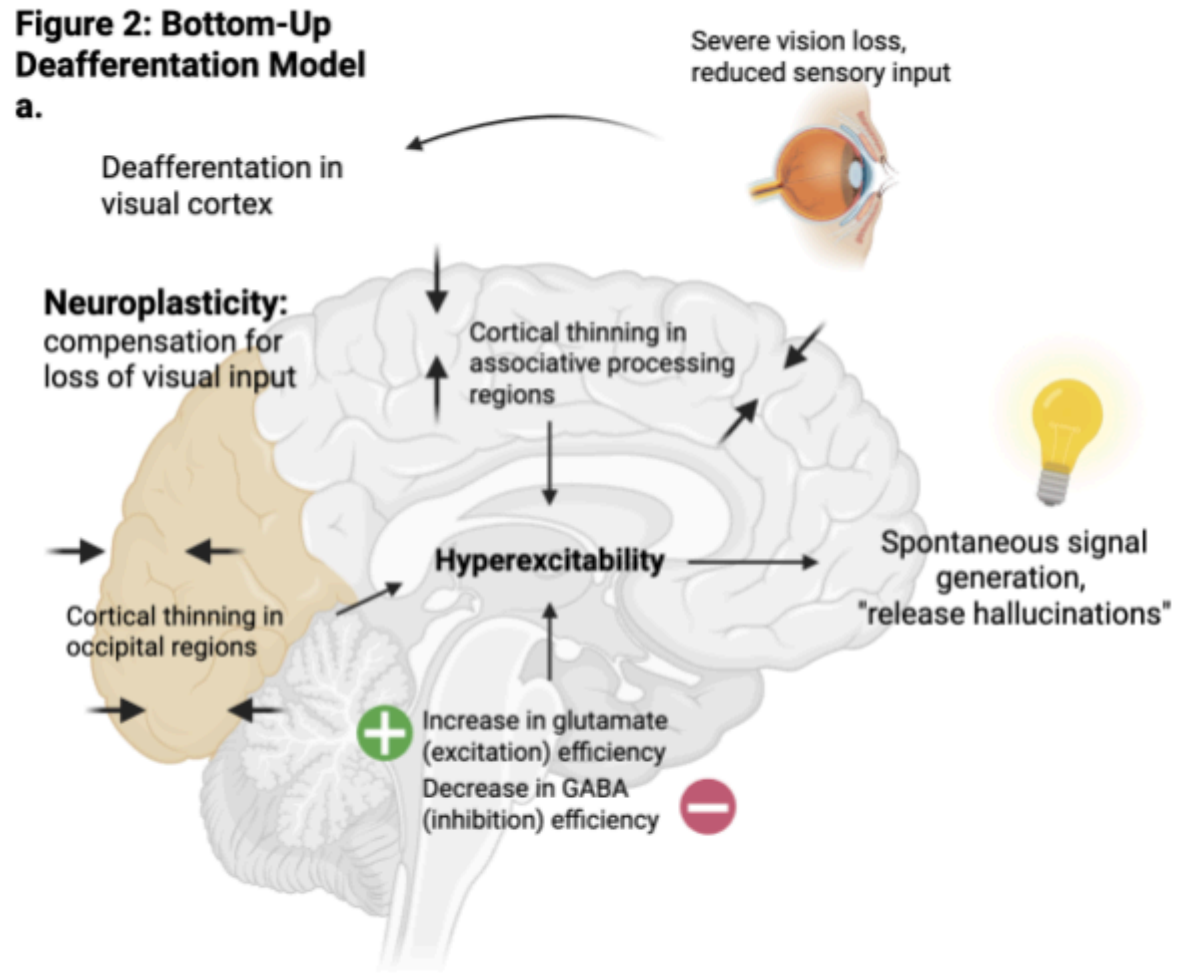
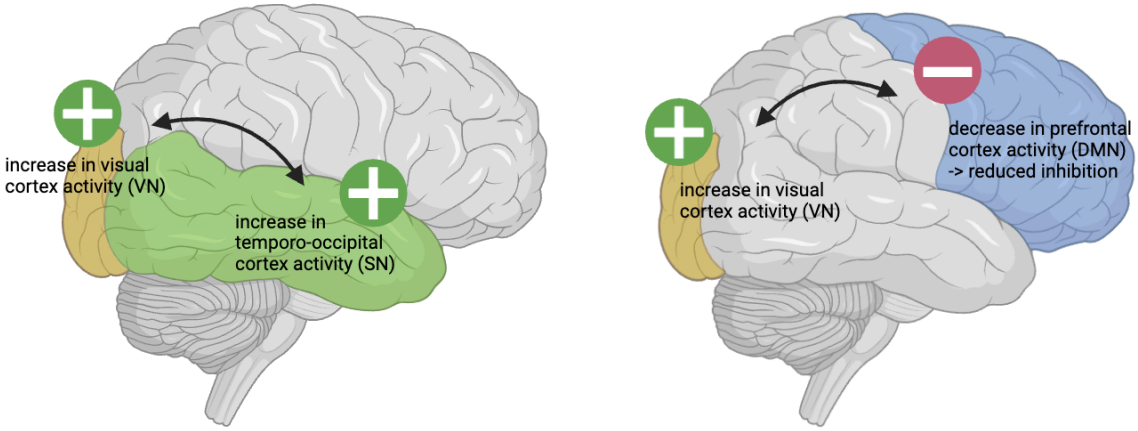


Figure 2: Bottom-Up Deafferentation Model. a, Severe vision loss reduces sensory input into the visual cortex, causing cortical deafferentation. In response, neuroplasticity occurs, shown through thinning in visual regions in the occipital cortex and other associative regions for signal processing. Neuroplasticity is also shown through an increase in glutamate efficiency and a decrease in GABA efficiency. Cortical thinning and this imbalance result in cortical

hyperexcitability. Hyperexcitable visual areas can produce spontaneous signals, generating “release hallucinations” in CBS patients. **b,** Martial et al. observed reductions in cortical thickness in visual regions: fusiform gyrus, cuneus, pericalcarine cortex. Reductions were also found in associative processing region gyri: inferior parietal, inferior temporal, lateral orbitofrontal, middle temporal, paracentral, pars opercularis, precuneus, superior frontal, superior parietal, and superior temporal

Figure 3: Top-Down Dysregulation Model

a. Functional Connectivity:



b. EEG:

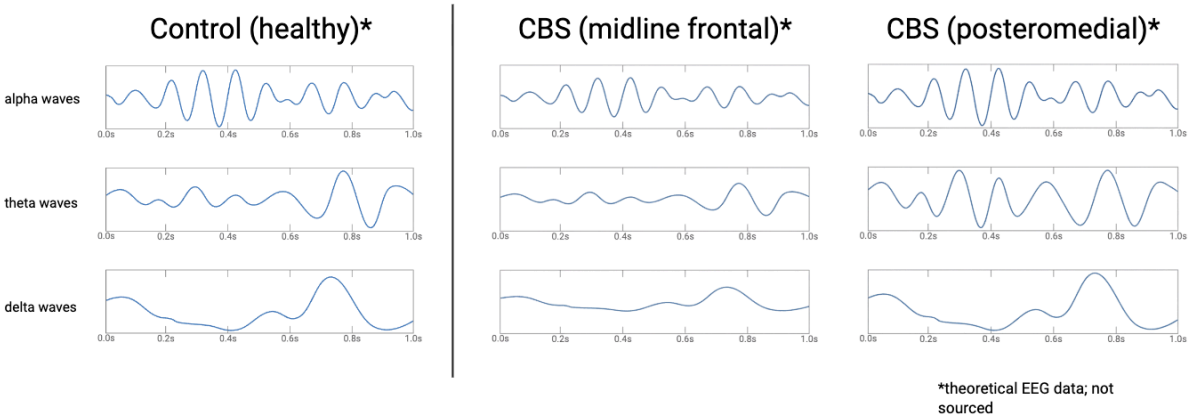


Figure 3: Top-Down Dysregulation Model. a, fMRI reveals a collective increase in functional connectivity between the VN and SN. This indicates the hyperexcitable visual cortex is associated with an overactive SN, which gives generated signals higher priority and overrides gating systems. fMRI also shows an increase in functional connectivity between the VN and DMN. This indicates the hyperexcitable visual cortex is associated with an underactive DMN, suggesting a gating failure for the images generated by the hyperactive visual cortex. **b,** EEG data shows a decrease in alpha power in the midline frontal region, associated with the DMN, suggesting a reduction in inhibition. An decrease in theta-delta power was demonstrated in the midline frontal cortex, followed by an increase in the posteromedial cortex. This reveals wide-scale desynchronization, as well as a communication failure between the DMN (midline frontal) and VN (posteromedial).

Acknowledgements:
I sincerely thank Tamara J. for her mentorship and enthusiasm in discussing this topic with me, as well as the Polygence Institute for giving me this opportunity. I would like to thank Jessica A. for her help in publishing my paper. I would also like to thank Michelle Smith for her feedback on the paper.

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