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Proposal for a Unified Framework to Understand the Functional Changes That Occur in Visual Hallucinations in Parkinson's Disease

Abstract

Visual hallucinations in Parkinson's disease are often viewed as isolated symptoms of neurodegeneration. However, growing evidence suggests that they reflect deeper disruptions in how the brain constructs perception. This paper reviews three major hypotheses—early visual dysfunction, cholinergic dysfunction, and serotonergic dysfunction—and proposes a unified framework linking these mechanisms across multiple levels of brain organization. By integrating electrophysiological, neurochemical, and network-level findings, this study argues that hallucinations arise from an imbalance between internally generated and externally driven signals. Specifically, serotonergic dysfunction, through alterations in 5-HT2A receptor density, may connect changes in early sensory processing with large-scale network dynamics, including impaired transitions between brain states. Understanding these mechanisms provides insight not only into Parkinson's disease, but also into the fundamental nature of perception as an active and dynamic process. More broadly, this work highlights the importance of approaching neurodegeneration as a distributed, multilevel phenomenon, with implications for developing more integrated and effective therapeutic strategies.

Keywords: Parkinson's disease; visual hallucinations; serotonin; 5-HT2A receptor; visual processing; attention networks; brain-state dynamics

Introduction

Parkinson's disease (PD) is a neurodegenerative disorder attributed to a dysfunction in the dopaminergic system (Lew, 2007). The main symptoms of PD and those that serve as a diagnosis are motor, but patients often show a spectrum of various non-motor symptoms as well. Moreover, it is possible for Parkinson's disease patients to develop dementia or psychotic symptoms. This last condition is known as Parkinson's disease psychosis (PDP) (Friedman, 2010), and its main symptom is visual hallucinations (VH).

Visual hallucinations can present in different forms, and they are commonly classified as elementary and complex.

Elementary VH generally consist of geometric patterns, such as lines, curves or spots (Billock & Tsou, 2012). These can also have additional features such as color or motion. Conversely, complex VH feature a variety of different contents, often depicting animal or human figures in absurd or unrealistic contexts (Manford & Andermann, 1998). Patients who suffer from a psychotic disorder often encounter both elementary and complex VH, but most PD patients recall having experienced complex VH (van Ommen et al., 2023).

It was initially believed that VH and PDP were a collateral effect of dopaminergic treatments, administered to alleviate the motor symptoms of the disorder; however, some PD patients develop PDP without medications (Friedman, 2010). This suggests that PDP is a progression of PD itself. Indeed, while dopamine is the main neurotransmitter attributed to PD motor symptoms, it is believed that the disorder also displays dysfunctions in other neurotransmitter systems and in the interactions between those; many motor and non-motor symptoms of the disease have been attributed to neurotransmitters such as serotonin, acetylcholine, glutamate and γ-aminobutyric acid (GABA) (Barone, 2010).

PD is the second most prevalent neurodegenerative disorder in the world population, and VH has a prevalence range of 8%–40% in PD patients (Barone, 2010; Manganelli et al., 2009). Moreover, there are a variety of correlates linking VH and PD. For example, VH in PD are reflected by aberrant event-related potential (ERP) components—such as increased P1 and P3b potentials. Moreover, some PD-VH patients present anomalous neural networks behavior, including enhanced excitability in the default mode network and in attention-related networks, or temporal imbalances in transitions between segregated and integrated states. Nevertheless, the underlying mechanisms giving rise to VH are largely unknown.

A complicating factor to this phenomenon is the high occurrence of dementia in PD, known to cause cognitive impairment and dysfunctions in many neural networks, namely in attention, memory and visual perception pathways, sometimes resulting in VH itself (Gratwicke et al., 2015). Since dementia and psychosis often coexist in PD patients, it is difficult to discern the distinct effects that the two conditions have on neural networks in PD, as well as to identify their respective causal factors.

At present there remains no unified framework able to explain how and which neural networks are involved in VH among nondemented PD patients. Investigating the functional changes that occur in VH in PD can offer new insights into visual processing and stimuli interpretation. Moreover, it may enhance treatments to alleviate VH, perhaps reducing the effects that they have on the overall health of the patient. VH are indeed linked with both a greater chance of developing dementia and a higher risk of mortality (Manganelli et al., 2009). Eventually, having a better understanding of the neural networks involved in VH in PD can lead to improvements in the quality of life of the patients. The present study reviews existing hypotheses of VH in PD and proposes that serotonergic dysfunction may provide an integrative bridge between early visual, cholinergic, and network-level abnormalities.

Method and Scope of the Review

This paper is a focused narrative review and theoretical synthesis. It compares evidence from electrophysiology, neuroimaging, pharmacological studies, postmortem receptor analyses, and network-control approaches. Relevant studies were identified through targeted searches of PubMed, Google Scholar, and reference lists of key reviews using combinations of terms related to Parkinson's disease, visual hallucinations, visual processing, cholinergic dysfunction, serotonin, 5-HT2A receptors, and brain-state dynamics. Studies were selected for their relevance to three recurring

explanatory levels: early visual processing, cholinergic modulation, and serotonergic/network-state dysfunction. Because the included studies differ substantially in population, task, and measurement method, and several do not examine nondemented Parkinson's disease patients directly, the proposed framework should be interpreted as a testable integrative hypothesis rather than a demonstrated causal model.

Literature Review on Visual Hallucinations in Parkinson's Disease

There are a few models that try to explain the functional changes that occur in PD patients causing VH. The present study focuses on three distinct frameworks. While the first hypothesis attributes VH to an early visual dysfunction (Schwartzman et al., 2008; van Ommen et al., 2023), the second and third present a broader explanation of VH as an imbalance between external and internal stimuli involving different parts of visual and attentional networks. The distinguishing factor between the last two models lies in the type of neurotransmitters involved: while the second attributes VH to a central cholinergic dysfunction (Manganelli et al., 2009), the third emphasizes serotonergic dysfunction and altered 5-HT2A receptor density (Kometer et al., 2013). Numerous studies have investigated VH in PD; each research presents experiments conducted in distinct ways, with different aims and results, offering a piece of the puzzle that eventually explains thoroughly how and which visual networks are involved in VH in PD.

Early Visual Dysfunction

A study conducted by Schwartzman et al. (2008) evaluated the hypothesis that considered aberrant early visual ERP components to reflect the individuals' proneness to hallucinate. While early visual disruption had been previously associated with various psychological and neurological disorders that present VH—e.g. Parkinson's, schizophrenia—it remained unclear whether an early impairment of visual processes was a key factor in the development of VH or rather a mere outcome of the disorder itself.

In order to isolate the possibly complicating factor of cognitive decline, which is a key component of most of the disorders that present VH, the study analyzed electroencephalogram (EEG) recordings of healthy individuals, dividing them based on their proneness to visually hallucinate. To assess this, the participants answered the Hallucination-proneness Questionnaire. Individuals were asked to provide a number on a scale from 0 to 5 for each of the 29 statements testing their experience with sensory hallucinations—with a particular focus on the visual sphere. The number indicated how much the participant related to the statement (from 5 – certainly applies to me; to 0 – certainly does not apply to me). The individuals were then shown photographs of faces, Mooney faces and scrambled Mooney faces (see Figure 1). The visual stimuli were shown both upright and upside down, and the participants were instructed to report whether they perceived a face in each image.

The Mooney Faces Test (MFT) is used to assess an individual's ability to perceive human faces in two-dimensional, black and white pictures (Silverstein et al., 2021). The MFT is normally used to measure visual perception; the images are created so that there are different stages of difficulty regarding face perception. Recognition of a Mooney face stimulates higher levels of visual processing, especially those linked with memory. This explains why normally inverted Mooney faces are not perceived as such, given that there is a lack of retrieval of upside-down representations of faces. Silverstein et al. investigated MFT results in individuals with a clinical high risk of developing a psychotic disorder, and found that higher MFT scores—meaning that the individual perceived faces in more pictures compared to control groups, both in an upright

and inverted condition—corresponded to aberrant visual perception and a higher occurrence of VH reported. During the experiment

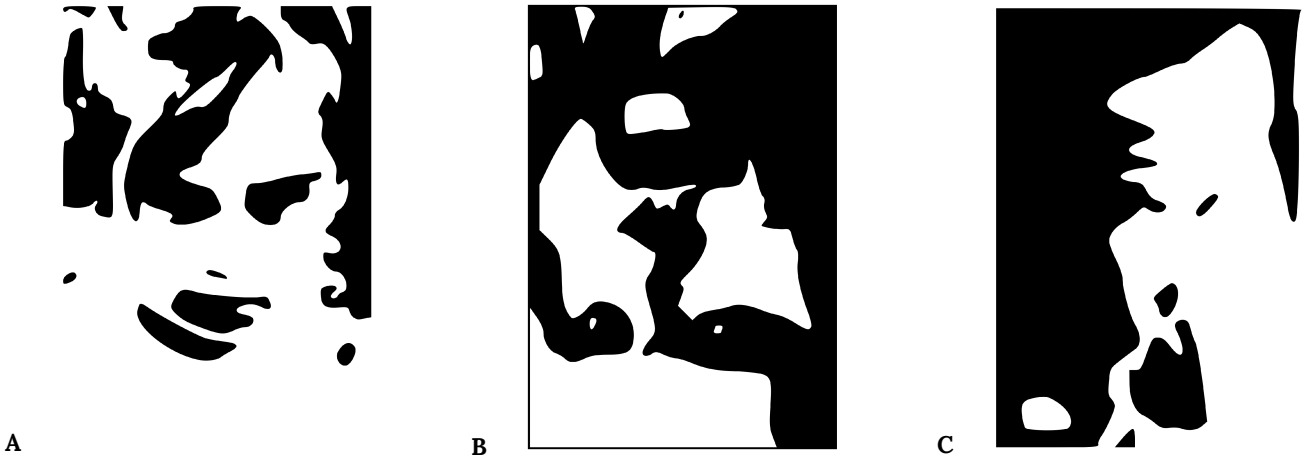


Figure 1. Representative stimuli from the Mooney Faces Test. The upright Mooney face (A) is typically perceived as a face, whereas the inverted Mooney face (B) is substantially more difficult to recognize due to disruption of holistic face processing. The scrambled image (C) serves as a non-face control stimulus. Stimuli adapted from the dataset of Schwiedrzik et al. (2018) and redrawn as vector graphics for presentation clarity under CC BY 4.0.

conducted by Schwartzman et al., the participants' brain activity was recorded through EEG; specifically, the study focused on ERP components that reflect early visual processes. The components analyzed were the N170, P1 and P2, respectively associated with face recognition, early extraction of information from face stimuli, and finally a higher level of visual processing involving categorization of face stimuli. The interpretation of the stimulus in P2 depends on the reception of information carried out in P1.

The study observed a lack of significant differences in the N170 component, while the P1 and P2 both showed an increased positivity in hallucination-prone individuals. The lack of variation in the N170 component between individuals with high and low hallucination proneness suggested that the changes observed in P1 and P2 were not influenced by the object observed—in this case, faces—but rather by an early visual process impairment. Conversely, the increased amplitude registered both in P1 and P2 could suggest a dysfunction in the extraction of fine information from visual stimuli, reflected by an increased positivity in P1. A disrupted extraction of information from the stimulus would also generate an impaired interpretation of the information, explaining the knock-on effects on P2. These findings indicate that hallucinating individuals present an increased amplitude in P1 due to a dysfunction in early visual processes.

An earlier study had shown a correlation between P1 ERP component in patients with PD and primary visual processes (Wang et al., 2001). Thus, the early visual dysfunction hypothesis would be supported by hallucinating PD patients presenting increased latency in P1, reflecting an impairment in early stages of visual processing.

Although there is evidence that early visual dysfunction is related to VH in PD, it appears to be highly unlikely for VH to be

explained as a focal pathology. Instead, a study led by van Ommen et al. (2023) correlated an impairment in primary visual processes to dysfunctions in other visual-related neural networks, proposing a more holistic explanation of VH. Indeed, they found that VH might be a result of a dysfunction in the primary visual cortex, V1, which consequently results in an aberrant activation of visual-related networks. A malfunction in the transfer of information between V1 and attention-related networks would eventually result in internally generated stimuli—coming from endogenous neural networks—being perceived as exogenous inputs from V1.

Van Ommen et al. (2023) aimed to evaluate the hypothesis previously postulated by Shine et al. (2014), which had explained VH as a consequence of a disconnection between the primary visual cortex, V1, and higher visual components, inducing a desynchronization between different parts of the visual network. This previous hypothesis was based on the reduced activity in the primary visual cortex observed in patients with psychotic VH.

In order to evaluate the postulated model from Shine et al. and assess what areas of the brain are involved in psychotic VH, van Ommen et al. conducted an experiment on hallucinating psychotic individuals, recording their brain activation data during an episode of VH, through functional magnetic resonance imaging (fMRI). The results showed lack of activation in V1 and increased activity across the visual and attention pathways, specifically in the Dorsal Attention Network (DAN), Default mode network (DMN) and Ventral Attention Network (VAN). These are respectively linked to processing external information, interpreting internal stimuli and coordinating memory and finally synchronizing the two networks—DAN and DMN (Van Calster et al., 2017). The results are therefore in line with the hypothesis postulated by Shine et al., 2014, as they show that psychotic VH is not a focal pathology. Instead, it affects a wide range of regions, namely the visual network (VIS)—excluding V1—and vision-related networks involved with memory and attention.

Shine et al. had postulated that an early dysfunction in V1 would cause an incorrect categorization of visual stimuli by relevance in the VAN. As a result, an imbalance between externally and internally generated visual stimuli (in the DAN and DMN) would originate VH. Instead, Van Ommen et al. have proposed a refined model that attributes VH to the activation of a loop across the VIS—with the exception of V1—and the DAN, DMN and VAN. Under normal circumstances, feed-forward impulses are sent from V1 to the surrounding visual network regions. This flow of information allows the stimulus to be recognized as external. In turn, a feedback inhibitory response is sent from the networks to V1. According to this model, the ability of V1 to provide feed-forward and receive feedback information from the surrounding areas is compromised in psychotic VH. This eventually causes the brain to misinterpret internally-generated information as external inputs, consequently creating VH.

Another piece of evidence in support of the model proposed by van Ommen et al. is given by a study from 2014, led by Yao et al., which investigated DMN activity in resting PD patients, both with (PD-VH) and without VH (PD-non-VH) and in healthy controls. Patients with symptoms of cognitive impairment and dementia were excluded. Resting-state functional magnetic resonance imaging (rsfMRI) data of the participants were acquired, and the results showed a decreased activity in the DMN in PD patients compared to controls; conversely, PD-VH patients had a greater excitability of the DMN compared to PD-non-VH. Yao et al., therefore, demonstrated that a higher connectivity in the DMN is associated with VH in PD patients, relative to PD-non-VH patients. Showing a correlation between DMN activity and VH in PD, these data support the model proposed by van Ommen et al.

Thus, while there are findings suggesting that early visual impairment has a role in generating VH in PD, this is treated as

one level of a distributed mechanism rather than a complete explanation of the condition. Moreover, the presented model fails to include the involvement of neurotransmitters in VH in PD. To fully comprehend the underlying neurological mechanisms of VH in PD, it is necessary to adopt a more holistic approach, recognizing the role of neurotransmitters in modulating attention and vision-related networks. Consistent with the model postulated by van Ommen et al., 2023, a second hypothesis attributes VH in PD to an imbalance between external and internal stimuli, as a consequence of a central cholinergic dysfunction.

Imbalance Between External and Internal Stimuli due to a Central Cholinergic Dysfunction

A study from 2009, conducted by Manganelli et al., found a correlation between nondemented PD-VH patients and a central cholinergic dysfunction. The research methodology included the use of short-latency afferent inhibition (SAI), a non-invasive protocol thought to reflect central cholinergic activity (Martin-Rodriguez et al., 2020). The participants were 22 non-demented PD patients, both with and without VH (Manganelli et al., 2009). The study found that most PD-VH patients presented aberrant SAI values, unlike PD-non-VH individuals. Therefore, Manganelli et al. concluded that VH in PD could be one of the factors that alter the balance of the cholinergic system. Alternatively, VH would cause a dysfunction between the cholinergic and other neurotransmitter systems. The study also confirmed the hypothesis of a correlation between cholinergic dysfunction and PD patients who are likely to develop dementia. VH are considered to be a predictive factor of dementia. Therefore, it is possible that there is a link between central cholinergic dysfunction and VH in PD.

However, there remains disagreement about the direction of causality, as other later studies consider cholinergic dysfunction as a causal factor of VH in PD. One of these is a study led by Chang et al. (2016).

While aberrant ERP values are an indicator of cognitive dysfunction in demented PD patients, increased P3 latency is thought to be correlated with VH in demented PD patients. Moreover, VH is a possible predictor of dementia in PD patients. Therefore, the study aimed to explore the correlation between ERP abnormalities and nondemented PD patients. The research analyzed differences in ERP components in nondemented PD patients with VH, comparing them to PD-non-VH and healthy control individuals. During the experiment, participants were shown different images, which were either target stimuli or nontarget stimuli. Each individual had previously been instructed to identify the target accurately. The participants' task was to respond as quickly as possible by pressing a button when the target stimulus appeared. During the duration of the experiment, the following ERP components were recorded: N1, P2, N2 and P3. Firstly, N1 and P2 are both considered to be related to sensory processing, as well as attention. They are exogenous components, i.e. components primarily driven by the physical properties of external stimuli, related to processing of external stimuli and not influenced by cognitive activity (Donchin et al., 1978). The N2 represents higher visual processing, involving early cognition such as identification of new stimuli, while the P3 responds to detection and categorization of new stimuli, a process involving memory (Chang et al., 2016). Specifically, the P3b occurs from 300 to 700 milliseconds, and it is linked with the update of memory based on new persistent stimuli. It allows the novel context to be stored in memory, and it occurs after the detection of stimulus novelty, reflected by the other part of P3, P3a (Polich, 2003). The results showed a prolonged latency of the P3b component in PD-VH individuals, compared to that of controls (Chang et al., 2016). VH had previously been linked with a cholinergic dysfunction in the pedunculopontine nucleus, and a prolonged P3 ERP component in Alzheimer's disease patients is thought to indicate central cholinergic function. Hence, the study hypothesized that VH in nondemented PD patients might be attributed to a central cholinergic dysfunction and could be indicated by aberrant P3 ERP components. In addition, the study found that neither the N1 nor P2 component presented significant differences

among the three groups.

This challenges the previously mentioned hypothesis that attributed VH to visual-related network dysfunctions, as both these components are thought to reflect attention-related sensory information. However, N1 and P2 are considered exogenous components, while the earlier stated model focuses on the roles of DAN, VAN and DMN. These also reflect certain cognitive processes and are therefore endogenous neural networks, suggesting that the two factors are independent from each other. Furthermore, there is no evidence that a dysfunction in the DAN, VAN and DMN is reflected by the N1 and P2 components; in turn, aberrant values of N1 and P2 are not necessarily related to these attentional networks. This suggests that the absence of significant findings in the N1 and P2 components does not necessarily contradict the model considered but rather points to a potential direction for further investigation.

Serotonergic Dysfunction, 5-HT2A Receptors, and Brain-State Dynamics

An aberrant density of 5-HT2A receptors in different cortical areas has often been connected to various forms of psychosis, including PDP (Huot, 2018), but the effect of this receptor's activation on VH is left unclear. A study conducted by Kometer et al. (2013) aimed to clarify this connection by investigating the effects that the activation of the 5-HT2A receptor has on parieto-occipital α waves.

Alpha oscillations, considered to be mostly present in the thalamic regions and visual cortex, have different associations with visual processing and have been correlated with visual processing dysfunctions and impairments (Clayton et al., 2018). Since they are strongly linked to visual processing, they are also influenced by visual-related potentials (Kometer et al., 2013). The study presented here hypothesized that α oscillations could mediate the creation of VH. According to their model, α waves would be stimulated by the activation of 5-HT2A receptors, in turn triggered by the administration of psilocybin, a serotonergic hallucinogen. A second hypothesis postulated by the study concerned how early visual ERP components—specifically the P1 and N170—were influenced by psilocybin-induced hallucinations.

Seventeen healthy participants were administered a pretreatment and a treatment—respectively: placebo + ketanserin, a 5-HT2A antagonist; placebo + psilocybin—on four different experimental days. After each treatment, the participants were shown some pictures with three "pacman" shapes, which were either arranged in a "Kanizsa," or in a "non-Kanizsa" condition, thus either giving or not the perception of an illusory triangle. The participants' task was to respond as quickly as possible by pressing a button whenever they perceived a triangle. EEGs were recorded during the visual stimulation. After the experiment, the participants completed a self-report questionnaire to state their experience under the effects of the hallucinogen, especially reflecting on any changes felt in their visual perception.

The experiment showed an increase in the amplitudes of the P1 potential over medial parieto-occipital regions in participants after the psilocybin administration, a trend that was inverted following the ketanserin pretreatment. The N170 showed a decreased positivity after psilocybin; conversely, the same component did not show any changes following the ketanserin treatment. Finally, a decrease in α power waves was observed after the psilocybin administration and was later linked to the increased P1 potentials. All the effects detected were suppressed by the ketanserin pretreatment, suggesting that they were caused by psilocybin administration and related to the consequent activation of the 5-HT2A receptors. Decreased α power waves were attributed to an increased cortical excitability especially in the parieto-occipital regions and in visual networks, reflecting the activation of 5-HT2A receptors. A reduction in alpha power had already been shown

to occur during moments of increased visual attention and cortical excitability in the occipital lobe, while an increase in alpha oscillations might directly suppress visual functions (Clayton et al., 2018). The decreased α power was also related to the increase in P1 medial potentials, which might represent an enhancement in early visual processing (Kometer et al., 2013).

This coordinated response between the P1 and α power would in turn originate an imbalance between perception of external and internal stimuli. Specifically, there is a loss of equilibrium between cortex excitability when external stimuli are perceived and the cortical excitability in the absence of external stimuli. This corresponds to a change in the activation of brain networks—reflected by decreased alpha oscillations and enhanced P1 medial potentials—with an increased attention towards internally-generated visual stimuli, rather than external stimuli. This model seems to be in line with the hypothesis proposed by van Ommen et al., in 2023.

Although the findings suggest that α power waves have a role in generating elementary psilocybin-induced VH, analytical studies showed little correlation between the two factors, perhaps revealing that the reduction in α power triggered by psilocybin is not sufficient to induce complex VH. This suggests that other factors contribute to generating VH in PD.

Finally, the psilocybin treatment produced a decrease in the N170, which is thought to play a key role in processing meaningful visual stimuli. An alteration in this component is therefore linked with altered visual perception, implying that its aberrant values are a consequence of the psilocybin-induced hallucinations. Alternatively, the effects on the N170 could be attributed to the increased cortical excitability triggered by the activation of the 5-HT2A receptor, eventually enhancing or originating an imbalance between external and internal stimuli.

A previous study had investigated the distribution of 5-HT2A receptors in postmortem PD patients' tissues, postulating a correlation between enhanced levels of this receptor and VH in PD (Huot et al., 2010). The results showed an increased density of this receptor in PD tissues with VH, compared to PD-non-VH, therefore substantiating the proposed hypothesis. While an existing postulate attributed the development of psychosis in PD to a polymorphism in the 5-HT2A receptor gene, a study led by Kiferle et al. (2007) refuted this hypothesis, and they concluded that aberrant levels of this receptor are not due to genetic variations.

Huot et al. (2010) proposed a new explanation of the enhanced levels of 5-HT2A receptors in PD patients with psychosis, defining it as a consequence of other neurotransmitter dysfunctions in PD. PD is known to present serotonin (5-HT) dysfunctions; specifically, degeneration in the serotonergic neurons in the brainstem causes a decline in the neurotransmitter levels. This would then result in an increased 5-HT2A density, as a biological attempt to balance the drop of 5-HT in different areas of the brain. Enhanced levels of 5-HT2A could also be attributed to the decrease in dopamine (DA) levels, which acts as a partial agonist to the receptor. These two possibilities are likely to be complementary, and this explanation can help explain the late occurrence of VH in the development of PD: the disorder disrupts the dopaminergic system more than it does to the serotonergic system, suggesting that it takes longer for the levels of 5-HT to drop below the threshold level. This eventually leads to the development of VH in the patient.

A possible limitation of the presented study is the interference of dementia, which was present in four out of the six PD-VH participants. Since dementia is known to cause dysfunctions in many neural networks, such as attention, memory and visual perception (Gratwicke et al., 2015), this factor limits the reliability of the findings and makes it unclear whether they

should be attributed to psychosis rather than dementia.

However, there is further evidence that provides support to the hypothesis that the 5-HT2A receptor plays a key role in the development of VH in PD. Specifically, an aberrant density of this receptor was attributed to temporal dysfunctions in transitions between the segregated and integrated states of the brain in hallucinating PD patients (Zarkali et al., 2022). The study used the definition of these states derived from the network control theory. This is a mathematical framework that identifies states of the brain as "the magnitude of haemodynamic activity across brain regions at a single time point." This framework defines the brain's activation state at a given time as a "linear function of a previous state, the underlying structural connectome and the additional control energy" (Zarkali et al., 2022). The theory also provides a method to estimate the amount of energy used either to switch from state to state or to dwell in a specific state. It is believed that these shifts in states are controlled by neurotransmitter systems.

The study aimed to investigate how temporal dynamics in transitions between integrated and segregated states are affected in PD patients with VH, using rsfMRI. Cognitive levels of all patients were measured through specific tests—e.g. Mini-Mental State Examination (MMSE). Integrated and segregated states were calculated individually for every participant from each group, PD-VH, PD-non-VH and controls. Integrated and segregated states are opposite methods of network organization, although they often coexist in the same functional system (Tononi et al., 1994). Integration means that the different areas of the network are interconnected and there is a fast flow of information among them; each component of the circuit is dependent on the others. Conversely, segregation happens when different regions function relatively independently of one another, with a limited amount of information flow among the whole system.

The results showed no difference between integrated and segregated states themselves but variations in the time frames and number of transitions between these (Zarkali et al., 2022). Specifically, the main finding was that PD-VH participants spent less time in the integrated and therefore a longer time in the segregated state compared to PD-non-VH individuals; moreover, PD-VH showed fewer transitions between the two states.

The study attempted to explain this observation by calculating the amount of energy used in transitions between states as well as when persisting in one state, for PD-VH individuals as well as PD-non-VH and controls. The main finding was that the minimum energy needed to transition from the integrated to the segregated was considerably lower in PD-VH compared to PD-non-VH. The study concluded that PD-VH individuals spend more time in the segregated state due to the ease at which they can transition to this state from the integrated one, rather than because persisting in the segregated state itself is less energy-demanding.

The framework presented by these findings suggests that the DMN and thalamic regions have a role in VH in PD, as these are the nodes responsible for modulating the transitions between integrated and segregated states. Furthermore, the study expanded on these findings, attempting to assess the role of neurotransmitters in the alterations observed. The data gathered by Zarkali et al. provide further evidence to show the key role of the 5-HT2A receptor in developing VH in PD, as they found significant correlations between regional energy and different neurotransmitter receptor densities—including 5-HT2A receptors.

Proposal for a Unified Framework

In light of the evidence considered and summarized in Table 1, this study proposes a unified framework to explain the functional changes that occur in PD-VH patients. Indeed, the three existing models present similar characteristics and points of convergence.

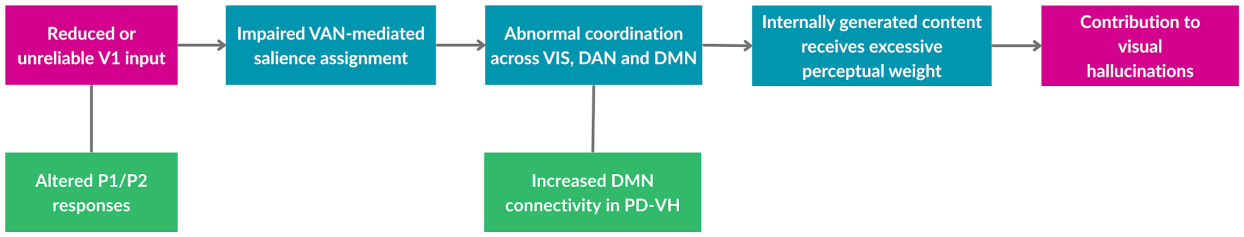
The first hypothesis, schematized in Figure 2A, attributes VH in PD to an early visual dysfunction. According to this model, an impairment in V1 would cause the activation of a loop across areas of the visual network, with an increased activity in the DMN (Yao et al., 2014) and a dysfunction across the DAN and VAN, resulting in the recognition of internally-generated stimuli as external inputs (van Ommen et al., 2023). The original dysfunction in V1 would presumably be reflected by aberrant ERP values in the P1 component (Schwartzman et al., 2008), which in PD patients is correlated to primary visual processes (Wang

Hypothesis	Study	Approach	Key finding/relevance
Early visual dysfunction	Schwartzman et al. (2008)	EEG/ERP in hallucination-prone healthy participants	Higher P1/P2 positivity supports altered early visual processing but does not establish PD-specific causality.
	Yao et al. (2014)	Resting-state fMRI in PD-VH, PD-non-VH, and controls	Greater DMN connectivity in PD-VH supports involvement of internally oriented network activity.
	van Ommen et al. (2023)	fMRI during hallucinations in psychosis	Reduced V1 involvement with increased VIS/DAN/DMN/VAN activity supports a distributed network account.
Cholinergic dysfunction	Manganelli et al. (2009)	SAI in nondemented PD patients	Abnormal SAI links PD-VH to central cholinergic dysfunction; direction of causality remains unresolved.
	Chang et al. (2016)	Visual ERP task in nondemented PD groups	Prolonged P3b latency is consistent with altered cholinergic/cognitive processing in PD-VH.
Serotonergic / 5-HT2A	Kometer et al. (2013)	Psilocybin/ketanserin EEG study in healthy adults	5-HT2A activation altered P1, N170, and alpha power, providing a mechanistic bridge to visual processing.
	Huot et al. (2010)	Postmortem temporal-cortex receptor analysis	Higher 5-HT2A receptor density in PD-VH supports receptor-level involvement, though dementia is a confound.

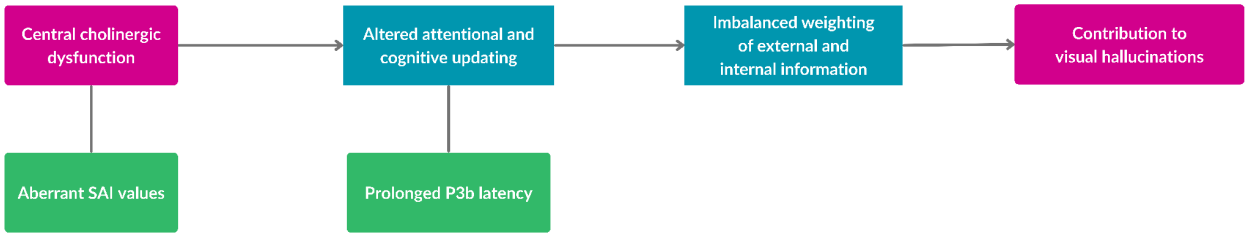
Table 1. Summary of reviewed literature.

Zarkali et al. (2022)	Resting-state fMRI and network-control analysis	PD-VH showed fewer transitions and longer segregation, linked regionally to neurotransmitter receptor density.

A Early visual dysfunction model



B Cholinergic dysfunction model



C 5-HT2A receptor dysfunction model

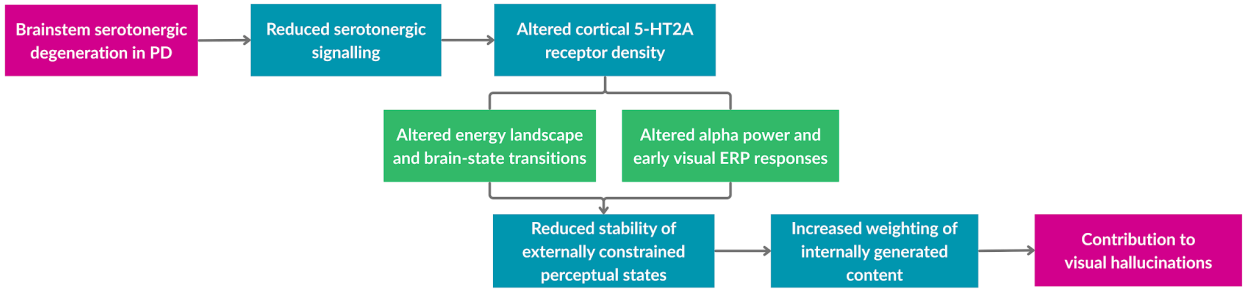


Figure 2. Schematic representations of the three models of visual hallucinations in Parkinson's disease. (A) Early visual dysfunction model. (B) Cholinergic dysfunction model. (C) 5-HT2A receptor dysfunction model. Color code: key nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships proposed within each model; continuous lines without arrowheads indicate observed associations for which causal direction has not been established.

et al., 2001).

The second hypothesis focuses on the role of a cholinergic dysfunction in PD-VH patients (see Figure 2B). However, there is divergent evidence regarding whether this is a causing factor of VH or rather a consequence of the condition. Manganelli et al. (2009) postulated the presence of a link between cholinergic dysfunction and VH in PD patients reflected by aberrant SAI values; the direction of causality remains unclear. Conversely, Chang et al. (2016) observed an increased latency of the P3b component in EEGs of PD-VH patients, hypothesizing that a central cholinergic dysfunction might be an underlying cause of VH in PD.

Lastly, the third hypothesis, outlined in Figure 2C, states that an aberrant density of 5-HT2A receptors in PD-VH patients, possibly due to the dysfunction of the 5-HT system in PD (Huot et al., 2010), would cause a temporal imbalance in the transitions between integrated and segregated states (Zarkali et al., 2022). Moreover, pharmacological activation of 5-HT2A receptors in healthy participants resulted in increased P1 potentials and decreased alpha power values, which might be the cause of an imbalance in the perception of external and internal stimuli (Kometer et al., 2013).

How Do These Models Relate to Each Other?

Firstly, it is interesting to note that both the first and third models present the idea that an underlying mechanism of VH in PD consists of an imbalance between internally-generated stimuli and external inputs, causing the patient to recognize fictive stimuli as exogenous.

Furthermore, another significant observation concerns the last hypothesis. While Kometer et al. (2013) observed increased P1 potentials and decreased alpha power following pharmacological activation of 5-HT2A receptors, Zarkali et al. (2022) found associations between receptor-density maps and altered brain-state transitions. Specifically, the latter study found that PD-VH patients spend more time in the segregated state rather than the integrated one, compared to PD-non-VH. There is evidence that alpha power increases during visual integration in various areas of the brain, including early visual cortex and dorsal visual networks (Costa et al., 2024), showing a link between alpha oscillations and states of the brain. Thus, the increased dwelling time in segregated states in PD-VH patients is convergent with the decreased alpha power value identified by Kometer et al. and reflected by increased P1 potentials.

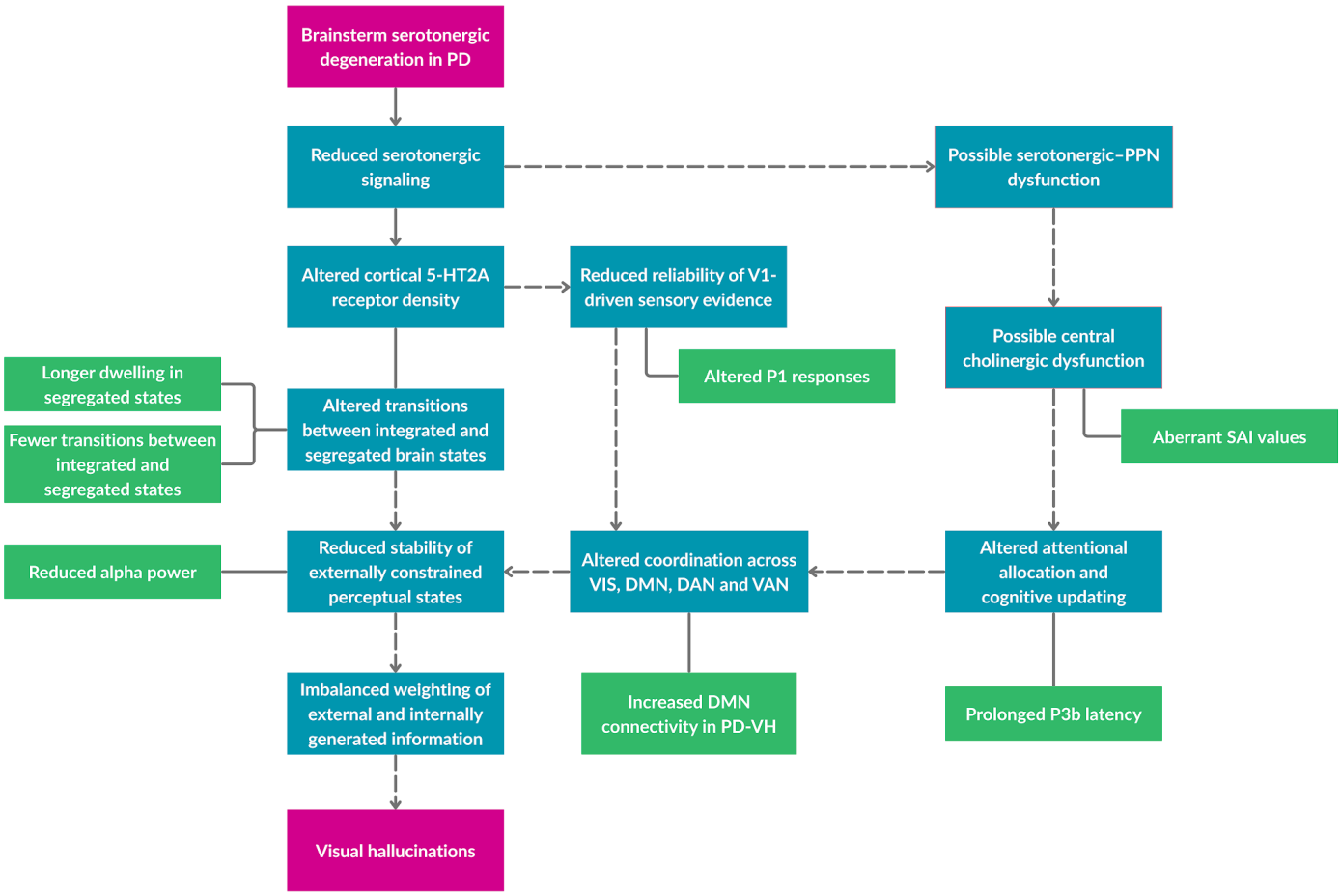
Additionally, an aberrant value of the P1 ERP component has also been observed by Schwartzman et al. (2008), attributed to primary visual dysfunction and reflecting VH. As previously explained, this last piece of evidence supports the model proposed by van Ommen et al. (2023), according to which VH arise from an early visual dysfunction in V1, involving the DAN, DMN and VAN, and resulting in an imbalance between external and internally-generated stimuli.

One last piece of evidence that reveals a correlation between the presented hypotheses is the notion that segregated and integrated states are highly influenced by the activity of the DMN and thalamic regions (Zarkali et al., 2022), therefore linking the attention and memory-related networks to the imbalance of brain states.

Drawing on the convergent—but not yet causally unified—evidence considered, the present study proposes a model of VH in PD that assigns a key role to serotonin dysfunction (see Figure 3). PD is associated with degeneration of serotonergic neurons in the brainstem, leading to reduced 5-HT levels. Huot et al. (2010) proposed that reduced serotonergic signaling may be accompanied by a compensatory increase in 5-HT2A receptor density, which may contribute to abnormal activity in

visual

Figure 3. Proposed unified framework for visual hallucinations in Parkinson's disease. Color code: key framework nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships retained from the reviewed models; continuous lines without arrowheads indicate observed associations for which causal direction has not been established; dashed arrows indicate integrative or unresolved mechanistic links proposed by the unified framework. Red borders identify especially uncertain or indirect components.



and attention-related networks. Attributing VH in PD to a 5-HT dysfunction explains the late occurrence of this condition in the timeline of the disorder, as the serotonergic system is not as affected as the dopaminergic one in PD. Altered 5-HT2A receptor signaling may contribute to abnormal activity across the VIS and the network of the DAN, DMN and VAN, causing anomalous alpha power values and impaired transitions between integrated and segregated states, with a prolonged dwelling time in the segregated states and fewer transitions to the integrated state. An increased activity in the DMN found in PD-VH patients (Yao et al., 2014)—and linked with the dysfunction between segregated and integrated states—possibly explains the aberrant P3b values observed by Chang et al. (2016). Indeed, a study conducted by Baumeister et al. (2014) found that increased P3 amplitude is linked to higher excitability in areas related to memory recollection and internal stimuli processing. Therefore, it can be assumed that the P3 ERP component might reflect DMN activity, partly supporting the convergence of the data considered.

The previous models presented by van Ommen et al. (2023) theorized that the activation of the loop giving rise to VH—involving DMN, DAN and VAN—originated from a dysfunction in V1, which would indeed be reflected by the aberrant P1 medial potentials. There are some studies that link serotonin and acetylcholine to V1 functions in animals; for instance,

Shimegi et al. (2016) investigated how cholinergic and serotonergic systems modulate visual processing in monkey V1. However, further evidence is necessary to define the underlying mechanisms that activate the loop between the VIS and visual-related networks. It is important to understand how the loop itself begins, whether it arises from dysfunction in V1 or abnormal activity in attentional networks, and to clarify which neurotransmitters are involved.

This study also aims to draw attention to another possible key factor in the development of VH in PD patients: the role of the pedunculopontine nucleus (PPN). The PPN lies between the midbrain and the upper pons and is a multifunctional nucleus involved in many different neurotransmitter systems (Benarroch, 2013). It contains cholinergic neurons but also receives inputs from a variety of different neurotransmitters, including serotonergic neurons from the dorsal raphe nucleus (DRN), a multitransmitter nucleus located in the midbrain (Benarroch, 2013; Michelsen et al., 2007). Numerous studies mention the PPN in relation to VH in PD. With its cholinergic neurons, it is linked to attention networks, and it controls the visual cortex (Manganelli et al., 2009). Specifically, it modulates feedforward input to V1, exhibiting its crucial role in visual perception. Moreover, the neurotransmitters synthesized in the PPN modulate both the VAN and the DAN, together with other nuclei in the brainstem (Alves et al., 2022). These findings suggest that there is a connection between the PPN, attentional networks and other structures in the brainstem, especially the DRN, and that these connections are modulated by neurotransmitters.

It is known that degeneration in the serotonergic neurons in the brainstem causes a decline in the serotonin levels (Huot et al., 2010). This might imply that a dysfunction in the synthesis and release of serotonin in the DRN causes a decrease in 5-HT, as well as a dysfunction in the PPN. Lack of 5-HT would result in enhanced levels of 5-HT2A receptors—with the following progression previously explained. Furthermore, this model can justify the hypothesis of a cholinergic dysfunction, for a dysfunction in the PPN would likely affect its release of acetylcholine, perhaps resulting in an impaired functioning of the VAN and the DAN. Moreover, since it modulates feedforward input to V1, it could be an underlying cause of the disrupted connection between the visual cortex and the attentional networks, which results in the activation of the loop postulated by van Ommen et al. (2023).

Conclusions

This review proposes that serotonergic dysfunction may provide a mechanistic bridge between early visual abnormalities, altered neuromodulatory signaling, and large-scale network dynamics in Parkinson's disease with visual hallucinations. In the proposed framework, reduced serotonergic signaling and altered cortical 5-HT2A receptor density may contribute to electrophysiological changes, disrupted transitions between integrated and segregated brain states, and impaired coordination among visual and attention-related networks. A possible serotonergic-PPN-cholinergic pathway may offer an additional connection between these levels, although this component remains indirect and requires specific experimental validation.

The framework should therefore not be interpreted as demonstrating that serotonergic dysfunction is the single cause of visual hallucinations or that it necessarily precedes cholinergic and network abnormalities. Its principal contribution is to identify testable links among findings that are usually considered separately. Future longitudinal, multimodal, and pharmacological studies will be required to establish causal direction and determine whether these mechanisms represent upstream drivers, interacting contributors, or downstream consequences of hallucinations in Parkinson's disease.

Limitations and Future Research Directions

The central limitation of the proposed framework is that it integrates evidence obtained from heterogeneous populations and methods. Some studies involve healthy participants exposed to serotonergic hallucinogens, some examine psychosis outside Parkinson's disease, and some include PD-VH samples affected by dementia. Future work should therefore test the framework prospectively in carefully phenotyped, nondemented PD cohorts. The strongest design would combine receptor-sensitive imaging, EEG measures of P1/P3b and alpha power, and repeated fMRI measures of DMN–DAN–VAN coupling and integrated–segregated state transitions within the same participants. Longitudinal studies should determine whether serotonergic and cholinergic changes precede hallucination onset, while pharmacological studies should test whether modifying 5-HT2A or cholinergic signaling changes the predicted electrophysiological and network markers. These tests would distinguish correlation from causation and clarify whether the PPN and DRN are upstream drivers, downstream consequences, or interacting modulators of the proposed pathway.

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Author Biography

Redacted for double-blind review.

Mentor Contribution Statement

The research mentor provided conceptual guidance, recommended relevant literature, discussed the interpretation of evidence, and offered feedback on the manuscript's organization and argument. The author independently conducted the literature review, developed the proposed unified framework, and wrote and revised the manuscript. The mentor did not collect or analyze original data and is not listed as a co-author.

AI Use Statement

Generative AI tools were used for limited editorial support, including assistance with identifying typographical errors and awkward phrasing, checking reference formatting, and improving the organization of flowcharts. The author independently developed the research question, selected and interpreted the literature, constructed the proposed framework, evaluated the scientific claims, and approved all final wording. AI tools were not used to generate original data or conduct data analysis. The author verified the accuracy of all substantive claims, citations, and references and accepts full responsibility for the manuscript.

Short Answer Questions

Please reply to each question in 2-3 sentences. For any "yes or no" questions, please offer constructive, actionable guidance if the paper needs improvement.

What is the strongest feature of this paper?

The paper's strongest feature is its effort to synthesize several previously distinct explanations of visual hallucinations in Parkinson's disease into a single multilevel framework. In particular, the proposed connections among early visual processing abnormalities, cholinergic dysfunction, serotonergic/5-HT2A signaling, and large-scale network dynamics move the paper beyond a conventional literature review toward a testable theoretical model.

Evaluate the overall academic rigor of the paper. Are there any major issues with the student's data analysis, thesis, main claims, or citations / bibliography?

The paper demonstrates strong academic rigor for a theoretical/narrative review. The central thesis is clearly stated, relevant evidence is drawn from multiple methodological approaches, and the author appropriately distinguishes observed associations from proposed causal relationships.

The main limitation of this paper is that the framework integrates heterogeneous evidence (including studies of healthy participants, non-PD psychosis, and PD populations affected by dementia) so some mechanistic connections remain inferential rather than directly demonstrated; however, the author recognizes this limitation.

Comment on the overall clarity of the student's prose. Is there any part of the paper that the student needs to revise for clarity and style?

Overall, the prose is clear, technically appropriate, and generally easy to follow despite the complexity of the topic. The main clarity issue is that parts of the literature review devote substantial space to describing the procedures of individual studies when the manuscript's central purpose is to synthesize those studies into a unified framework.

For example, in the early visual dysfunction section, the paper gives a detailed explanation of the Hallucination-Proneness Questionnaire, including the 0–5 response scale, the number of statements, and the sequence of Mooney face stimuli shown to participants. Some of this methodological detail could be condensed to a sentence explaining that Schwartzman et al. compared visual ERP responses in participants with differing levels of hallucination proneness using face-perception tasks. The more important material for this paper is the finding that P1 and P2 amplitudes differed and how those abnormalities support the argument for disrupted early visual processing.

A similar issue occurs in the cholinergic dysfunction section, where the manuscript describes the visual target-detection task and then explains N1, P2, N2, P3, P3a, and P3b in considerable detail before arriving at the main finding of prolonged P3b latency in PD patients with hallucinations. Because the paper ultimately uses this study to support a possible relationship between cholinergic dysfunction and altered cognitive/attentional processing, the procedural description and ERP background could be shortened and the interpretation of the P3b finding could receive greater emphasis.

The serotonergic section provides another example. The description of the Kometer et al. experiment includes the four experimental conditions, the specific "pacman"/Kanizsa stimuli, button-press task, EEG procedure, and post-experiment questionnaire. Much of that could be compressed so the reader reaches the conceptually important result sooner: 5-HT2A activation was associated with altered P1/N170 responses and reduced alpha power, providing a potential mechanistic link between serotonergic signaling, early visual processing, and altered cortical/network activity.

The concern is therefore not that these descriptions are unclear or scientifically irrelevant. Rather, their level of detail sometimes makes the manuscript read like a sequence of individual study summaries before returning to the author's larger argument. The review would be stronger if each study were presented more consistently as question → key result → limitation → relevance to the unified framework, with methodological details included only when they are necessary to interpret the findings.

Please identify the part of the paper that the student should spend the most time and energy revising. This "part" can be an actual section of the paper (e.g., "Introduction") or a feature of the paper (e.g., clear topic sentences, the thesis, the structure).

The student should devote the most revision to the transition from the literature review into the unified framework, particularly the section explaining how the three models relate to one another. This is the paper's most original contribution, so the synthesis should consistently distinguish evidence directly demonstrated by cited studies from mechanistic connections newly proposed by the author; Figure 3 already begins doing this effectively by visually distinguishing established associations, directional relationships, and unresolved links.

Introduction

Does the introduction offer clear context, helping the reader understand the question that the student is asking in your field? Further, has the student cited recent studies in the field to show why this question or topic matters, demonstrating the paper's stakes?

- Yes. The introduction provides sufficient clinical and scientific context, establishes the importance of visual hallucinations in PD, identifies the absence of a unified explanatory framework, and ends with a clear statement of the paper's purpose: reviewing existing hypotheses and proposing serotonergic dysfunction as an integrative bridge. The introduction could be strengthened further by making the paper's specific conceptual novelty even more explicit (i.e., briefly stating what this framework contributes beyond the models already present in the literature).

Structure

Are the paper's body sections in a logical order? Within each section, are the main steps of the argument in a logical order? If not, how would you recommend rearranging the body sections–or the paragraphs within a section–to improve the structure?

- Yes, overall. The organization is logical: the paper establishes the scope of the review, examines the three explanatory models separately, then explicitly compares them before proposing an integrated framework and discussing its limitations. The main structural improvement would be to tighten some of the study-by-study descriptions in Section 3 so that the reader reaches the comparative synthesis (the intellectual center of the paper) more efficiently.

Content

Does each paragraph communicate a claim / idea? Are there any problem paragraphs that need particularly intensive revisions?

- Generally yes; paragraphs typically have identifiable purposes and progress logically through the evidence. The strongest analytical writing occurs when the author explicitly compares apparently conflicting findings or explains why one finding does or does not challenge another model, rather than simply describing an individual study

Does every paragraph contain evidence to back up its claim[s]? Is the student consistently analyzing their evidence, or are they merely summarizing?

- Claims are consistently supported by citations, but the balance between summary and analysis could be improved. Some experimental descriptions could be shortened, with more space devoted to explaining exactly how the findings support, contradict, or constrain the proposed unified framework.

If the paper includes secondary data analysis or reproduces a graphical representation from a previously published paper, has the student clearly identified where the data or figure came from and explained what statistical methods they used to analyze it?

- The paper does not appear to conduct a new secondary statistical analysis; rather, it is explicitly described as a focused narrative review and theoretical synthesis. The figures appropriately identify their evidentiary status (for example, Figure 3 distinguishes observed associations from proposed or unresolved mechanistic links) which is especially important given the theoretical nature of the framework.

Conclusion

Has the student pointed the reader towards the outcomes of this paper: questions for further research, policy arguments, what they want the reader to learn, etc? If not, can you suggest any outcomes for the student to draw out?

- Yes. The conclusion clearly states the principal contribution while appropriately avoiding the claim that serotonergic dysfunction has been established as the singular cause of PD visual hallucinations. The subsequent limitations/future-directions section is particularly strong because it translates the proposed model into concrete testable studies involving multimodal imaging, EEG, longitudinal designs, and pharmacological manipulation.

Citations

Is there a Works Cited page, and are there corresponding citations throughout the paper?

- Yes. The manuscript contains corresponding in-text citations throughout and a substantial References section containing full bibliographic information and DOIs where applicable. I did not identify an obvious systemic citation problem from the manuscript, although final copyediting should verify that every in-text citation has a corresponding reference and vice versa.

Other Comments?
Please offer comments on specific passages by simply writing in reply to the final question on the form:

Page 3, "Because the included studies differ substantially in population, task, and measurement method…": This is an important qualification and should remain prominent; it appropriately establishes that the unified framework is a testable hypothesis rather than a demonstrated causal model.

Page 12, "How Do These Models Relate to Each Other?": This section contains some of the manuscript's strongest original reasoning. Consider emphasizing it further and trimming earlier descriptive material so that the comparative synthesis occupies a proportionally larger part of the manuscript.

Page 15, "Its principal contribution is to identify testable links among findings that are usually considered separately.": This is an excellent articulation of what the manuscript actually contributes and could potentially be stated earlier, perhaps near the end of the introduction, to sharpen the paper's thesis from the outset.

Manuscript Evaluation Rubric
Student Name:
Subject:
Title of Paper:
Proposal for a Unified Framework to Understand the Functional Changes That Occur in Visual Hallucinations in Parkinson's Disease

I. Appropriateness of the Topic				
Inappropriate _____	Doubtful _____	Marginal _____	Suitable _____	Highly Appropriate __X___

II. Conceptual Adequacy				
Inadequate _____	Weak _____	Marginal _____	Good _____	Outstanding __X___

III. Mastery of Relevant Literature				
Inadequate _____	Weak _____	Marginal _____	Good _____	Outstanding __X___

IV. Technical Adequacy				
Completely Inadequate _____	Major Problems _____	Minor Problems _____	Good __X___	Outstanding _____

V. Clarity of Presentation				
Unclear, requires extensive rewriting _____	Major Problems _____	Minor Problems _____	Good __X___	Outstanding _____

VI. Significance of Contribution to the Field				
None _____	Trivial _____	Modest _____	Good __X___	Outstanding _____

VII. Reviewer Recommendation				
REJECT Almost no chance that problems can be resolved. ____	REJECT, DESPITE MERIT Although parts of the manuscript have merit, it is unlikely that the problems can be resolved. _____	INVITE REVISION Possibly publishable if problems noted in my review are resolved. _____	CONDITIONAL ACCEPTANCE Publishable if the minor problems noted in my review are resolved. __X___	ACCEPT Subject only to normal copy editing, if any. _____

Conditional Acceptance.

The manuscript already has a coherent thesis, substantial literature support, a clearly delineated original contribution, explicit acknowledgment of evidentiary limitations, and concrete future directions. The revisions I would request are primarily tightening and sharpening (as in, reduce excessive study-level description, bring the synthesis forward, and make the distinction between established evidence and proposed mechanistic connections maximally explicit) rather than restructuring or reconceptualizing the paper in general.

REVIEWER 2:

This is a review article focused on understanding the neurobiological basis of visual hallucinations in Parkinson's disease. The author reviews multiple models aimed at elucidating the neurobiological basis of visual hallucinations. The author argues that the evidence supports the view that a deficit in serotonergic neurotransmission may be the best model for understanding visual hallucinations in Parkinson's disease.

I found the manuscript to be detailed, and to be a thorough analysis of the literature.The table is a great addition and helps explain the results from the different studies. I found some areas hard to follow. The author goes into much detail about the study The author, at times, loses track of how these observations support the different models underlying visual hallucinations.

I am not convinced that the serotonergic system is the best model to explain visual hallucinations in Parkinson's disease (PD). I think the survey of the literature supports the notion that multiple systems may be contributing to visual hallucinations in PD. Alterations in serotonergic receptors individuals with PD may be a downstream consequence of other neurobiological changes.

My comments below focus on improving clarity:

Introduction: The author discusses ERP components such as the P1 and P3b, but does not introduce them or provide additional information about what these are or what they measure. It would be good to tell the reader more about the P1 and P3b potentials and what information these components capture. The author uses a range of terms to discuss modifications in neural activity, but the information is hard to read because the use of terms is rather vague . What does, for example, "temporal imbalances in transitions between segregated and integrated states" mean? It would be best to use more precise language.

1.1 Early Visual Dysfunction

The first paragraph should overview the different topics covered. Please introduce the various studies described in this section and how they relate to the model.
The author describes how visual stimuli differentially impact the P1 in individuals with and without visual hallucinations. Rather than only discussing changes to P1, specify how neural activity is impacted in individuals with and without visual hallucinations.

1.1 Imbalance Between External and Internal Stimuli due to a Central Cholinergic Dysfunction

This section should introduce us to the various studies presented in this section.
The author discusses "short-latency afferent inhibition (SAI)" but does not define what this is. Please define the term as soon as it is introduced.

1.1 Serotonergic Dysfunction, 5-HT2A Receptors, and Brain-State Dynamics

The author goes into details of the study, but should focus on performing a synthesis of these findings.

1.1 How Do These Models Relate to Each Other?

I don't see how the results from these different studies are mutually exclusive in supporting one model or another. There could be dysfunctions in the cholinergic, serotonergic, and dopaminergic systems that contribute to visual hallucinations.

The story about the pedunculopontine nucleus appears at the end of the manuscript. It was not properly introduced. I think that the inclusion of the role of pedunculopontine nucleus is not necessary here. It would be best to focus on providing a clear picture for the evidence supporting the three different models in visual hallucinations.

Additional suggestions:

Please make sure to introduce the reader to the methods used to monitor brain activity. Please consider a figure to explain the different metrics—such as ERPs, rsfMRI, and short-latency afferent inhibition (SAI)—what they measure, and their limitations

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Proposal for a Unified Framework to Understand the Functional Changes That Occur in Visual Hallucinations in Parkinson's Disease

Abstract

Visual hallucinations in Parkinson's disease are often viewed as isolated symptoms of neurodegeneration. However, growing evidence suggests that they reflect deeper disruptions in how the brain constructs perception. This paper reviews three major hypotheses—early visual dysfunction, cholinergic dysfunction, and serotonergic dysfunction—and proposes a unified framework linking these mechanisms across multiple levels of brain organization. By integrating electrophysiological, neurochemical, and network-level findings, this study argues that hallucinations arise from an imbalance between internally generated and externally driven signals. Specifically, serotonergic dysfunction, through alterations in 5-HT2A receptor density, may be a mechanistic bridge linking early sensory processing with large-scale network dynamics, including impaired transitions between brain states. Understanding these mechanisms provides insight not only into Parkinson's disease, but also into the fundamental nature of perception as an active and dynamic process. More broadly, this work highlights the importance of approaching neurodegeneration as a distributed, multilevel phenomenon, with implications for developing more integrated and effective therapeutic strategies.

Keywords: Parkinson's disease; visual hallucinations; serotonin; 5-HT2A receptor; visual processing; attention networks; brain-state dynamics

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder attributed to a dysfunction in the dopaminergic system (Lew, 2007). The main symptoms of PD and those that serve as a diagnosis are motor, but patients often show a spectrum of various non-motor symptoms as well. Moreover, it is possible for PD patients to develop dementia or psychotic symptoms. This last condition is known as Parkinson's disease psychosis (PDP) (Friedman, 2010), and its main symptom is visual hallucinations (VH).

VH can present in different forms, and they are commonly classified as elementary and complex. Elementary VH generally

consist of geometric patterns, such as lines, curves or spots (Billock & Tsou, 2012). These can also have additional features such as color or motion. Conversely, complex VH feature a variety of different contents, often depicting animal or human figures in absurd or unrealistic contexts (Manford & Andermann, 1998). Patients who suffer from a psychotic disorder often encounter both elementary and complex VH, but most PD patients recall having experienced complex VH (van Ommen et al., 2023).

It was initially believed that VH and PDP were a collateral effect of dopaminergic treatments, administered to alleviate the motor symptoms of the disorder; however, some PD patients develop PDP without medications (Friedman, 2010). This suggests that PDP is a progression of PD itself. Indeed, while dopamine is the main neurotransmitter attributed to PD motor symptoms, it is believed that the disorder also displays dysfunctions in other neurotransmitter systems and in the interactions between those; many motor and non-motor symptoms of the disease have been attributed to neurotransmitters such as serotonin, acetylcholine, glutamate and γ-aminobutyric acid (GABA) (Barone, 2010).

PD is the second most prevalent neurodegenerative disorder in the world population, and VH has a prevalence range of 8%–40% in PD patients (Barone, 2010; Manganelli et al., 2009). Moreover, there are a variety of correlates linking VH and PD. For example, VH in PD are associated with aberrant event-related potential (ERP) components, including alterations in P1, which reflects early visual processing, and P3b, associated with later cognitive processing of stimuli. Moreover, some PD-VH patients present anomalous neural network behavior, including enhanced excitability in the default mode network and in attention-related networks, as well as longer periods in segregated brain states and fewer transitions toward integrated states. Nevertheless, the underlying mechanisms giving rise to VH are largely unknown.

A complicating factor to this phenomenon is the high occurrence of dementia in PD, known to cause cognitive impairment and dysfunctions in many neural networks, namely in attention, memory and visual perception pathways, sometimes resulting in VH itself (Gratwicke et al., 2015). Since dementia and psychosis often coexist in PD patients, it is difficult to discern the distinct effects that the two conditions have on neural networks in PD, as well as to identify their respective causal factors.

At present there remains no unified framework able to explain how and which neural networks are involved in VH among nondemented PD patients. Investigating the functional changes that occur in VH in PD can offer new insights into visual processing and stimuli interpretation. Moreover, it may enhance treatments to alleviate VH, perhaps reducing the effects that they have on the overall health of the patient. VH are indeed linked with both a greater chance of developing dementia and a higher risk of mortality (Manganelli et al., 2009). Eventually, having a better understanding of the neural networks involved in VH in PD can lead to improvements in the quality of life of the patients.

The present study reviews existing hypotheses of VH in PD and examines how findings from early visual, cholinergic, serotonergic, and network-level models may interact rather than represent mutually exclusive explanations. In particular, it proposes that serotonergic dysfunction may provide one possible integrative bridge between these abnormalities.

2. Method and Scope of the Review

This paper is a focused narrative review and theoretical synthesis. It compares evidence from electroencephalography, neuroimaging, pharmacological studies, network-control approaches and postmortem receptor analyses (see Table 1).

76 ***Table 1. Methods Used to Characterize Neural Dysfunction in Visual Hallucinations***

Method	What it measures	Main strength	Main limitation
Electroencephalography (EEG) and Event-Related Potentials (ERPs)	EEG records electrical activity from the scalp; ERPs isolate activity time-locked to specific stimuli or events (Fabiani et al., 2007; Beres, 2017).	Excellent temporal resolution, allowing neural responses to be tracked on the millisecond scale (Beres, 2017).	Limited ability to precisely localize the neural source of the recorded activity (Beres, 2017).
Resting-state fMRI (rsfMRI)	Measures spontaneous fluctuations in the blood-oxygen-level-dependent (BOLD) signal at rest and their correlations across brain regions, allowing functional connectivity to be estimated (Van Den Heuvel & Pol, 2010).	Allows investigation of large-scale functional networks across the brain.	BOLD is an indirect measure of neural activity and has relatively poor temporal resolution because of the delayed haemodynamic response.
Short-latency afferent inhibition (SAI)	A neurophysiological measure of sensorimotor inhibition that is used as a putative marker of central cholinergic function (Martin-Rodriguez & Mir, 2020).	Provides a non-invasive physiological measure associated with cholinergic function in humans.	It is an indirect marker rather than a direct measurement of acetylcholine, and it can be influenced by factors such as disease duration and dopaminergic medication (Martin-Rodriguez & Mir, 2020).
Network-control analysis	Uses structural and functional brain-network data to estimate transitions between brain states and the control energy required for those transitions (Zarkali et al., 2022).	Can characterize dynamic differences in integrated and segregated brain states.	The inferred transitions and energy values depend on the assumptions of the mathematical model used and do not directly measure neurotransmitter activity.

Postmortem receptor analysis	Uses receptor-binding techniques in brain tissue to quantify receptor density; Huot et al. (2010), for example, measured 5-HT2A receptor binding in cortical tissue from PD patients.	Provides direct anatomical evidence of receptor-level differences in human brain tissue.	It is cross-sectional and cannot establish whether receptor changes precede or result from VH.

Relevant studies were identified through targeted searches of PubMed, Google Scholar, and reference lists of key reviews using combinations of terms related to PD, VH, visual processing, cholinergic dysfunction, serotonin, 5-HT2A receptors, and brain-state dynamics. Studies were selected for their relevance to three recurring explanatory levels: early visual processing, cholinergic modulation, and serotonergic/network-state dysfunction. Because the included studies differ substantially in population, task, and measurement method, and several do not examine nondemented PD patients directly, the proposed framework should be interpreted as a testable integrative hypothesis rather than a demonstrated causal model.

3. Literature Review on Visual Hallucinations in Parkinson's Disease

There are several models that try to explain the functional changes that occur in PD patients causing VH. The present study focuses on three frameworks that emphasize different but potentially interacting levels of dysfunction. The first hypothesis focuses on early visual dysfunction (Schwartzman et al., 2008; van Ommen et al., 2023), while the second and third present a broader explanation of VH involving an imbalance between external and internal stimuli and the modulation of visual and attentional networks. The distinguishing factor between the last two models lies in the type of neurotransmitters involved: the second emphasizes central cholinergic dysfunction (Manganelli et al., 2009), whereas the third focuses on serotonergic dysfunction and altered 5-HT2A receptor density (Kometer et al., 2013).

3.1 Early Visual Dysfunction

The early visual dysfunction model proposes that abnormalities in the initial processing of visual information may contribute to VH and, through disrupted communication with higher-order visual and attentional networks, lead to the misinterpretation of internally generated information as external. Evidence for this model comes from studies examining both early electrophysiological responses to visual stimuli and the interaction between primary visual processing and broader visual-attentional networks.

A study conducted by Schwartzman et al. (2008) evaluated the hypothesis that aberrant early visual ERP components reflect individuals' proneness to hallucinate. While early visual disruption had been previously associated with various psychological and neurological disorders that present VH—e.g. PD, schizophrenia—it remained unclear whether an early impairment of visual processes was a key factor in the development of VH or rather a mere outcome of the disorder itself.

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In order to reduce the possibly confounding influence of cognitive decline, the study analyzed electroencephalogram (EEG) recordings from healthy individuals divided according to their proneness to hallucinate. Hallucination proneness was assessed using a questionnaire, after which participants completed a face-perception task involving photographs, Mooney faces, and scrambled Mooney faces (see Figure 1). The Mooney Faces Test (MFT) evaluates an individual's ability to perceive human faces in two-dimensional, black and white pictures, shown both upright and upside down (Silverstein et al., 2021).

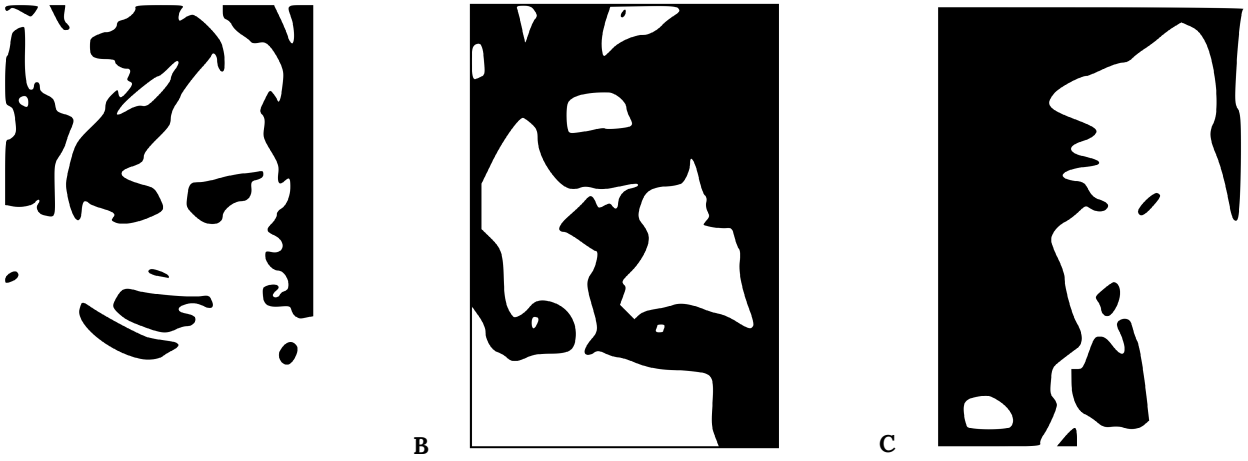


Figure 1. Representative stimuli from the Mooney Faces Test. *The upright Mooney face (A) is typically perceived as a face, whereas the inverted Mooney face (B) is substantially more difficult to recognize due to disruption of holistic face processing. The scrambled image (C) serves as a non-face control stimulus. Stimuli adapted from the dataset of Schwiedrzik et al. (2018) and redrawn as vector graphics for presentation clarity under CC BY 4.0.*

During the experiment conducted by Schwartzman et al., the participants' brain activity was recorded through EEG; specifically, the study focused on ERP components that reflect early visual processes. The components analyzed were the N170, P1 and P2, respectively associated with face recognition, early extraction of information from face stimuli, and finally a higher level of visual processing involving categorization of face stimuli. The interpretation of the stimulus in P2 depends on the reception of information carried out in P1.

The study observed no significant differences in the N170 component, while P1 and P2 showed increased positivity in hallucination-prone individuals. The lack of significant N170 differences suggests that the observed changes in P1 and P2 were not specific to face recognition but may instead reflect abnormalities in earlier stages of visual processing. Conversely, the increased amplitude registered in P1 suggests a dysfunction in the extraction of fine information from visual stimuli, which would in turn impair the interpretation of the visual information itself, explaining the knock-on effects on P2. Thus, compared with individuals with low hallucination proneness, hallucination-prone participants showed altered stimulus-evoked electrophysiological responses during early visual processing. However, because the study involved healthy participants rather than PD patients with VH, these findings support an association with hallucination susceptibility rather than establishing a PD-specific causal mechanism.

An earlier study had shown a correlation between P1 ERP component in patients with PD and primary visual processes

(Wang et al., 2001). The association between P1 and primary visual processing in PD provides a basis for considering abnormal P1 responses as a possible marker of early visual dysfunction in PD-VH.

Although there is evidence that early visual dysfunction is related to VH in PD, it appears to be highly unlikely for VH to be explained as a focal pathology. Instead, a study led by van Ommen et al. (2023) correlated an impairment in primary visual processes to dysfunctions in other visual-related neural networks, proposing a more holistic explanation of VH.

They aimed to evaluate a hypothesis previously postulated by Shine et al. (2014), which had explained VH as a consequence of a disconnection between the primary visual cortex, V1, and higher visual components, inducing a desynchronization between different parts of the visual network. This previous hypothesis was supported by the reduced activity registered in the primary visual cortex in patients with psychotic VH.

In order to evaluate the postulated model from Shine et al. and assess what areas of the brain are involved in psychotic VH, van Ommen et al. (2023) conducted an experiment on hallucinating psychotic individuals, recording their brain activation data during an episode of VH, through functional magnetic resonance imaging (fMRI). The results showed a lack of activation in V1 and increased activity across the visual and attention pathways, specifically in the Dorsal Attention Network (DAN), Default mode network (DMN) and Ventral Attention Network (VAN). These are respectively linked to processing external information, interpreting internal stimuli and coordinating memory and finally synchronizing the two networks—DAN and DMN (Van Calster et al., 2017). The results are therefore in line with the hypothesis postulated by Shine et al., 2014, as they show that psychotic VH is not a focal pathology. Instead, it affects a wide range of regions, namely the visual network (VIS)—excluding V1—and vision-related networks involved with memory and attention.

Based on these findings, Van Ommen et al. proposed a refinement of the model postulated by Shine et al., attributing VH in PD to the activation of a loop across the VIS—with the exception of V1—and the DAN, DMN and VAN. Under normal circumstances, feed-forward impulses are sent from V1 to the surrounding visual network regions. This flow of information allows the stimulus to be recognized as external. In turn, a feedback inhibitory response is sent from the networks to V1. According to this model, the ability of V1 to provide feed-forward and receive feedback information from the surrounding areas is compromised in psychotic VH. This disruption may cause internally generated information to be misinterpreted as external sensory input, thereby contributing to the generation of VH.

However, since van Ommen et al. investigated VH in individuals with psychosis rather than specifically in PD patients, the extent to which this network mechanism applies directly to PD-VH remains to be established.

Another piece of evidence in support of the model proposed by van Ommen et al. is given by a study from 2014, led by Yao et al., which investigated DMN activity in resting PD patients, both with (PD-VH) and without VH (PD-non-VH) and in healthy controls. Patients with symptoms of cognitive impairment and dementia were excluded. Resting-state functional magnetic resonance imaging (rsfMRI) data of the participants were acquired, and the results showed a decreased activity in the DMN in PD patients compared to controls. Conversely, PD-VH patients had a greater excitability of the DMN compared to PD-non-VH. Yao et al., therefore, demonstrated that a higher connectivity in the DMN is associated with VH in PD patients, relative to PD-non-VH patients. Showing a correlation between aberrant DMN activity and VH in PD, these data support the model proposed by van Ommen et al.

Thus, while there are findings suggesting that early visual impairment has a role in generating VH in PD, this is treated as

one level of a distributed mechanism rather than a complete explanation of the condition. Moreover, this presented model fails to include the involvement of neurotransmitters in VH in PD. To fully comprehend the underlying neurological mechanisms of VH in PD, it is necessary to adopt a more holistic approach, recognizing the role of neurotransmitters in modulating attention and vision-related networks. Consistent with the model postulated by van Ommen et al., 2023, a second hypothesis attributes VH in PD to an imbalance between external and internal stimuli, and specifically as a consequence of a central cholinergic dysfunction.

3.2 Imbalance Between External and Internal Stimuli due to a Central Cholinergic Dysfunction

The cholinergic model proposes that VH arise partly from impaired cholinergic modulation of attention, contributing to an imbalance between externally driven and internally generated information. Evidence for this model comes from both physiological measures of central cholinergic function and ERP studies of cognitive processing in nondemented PD patients with VH.

A study from 2009, conducted by Manganelli et al., found a correlation between nondemented PD-VH patients and a central cholinergic dysfunction. The research methodology included the use of short-latency afferent inhibition (SAI), a physiological measure commonly used as an indirect marker of central cholinergic function (Martin-Rodriguez & Mir, 2020). The participants were 22 non-demented PD patients, both with and without VH (Manganelli et al., 2009). The study found that most PD-VH patients presented aberrant SAI values, unlike PD-non-VH individuals. Therefore, Manganelli et al. concluded that VH in PD could be one of the factors that alter the balance of the cholinergic system. Alternatively, VH would cause a dysfunction between the cholinergic and other neurotransmitter systems. The study also confirmed the hypothesis of a correlation between cholinergic dysfunction and PD patients who are likely to develop dementia. Similarly, VH are considered to be a predictive factor of dementia. Therefore, there is a possible link between central cholinergic dysfunction and VH in PD.

However, there remains disagreement about the direction of causality, as other later studies consider cholinergic dysfunction as a causal factor of VH in PD. One of these is a study led by Chang et al. (2016).

While aberrant ERP values are considered an indicator of cognitive dysfunction in demented PD patients, their role in nondemented PD patients, both with and without VH, remained unclear. Specifically, some studies had found a correlation between PD-VH patients and impaired P3 responses, a component related to attentional allocation and cognitive processing of task-relevant stimulus (Kurita et al., 2010; Chang et al., 2016). To address this gap in the literature, Chang et al. compared ERP responses in nondemented PD patients with and without VH, and in healthy controls during a visual target-detection task. They reported that PD-VH individuals showed a prolonged latency of one subcomponent of the P3, namely the P3b component, compared with controls. Since P3b is associated with later cognitive processing and memory updating, this result was interpreted as evidence of altered cognitive processing in PD-VH and was considered compatible with central cholinergic dysfunction (Chang et al., 2016; Polich, 2003).

This study also investigated N1 and P2, two exogenous ERP responses associated with sensory and attentional processing respectively (Chang et al., 2016; Donchin et al., 1978). Chang et al. reported no significant differences in either component across the groups. This finding does not necessarily contradict the visual-network dysfunction model described previously. These ERP components and the DAN, VAN, and DMN reflect different levels of neural processing, and there is no evidence

that abnormalities in these large-scale networks must be accompanied by altered N1 or P2 responses. The Chang et al. findings therefore add evidence of altered later cognitive processing rather than excluding the involvement of visual and attentional networks.

3.3 Serotonergic Dysfunction, 5-HT2A Receptors, and Brain-State Dynamics

The serotonergic model proposes that altered serotonergic signaling, particularly through 5-HT2A receptors, may contribute to VH by modifying visual processing and the balance between internally and externally driven neural activity. Evidence for this model comes from pharmacological manipulation of 5-HT2A signaling, postmortem receptor analyses in PD, and studies of large-scale brain-state dynamics.

An aberrant density of 5-HT2A receptors in different cortical areas has often been connected to various forms of psychosis, including PDP (Huot, 2018), but the effect of this receptor's activation on VH is left unclear. A study conducted by Kometer et al. (2013) aimed to clarify this connection by investigating the effects that the activation of the 5-HT2A receptor has on parieto-occipital α waves.

α oscillations, considered to be mostly present in the thalamic regions and visual cortex, have been correlated with visual processing dysfunctions and impairments (Clayton et al., 2018). Since they are strongly linked to visual processing, they are also associated with visual-related potentials (Kometer et al., 2013). The study presented here hypothesized that α oscillations could contribute to the generation of VH. According to their model, activation of 5-HT2A receptors, triggered by the administration of psilocybin, a serotonergic hallucinogen, would alter α oscillations. A second hypothesis postulated by the study concerned how early visual ERP components—specifically the P1 and N170—would be influenced by psilocybin-induced hallucinations. Thus, the investigation examined the effects of 5-HT2A activation on visual processing in healthy participants by comparing the effects of psilocybin with those observed after pretreatment with the 5-HT2A antagonist ketanserin. EEG responses were recorded during a visual perception task.

Psilocybin increased P1 amplitude over medial parieto-occipital regions, altered N170 responses, and decreased α power. These effects were suppressed by ketanserin pretreatment, supporting their relationship with 5-HT2A activation. Decreased α power was attributed to increased cortical excitability especially in the parieto-occipital regions and visual networks, following activation of 5-HT2A receptors. A reduction in α power had previously been associated with increased visual attention and cortical excitability in the occipital lobe, while increased α oscillations might directly suppress visual processing (Clayton et al., 2018). The decreased α power was also related to the increase in P1 medial potential, which might represent an enhancement in early visual processing (Kometer et al., 2013). This coordinated response between the P1 and α power would in turn contribute to an imbalance between perception of external and internal stimuli.

Specifically, altered cortical excitability may reduce the normal distinction between neural activity driven by external visual input and activity occurring in the absence of external stimuli. This corresponds to a change in the activation of brain networks—reflected by decreased α oscillations and enhanced P1 medial potentials—with an increased attention towards internally generated visual stimuli, rather than external stimuli. This model seems to be in line with the hypothesis proposed by van Ommen et al. (2023), in which VH arise from an altered balance between externally and internally generated signals.

Although the findings suggest that α power waves may have a role in psilocybin-induced VH, analytical studies showed little correlation between reduced α power and the occurrence of hallucinations, perhaps revealing that the reduction in α power triggered by psilocybin is not sufficient to induce complex VH. Moreover, the study involved psilocybin-induced perceptual alterations in healthy participants rather than in the PD population. Therefore, the study does not establish that the same mechanism causes complex VH in PD.

Finally, the psilocybin treatment produced a decrease in the N170, which is thought to play a key role in processing meaningful visual stimuli. An alteration in this component is associated with altered visual perception, and may therefore reflect changes produced during psilocybin-induced hallucinations. Alternatively, the effects on the N170 could be attributed to the increased cortical excitability triggered by the activation of the 5-HT2A receptor, further contributing to an imbalance between external and internal stimuli.

Taken together, the effects of 5-HT2A activation on P1, N170, and α power demonstrate that serotonergic signaling can alter neural processes involved in visual perception and cortical excitability, although these findings do not establish that the same mechanism causes VH in PD.

A previous study had investigated the distribution of 5-HT2A receptors in postmortem PD patients' tissues, postulating a correlation between increased receptor density and VH in PD (Huot et al., 2010). The results showed an increased density of this receptor in PD tissues with VH, compared to PD-non-VH, therefore providing PD-specific evidence supporting the involvement of 5-HT2A signaling in VH. While an existing postulate attributed the development of psychosis in PD to a polymorphism in the 5-HT2A receptor gene, a study led by Kiferle et al. (2007) refuted this hypothesis, and they concluded that aberrant levels of this receptor are not due to the genetic variations examined.

Huot et al. (2010) proposed a new explanation of the enhanced levels of 5-HT2A receptors in PD patients with psychosis, defining it as a consequence of other neurotransmitter dysfunctions in PD. PD is known to present serotonin (5-HT) dysfunctions; specifically, degeneration in the serotonergic neurons in the brainstem causes a decline in the neurotransmitter levels. Huot et al. proposed that this may contribute to a compensatory increase in 5-HT2A receptor density, as a biological attempt to balance the drop of 5-HT in different areas of the brain. Enhanced levels of 5-HT2A could also be attributed to the decrease in dopamine (DA) levels, which acts as a partial agonist to the receptor. These two possibilities are likely to be complementary, and this explanation would help explain the late occurrence of VH in the development of PD: the disorder disrupts the dopaminergic system more than the serotonergic system, suggesting that it takes longer for the levels of 5-HT to drop below the threshold level. According to this hypothesis, the resulting serotonergic and receptor-level changes could eventually contribute to the development of VH. This proposed compensatory increase in 5-HT2A receptor density further supports the hypothesis that dysfunction of the serotonergic system, and particularly altered 5-HT2A signaling, may have a role in VH in PD.

A possible limitation of the presented study is the interference of dementia, which was present in four out of the six PD-VH participants. Since dementia is known to cause dysfunctions in many neural networks, such as attention, memory and visual perception (Gratwicke et al., 2015), this factor limits the reliability of the findings and makes it unclear whether they should be attributed to psychosis rather than dementia.

However, there is further evidence that provides support to the hypothesis that the 5-HT2A receptor plays a key role in the

development of VH in PD. Specifically, an aberrant density of this receptor was attributed to temporal dysfunctions in transitions between the segregated and integrated states of the brain in hallucinating PD patients (Zarkali et al., 2022). Integrated and segregated states are opposite methods of network organization, although they often coexist in the same functional system (Tononi et al., 1994). Integration means that the different areas of the network are interconnected and there is a fast flow of information among them; each component of the circuit is dependent on the others. Conversely, segregation happens when different regions function relatively independently of one another, with a limited amount of information flow among the whole system.

It is believed that shifts between integration and segregation are controlled by neurotransmitter systems (Zarkali et al., 2022). The study aimed to investigate how temporal dynamics in transitions between integrated and segregated states are affected in PD patients with VH, using rsfMRI.

The main difference reported was not the presence of distinct integrated or segregated states, but their temporal dynamics: PD-VH participants spent less time in integrated states, more time in segregated states, and made fewer transitions between them than PD-non-VH participants.

The framework presented by these findings suggests that the DMN and thalamic regions have a role in VH in PD, as these are the nodes responsible for modulating the transitions between integrated and segregated states. Furthermore, the study expanded on these findings, attempting to assess the role of neurotransmitters in the alterations observed. The data gathered by Zarkali et al. provide further evidence for a possible involvement of serotonergic signaling in developing VH in PD, as they found significant correlations between regional transition energy and neurotransmitter receptor-density maps, including 5-HT2A receptors.

4. Proposal for a Unified Framework

In light of the evidence considered and summarized in Table 2, this study proposes a unified framework to explain the functional changes that occur in PD-VH patients. Although the three models emphasize different mechanisms, their findings are not necessarily mutually exclusive. Instead, they may describe abnormalities occurring at different levels of the same distributed perceptual system. The following comparison therefore focuses on points of convergence while distinguishing direct empirical findings from mechanistic links proposed by the present framework.

The first hypothesis, schematized in Figure 2A, attributes VH in PD to an early visual dysfunction. According to this model, an impairment in V1 would cause the activation of a loop across areas of the visual network, with an increased activity in the DMN (Yao et al., 2014) and a dysfunction across the DAN and VAN, resulting in the recognition of internally generated stimuli as external inputs (van Ommen et al., 2023). The original dysfunction in V1 would presumably be reflected by aberrant ERP values in the P1 component (Schwartzman et al., 2008), which in PD patients is correlated to primary visual processes (Wang et al., 2001).

The second hypothesis focuses on the role of a cholinergic dysfunction in PD-VH patients (see Figure 2B). However, there is

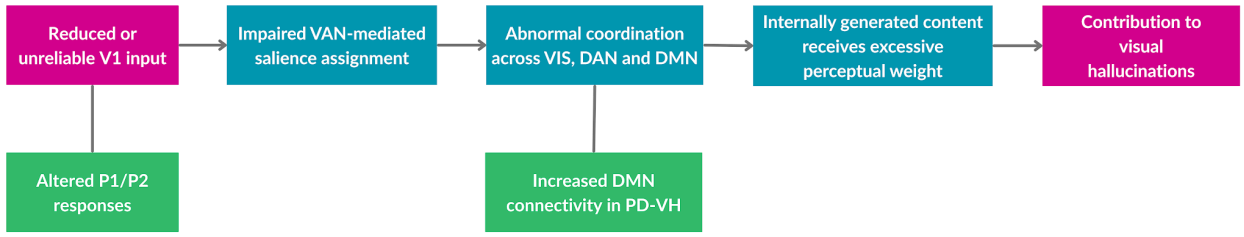
303 ***Table 2. Summary of reviewed literature***

Hypothesis	Study	Approach	Key finding/relevance
Early visual dysfunction	Schwartzman et al. (2008)	EEG/ERP in hallucination-prone healthy participants	Higher P1/P2 positivity supports altered early visual processing but does not establish PD-specific causality.
	Yao et al. (2014)	Resting-state fMRI in PD-VH, PD-non-VH, and controls	Greater DMN connectivity in PD-VH supports involvement of internally oriented network activity.
	van Ommen et al. (2023)	fMRI during hallucinations in psychosis	Reduced V1 involvement with increased VIS/DAN/DMN/VAN activity supports a distributed network account.
Cholinergic dysfunction	Manganelli et al. (2009)	SAI in nondemented PD patients	Abnormal SAI links PD-VH to central cholinergic dysfunction; direction of causality remains unresolved.
	Chang et al. (2016)	Visual ERP task in nondemented PD groups	Prolonged P3b latency is consistent with altered cholinergic/cognitive processing in PD-VH.
Serotonergic/ 5-HT2A	Kometer et al. (2013)	Psilocybin/ketanserin EEG study in healthy adults	5-HT2A activation altered P1, N170, and α power, supporting serotonergic involvement in visual processing and cortical excitability.
	Huot et al. (2010)	Postmortem temporal-cortex receptor analysis	Higher 5-HT2A receptor density in PD-VH supports receptor-level involvement, though dementia is a confound.
	Zarkali et al. (2022)	Resting-state fMRI and network-control analysis	PD-VH showed fewer transitions and longer segregation, linked regionally to neurotransmitter receptor density.

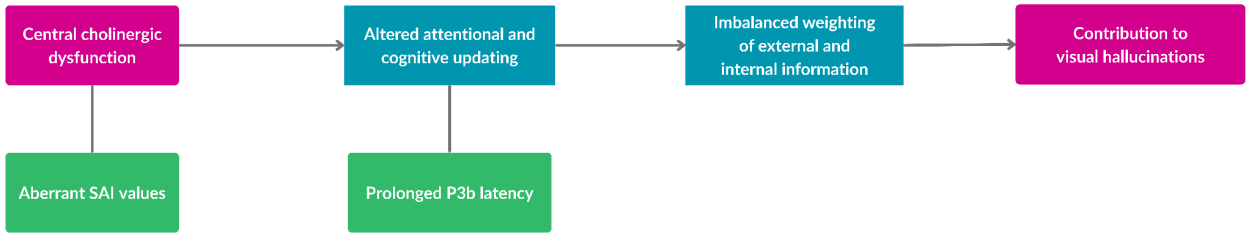
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A. Early visual dysfunction model



B. Cholinergic dysfunction



C. 5-HT2A receptor dysfunction model

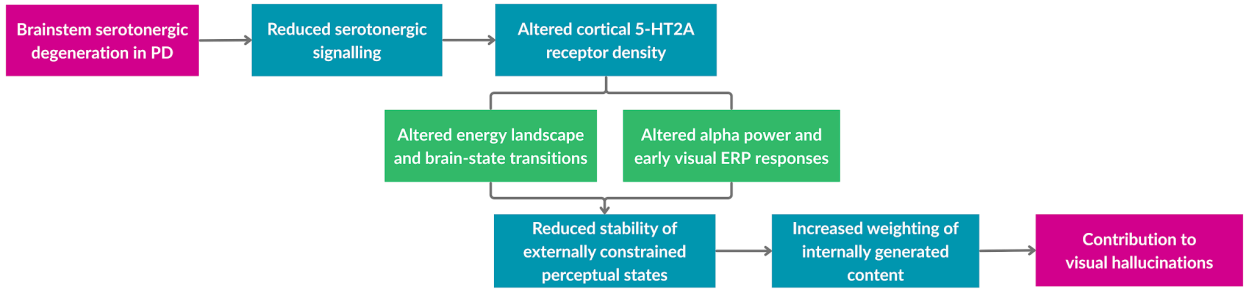


Figure 2. Schematic representations of the three models of visual hallucinations in Parkinson's disease. (A) Early visual dysfunction model. (B) Cholinergic dysfunction model. (C) 5-HT2A receptor dysfunction model. *Color code: key nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships proposed within each model; continuous lines without arrowheads indicate observed associations for which causal direction has not been established.*

divergent evidence regarding whether this is a causing factor of VH or rather a consequence of the condition. Manganelli et al. (2009) postulated the presence of a link between cholinergic dysfunction and VH in PD patients reflected by aberrant SAI values; the direction of causality remains unclear. Conversely, Chang et al. (2016) observed an increased latency of the

P3b component in EEGs of PD-VH patients, hypothesizing that a central cholinergic dysfunction might be an underlying cause of VH in PD.

Lastly, the third hypothesis, outlined in Figure 2C, suggests that an aberrant density of 5-HT2A receptors in PD-VH patients, possibly due to the dysfunction of the 5-HT system in PD (Huot et al., 2010), may be associated with altered transitions between integrated and segregated states (Zarkali et al., 2022). Moreover, pharmacological activation of 5-HT2A receptors in healthy participants resulted in increased amplitudes of the P1 potential and decreased α power values, providing causal evidence that 5-HT2A activation can alter early visual processing and cortical excitability. These changes may, in turn, contribute to an imbalance between the processing of external and internally generated stimuli (Kometer et al., 2013).

4.1 How Do These Models Relate to Each Other?

The models reviewed above can be related across different levels of processing rather than treated as competing explanations. The early visual model emphasizes altered processing of external sensory information, while the network-level models describe how this information may interact abnormally with internally generated activity. Cholinergic and serotonergic dysfunction may in turn modulate these sensory and network processes.

Another significant observation concerns the last hypothesis. While Kometer et al. (2013) observed increased P1 amplitudes and decreased α power following pharmacological activation of 5-HT2A receptors, Zarkali et al. (2022) found associations between receptor-density maps and altered brain-state transitions. Specifically, the latter study found that PD-VH patients spend more time in the segregated state rather than the integrated one, compared to PD-non-VH. There is evidence that α power increases during visual integration in various areas of the brain, including early visual cortex and dorsal visual networks (Costa et al., 2024), showing a link between α oscillations and states of the brain. Thus, the increased dwelling time in segregated states in PD-VH patients is convergent with the decreased α power value identified by Kometer et al. and reflected by increased P1 potentials. However, these findings were obtained using different methods and populations and do not establish that reduced α power directly causes, or indexes, increased network segregation. Their relationship should therefore be considered a testable cross-scale hypothesis.

Additionally, an aberrant value of the P1 ERP component has also been observed by Schwartzman et al. (2008), attributed to primary visual dysfunction and reflecting VH. As previously explained, this last piece of evidence supports the model proposed by van Ommen et al. (2023), according to which VH arise from an early visual dysfunction in V1, involving the DAN, DMN and VAN, and resulting in an imbalance between external and internally generated stimuli.

A further point of convergence between the proposed models is the finding that transitions between segregated and integrated states are highly influenced by the activity of the DMN and thalamic regions (Zarkali et al., 2022), thereby linking attention- and memory-related networks to altered brain-state dynamics.

Drawing on the convergent—but not yet causally unified—evidence considered, the present study proposes a model in which serotonergic dysfunction may act as a central neuromodulatory link, interacting with cholinergic and dopaminergic abnormalities and contributing to downstream changes in visual and attentional networks (see Figure 3).

PD is associated with degeneration of serotonergic neurons in the brainstem, leading to reduced 5-HT levels. Huot et al.

(2010) proposed that reduced serotonergic signaling may be accompanied by a compensatory increase in 5-HT2A receptor density, which may contribute to abnormal activity in visual and attention-related networks.

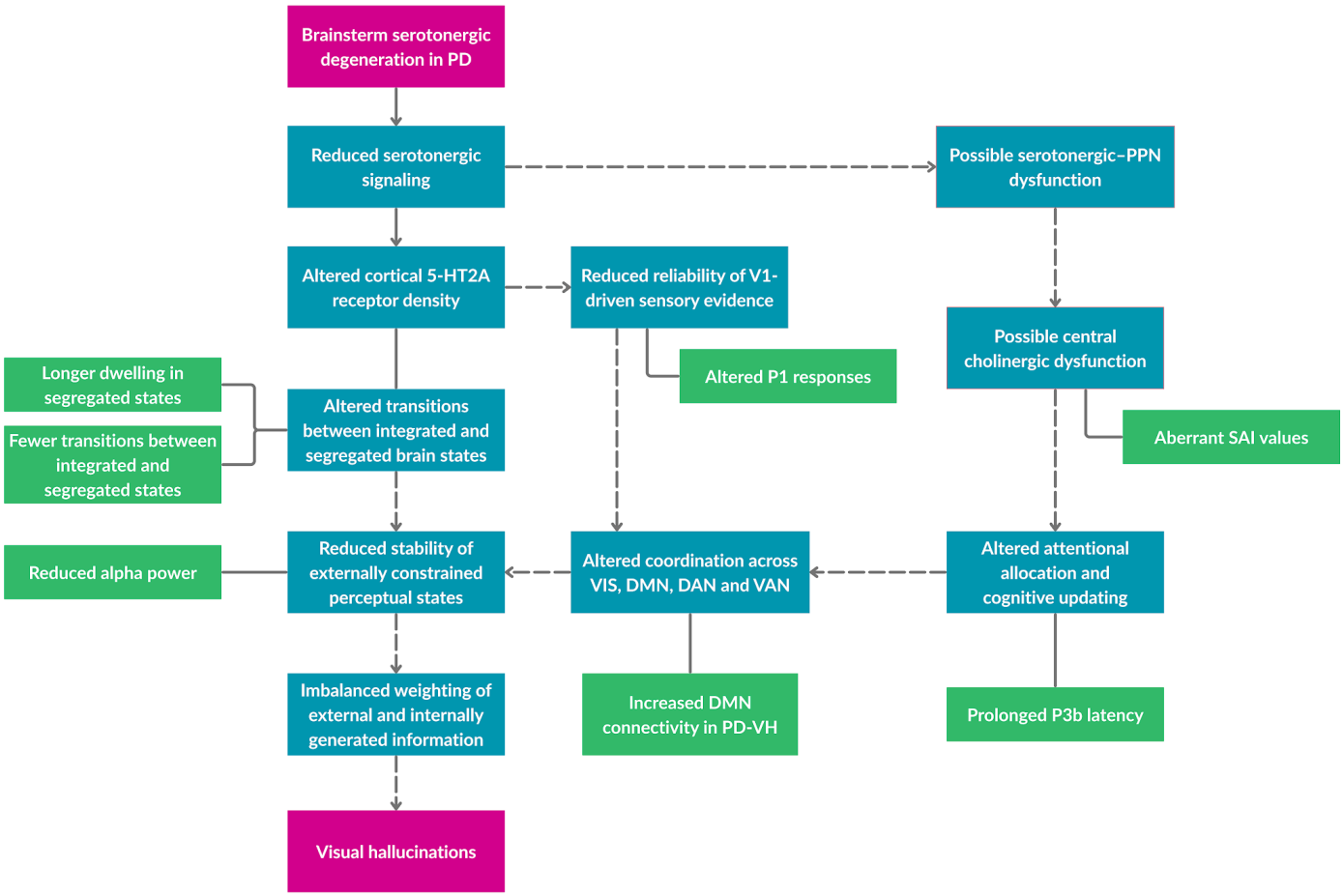


Figure 3. Proposed unified framework for visual hallucinations in Parkinson's disease. *Color code: key framework nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships retained from the reviewed models; continuous lines without arrowheads indicate observed associations for which causal direction has not been established; dashed arrows indicate integrative or unresolved mechanistic links proposed by the unified framework. Red borders identify especially uncertain or indirect components.*

Within this framework, the comparatively later involvement of the serotonergic system in PD may help explain the delayed emergence of VH, while serotonergic dysfunction may also interact with other neurotransmitter systems and contribute to the downstream cascade of visual, attentional and network abnormalities.

Altered 5-HT2A receptor signaling may contribute to abnormal activity across the VIS and the DAN, DMN and VAN, and may be associated with altered α power and impaired transitions between integrated and segregated states, with a

prolonged dwelling time in the segregated states and fewer transitions to the integrated state. An increased activity in the DMN found in PD-VH patients (Yao et al., 2014)—and linked with the dysfunction between segregated and integrated states—possibly explains the aberrant P3b values observed by Chang et al. (2016). Indeed, a study conducted by Baumeister et al. (2014) found that increased P3 amplitude is linked to higher excitability in areas related to memory recollection and internal stimuli processing. These findings raise the possibility that abnormalities in P3 activity and DMN function reflect overlapping disturbances in internally oriented cognitive processing. However, the available evidence does not establish that P3 directly reflects DMN activity.

The previous models presented by van Ommen et al. (2023) theorized that the activation of the loop giving rise to VH—involving DMN, DAN and VAN—originated from a dysfunction in V1, which would indeed be reflected by the aberrant P1 medial potentials. There are some studies that link serotonin and acetylcholine to V1 functions in animals; for instance, Shimegi et al. (2016) investigated how cholinergic and serotonergic systems modulate visual processing in monkey V1. However, further evidence is necessary to define the underlying mechanisms that activate the loop between the VIS and visual-related networks. It is important to understand how the loop itself begins, whether it arises from dysfunction in V1 or abnormal activity in attentional networks, and to clarify which neurotransmitters are involved.

5. Conclusions

This review proposes that serotonergic dysfunction may play an integrative role in linking early visual abnormalities, altered neuromodulatory signaling, and large-scale network dynamics in PD with VH. Rather than implying that serotonergic dysfunction represents the single or primary cause of VH, the reviewed evidence supports a model in which multiple sensory, cholinergic, serotonergic, and network-level abnormalities may interact.

The framework should therefore not be interpreted as demonstrating that serotonergic dysfunction is the single cause of VH or that it necessarily precedes cholinergic and network abnormalities. Its principal contribution is to identify testable links among findings that are usually considered separately. Future longitudinal, multimodal, and pharmacological studies will be required to establish causal direction and determine whether these mechanisms represent upstream drivers, interacting contributors, or downstream consequences of VH in PD.

6. Limitations and Future Research Directions

Accordingly, apparent convergence across studies should not be interpreted as evidence that the reported abnormalities belong to a single established causal sequence. In fact, the central limitation of the proposed framework is that it integrates evidence obtained from heterogeneous populations and methods. Some studies involve healthy participants exposed to serotonergic hallucinogens, some examine psychosis outside PD, and some include PD-VH samples affected by dementia.

Future work should therefore test the framework prospectively in carefully phenotyped, nondemented PD cohorts. The strongest design would combine receptor-sensitive imaging, EEG measures of P1/P3b and α power, and repeated fMRI measures of DMN–DAN–VAN coupling and integrated–segregated state transitions within the same participants. Longitudinal studies should determine whether serotonergic and cholinergic changes precede hallucination onset, while pharmacological studies should test whether modifying 5-HT2A or cholinergic signaling changes the predicted electrophysiological and network markers. These tests would distinguish correlation from causation and clarify whether

the PPN and DRN are upstream drivers, downstream consequences, or interacting modulators of the proposed pathway.

Future studies could also investigate the role of the pedunculopontine nucleus (PPN) in modulating cholinergic and serotonergic dysfunction. The PPN contains cholinergic neurons and receives serotonergic input from brainstem nuclei including the dorsal raphe nucleus (DRN) (Benarroch, 2013; Michelsen et al., 2007). Numerous studies mention the PPN in relation to VH in PD. With its cholinergic neurons, it is linked to attention networks, and it controls the visual cortex (Manganelli et al., 2009). Specifically, it modulates feedforward input to V1, exhibiting its crucial role in visual perception. Moreover, the neurotransmitters synthesized in the PPN modulate both the VAN and the DAN, together with other nuclei in the brainstem (Alves et al., 2022). These findings suggest that there is a connection between the PPN, attentional networks and other structures in the brainstem, especially the DRN, and that these connections are modulated by neurotransmitters. However, the proposed role of the PPN as a link between serotonergic and cholinergic dysfunction and altered visual-attentional processing remains indirect and has not been demonstrated as a causal mechanism of VH in PD. Future studies should therefore determine whether PPN dysfunction contributes to VH by disrupting cholinergic and serotonergic modulation of visual and attentional networks.

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9. Author Biography

Redacted for double-blind review.

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Generative AI tools were used for limited editorial support, including assistance with identifying typographical errors and awkward phrasing, checking reference formatting, and improving the organization of flowcharts. The author independently developed the research question, selected and interpreted the literature, constructed the proposed framework, evaluated the scientific claims, and approved all final wording. AI tools were not used to generate original data or conduct data analysis. The author verified the accuracy of all substantive claims, citations, and references and accepts full responsibility for the manuscript.

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Proposal for a Unified Framework to Understand the Functional Changes That Occur in Visual Hallucinations in Parkinson's Disease

Abstract

Visual hallucinations in Parkinson's disease are often viewed as isolated symptoms of neurodegeneration. However, growing evidence suggests that they reflect deeper disruptions in how the brain constructs perception. This paper reviews three major hypotheses—early visual dysfunction, cholinergic dysfunction, and serotonergic dysfunction—and proposes a unified framework linking these mechanisms across multiple levels of brain organization. By integrating electrophysiological, neurochemical, and network-level findings, this study argues that hallucinations arise from an imbalance between internally generated and externally driven signals. Specifically, serotonergic dysfunction, through alterations in 5-HT2A receptor density, mayearly sensory processing with large-scale network dynamics, including impaired transitions between brain states. Understanding these mechanisms provides insight not only into Parkinson's disease, but also into the fundamental nature of perception as an active and dynamic process. More broadly, this work highlights the importance of approaching neurodegeneration as a distributed, multilevel phenomenon, with implications for developing more integrated and effective therapeutic strategies.

Keywords: Parkinson's disease; visual hallucinations; serotonin; 5-HT2A receptor; visual processing; attention networks; brain-state dynamics

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder attributed to a dysfunction in the dopaminergic system (Lew, 2007). The main symptoms of PD and those that serve as a diagnosis are motor, but patients often show a spectrum of various non-motor symptoms as well. Moreover, it is possible for PD patients to develop dementia or psychotic symptoms. This last condition is known as Parkinson's disease psychosis (PDP) (Friedman, 2010), and its main symptom is visual hallucinations (VH).

VH can present in different forms, and they are commonly classified as elementary and complex. Elementary VH generally

consist of geometric patterns, such as lines, curves or spots (Billock & Tsou, 2012). These can also have additional features such as color or motion. Conversely, complex VH feature a variety of different contents, often depicting animal or human figures in absurd or unrealistic contexts (Manford & Andermann, 1998). Patients who suffer from a psychotic disorder often encounter both elementary and complex VH, but most PD patients recall having experienced complex VH (van Ommen et al., 2023).

It was initially believed that VH and PDP were a collateral effect of dopaminergic treatments, administered to alleviate the motor symptoms of the disorder; however, some PD patients develop PDP without medications (Friedman, 2010). This suggests that PDP is a progression of PD itself. Indeed, while dopamine is the main neurotransmitter attributed to PD motor symptoms, it is believed that the disorder also displays dysfunctions in other neurotransmitter systems and in the interactions between those; many motor and non-motor symptoms of the disease have been attributed to neurotransmitters such as serotonin, acetylcholine, glutamate and γ-aminobutyric acid (GABA) (Barone, 2010).

PD is the second most prevalent neurodegenerative disorder in the world population, and VH has a prevalence range of 8%–40% in PD patients (Barone, 2010; Manganelli et al., 2009). Moreover, there are a variety of correlates linking VH and PD. For example, VH in PD are ~~reflected by~~associated by aberrant event-related potential (ERP) components ~~such as increased~~, including alterations in P1, which reflects early visual processing, and P3b, associated with later cognitive processing of stimuli ~~potentials~~. Moreover, some PD-VH patients present anomalous neural networks behavior, including enhanced excitability in the default mode network and in attention-related networks, as well as longer periods in segregated brain states and fewer transitions toward integrated states ~~or temporal imbalances in transitions between segregated and integrated states~~. Nevertheless, the underlying mechanisms giving rise to VH are largely unknown.

A complicating factor to this phenomenon is the high occurrence of dementia in PD, known to cause cognitive impairment and dysfunctions in many neural networks, namely in attention, memory and visual perception pathways, sometimes resulting in VH itself (Gratwicke et al., 2015). Since dementia and psychosis often coexist in PD patients, it is difficult to discern the distinct effects that the two conditions have on neural networks in PD, as well as to identify their respective causal factors.

At present there remains no unified framework able to explain how and which neural networks are involved in VH among nondemented PD patients. Investigating the functional changes that occur in VH in PD can offer new insights into visual processing and stimuli interpretation. Moreover, it may enhance treatments to alleviate VH, perhaps reducing the effects that they have on the overall health of the patient. VH are indeed linked with both a greater chance of developing dementia and a higher risk of mortality (Manganelli et al., 2009). Eventually, having a better understanding of the neural networks involved in VH in PD can lead to improvements in the quality of life of the patients.

The present study reviews existing hypotheses of VH in PD and examines how findings from early visual, cholinergic, serotonergic, and network-level models may interact rather than represent mutually exclusive explanations. In particular, it proposes that serotonergic dysfunction may provide one possible integrative bridge between these abnormalities. ~~The present study reviews existing hypotheses of VH in PD and proposes that serotonergic dysfunction may provide an integrative bridge between early visual, cholinergic, and network-level abnormalities.~~

2. Method and Scope of the Review

This paper is a focused narrative review and theoretical synthesis. It compares evidence from ~~electrophysiology~~electroencephalography, neuroimaging, pharmacological studies, network-control approaches and postmortem receptor analyses (see Table 1)~~, and network-control approaches~~. ~~Relevant studies were identified through targeted searches of PubMed, Google Scholar, and reference lists of key reviews~~

~~using combinations of terms related to PD, VH, visual processing, cholinergic dysfunction, serotonin, 5-HT2A receptors, and brain-state dynamics. Studies were selected for their relevance to three recurring explanatory levels: early visual processing, cholinergic modulation, and serotonergic/network-state dysfunction. Because the included studies differ substantially in population, task, and measurement method, and several do not examine nondemented PD patients directly, the proposed framework should be interpreted as a testable integrative hypothesis rather than a demonstrated causal model.~~ ~~The~~ ¶

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Table 1. Methods Used to Characterize Neural Dysfunction in Visual Hallucinations

Method	What it measures	Main strenghtstrength	Main limitation
Electroencephalography (EEG) and Event-Related Potentials (ERPs)	EEG records electrical activity from the scalp; ERPs isolate activity time-locked to specific stimuli or events (Fabiani et al., 2007; Beres, 2017).	Excellent temporal Resolution, allowing neural responses to be tracked on the millisecond scale (Beres, 2017).	Limited ability to precisely localize the neural source of the recorded activity (Beres, 2017).
Resting-state fMRI (rsfMRI)	Measures spontaneous fluctuations in the blood-oxygen-level-dependent (BOLD) signal at rest and their correlations across brain regions, allowing functional connectivity to be estimated (Van Den Heuvel & Pol, 2010).	Allows investigation of large-scale functional networks across the brain.	BOLD is an indirect measure of neural activity and has relatively poor temporal resolution because of the delayed haemodynamic response.

Short-latency afferent inhibition (SAI)	A neurophysiological measure of sensorimotor inhibition that is used as a putative marker of central cholinergic function (Martin-Rodriguez & Mir, 2020).	Provides a non-invasive physiological measure associated with cholinergic function in humans.	It is an indirect marker rather than a direct measurement of acetylcholine, and it can be influenced by factors such as disease duration and dopaminergic medication (Martin-Rodriguez & Mir, 2020)
Network-control analysis	Uses structural and functional brain-network data to estimate transitions between brain states and the control energy required for those transitions (Zarkali et al., 2022).	Can characterize dynamic differences in integrated and segregated brain states.	The inferred transitions and energy values depend on the assumptions of the mathematical model used and do not directly measure neurotransmitter activity.
Postmortem receptor analysis	Uses receptor-binding techniques in brain tissue to quantify receptor density; Huot et al. (2010), for example, measured 5-HT2A receptor binding in cortical tissue from PD patients.	Provides direct anatomical evidence of receptor-level differences in human brain tissue.	It is cross-sectional and cannot establish whether receptor changes precede or result from VH.

Relevant studies were identified through targeted searches of PubMed, Google Scholar, and reference lists of key reviews using combinations of terms related to PD, VH, visual processing, cholinergic dysfunction, serotonin, 5-HT2A receptors, and brain-state dynamics. Studies were selected for their relevance to three recurring explanatory levels: early visual processing, cholinergic modulation, and serotonergic/network-state dysfunction. Because the included studies differ substantially in population, task, and measurement method, and several do not examine nondemented PD patients directly, the proposed framework should be interpreted as a testable integrative hypothesis rather than a demonstrated causal model.

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~~3.~~ Literature Review on Visual Hallucinations in Parkinson's Disease

There are several ~~a few~~ models that try to explain the functional changes that occur in PD patients causing VH. The present study focuses on three ~~distinct~~ frameworks that emphasize different but potentially interacting levels of dysfunction. ~~While the~~ The first hypothesis ~~attributes VH to an~~focuses on early visual dysfunction (Schwartzman et al., 2008; van Ommen et al., 2023), while the second and third present a broader explanation of VH ~~as~~ involving an imbalance between external and internal stimuli ~~involving different parts~~and the modulation of visual and attentional networks. The distinguishing factor between the last two models lies in the type of neurotransmitters involved: ~~while~~ the second ~~attributes VH to a~~emphasizes central cholinergic dysfunction (Manganelli et al., 2009), whereas the third ~~emphasizes~~ focuses on serotonergic dysfunction and altered 5-HT2A receptor density (Kometer et al., 2013). ~~Numerous studies have investigated VH in PD; each research presents experiments conducted in distinct ways, with different aims and results, offering a piece of the puzzle that eventually explains thoroughly how and which visual networks are involved in VH in PDThese models are considered separatelyindividually before examining the points at which their findings may converge, with the principal aim of identifying testable links among mechanismsfindings that are usually considered separately.These models are considered separately before examining the points at which their findings may converge~~.

3.1 Early Visual Dysfunction

The early visual dysfunction model proposes that abnormalities in the initial processing of visual information may contribute to VH and, through disrupted communication with higher-order visual and attentional networks, lead to the misinterpretation of internally generated information as external. Evidence for this model comes from studies examining both early electrophysiological responses to visual stimuli and the interaction between primary visual processing and broader visual-attentional networks.

A study conducted by Schwartzman et al. (2008) evaluated the hypothesis that considered aberrant early visual ERP components to reflect the individuals' proneness to hallucinate. While early visual disruption had been previously associated with various psychological and neurological disorders that present VH—e.g. PD, schizophrenia—it remained unclear whether an early impairment of visual processes was a key factor in the development of VH or rather a mere outcome of the disorder itself.

~~In order to isolate the possibly complicating factor of cognitive decline, which is a key component of most of the disorders that present VH, the study analyzed electroencephalogram (EEG) recordings of healthy individuals, dividing them based on their proneness to visually hallucinate. To assess this, the participants answered the Hallucination-proneness Questionnaire. Individuals were asked to provide a number on a scale from 0 to 5 for each of the 29 statements testing their experience with sensory hallucinations—with a particular focus on the visual sphere. The number indicated how much the participant related to the statement (from 5 – certainly applies to me; to 0 – certainly does not apply to me). The individuals were then shown photographs of faces, Mooney faces and scrambled Mooney faces (see Figure 1). The visual stimuli were shown both upright and upside down, and the participants were instructed to report whether they perceived a face in each image.~~In order to reduce the possibly confounding influence of cognitive decline, the study analyzed electroencephalogram (EEG) recordings from healthy individuals divided according to their proneness to hallucinate. Hallucination proneness was assessed using a questionnaire, after which participants completed a face-perception task involving photographs, Mooney faces, and scrambled Mooney faces (see Figure 1).¶

The Mooney Faces Test (MFT) ~~is used to assess~~evaluates an individual's ability to perceive human faces in two-dimensional, black and white pictures, shown both upright and upside down (Silverstein et al., 2021). ~~The MFT is normally commonly used to measure assess visual perception under conditions in which recognition depends strongly on higher-order processing. ; the images are created so that there are different stages of difficulty regarding face perception. Recognition of a Mooney face stimulates higher levels of visual processing, especially those linked with memory. This explains why normally inverted Mooney faces are not perceived as such, given that there is a lack of retrieval of upside-down representations of faces. Silverstein et al. investigated MFT results in individuals with a clinical high risk of developing a psychotic disorder, and found that higher MFT scores—meaning that the individual perceived faces in more pictures compared to control groups, both in an upright and inverted condition—corresponded to aberrant visual perception and a higher occurrence of VH reported. ¶~~

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~~higher level of visual processing involving categorization of face stimuli. The interpretation of the stimulus in P2 depends on the reception of information carried out in P1.¶~~

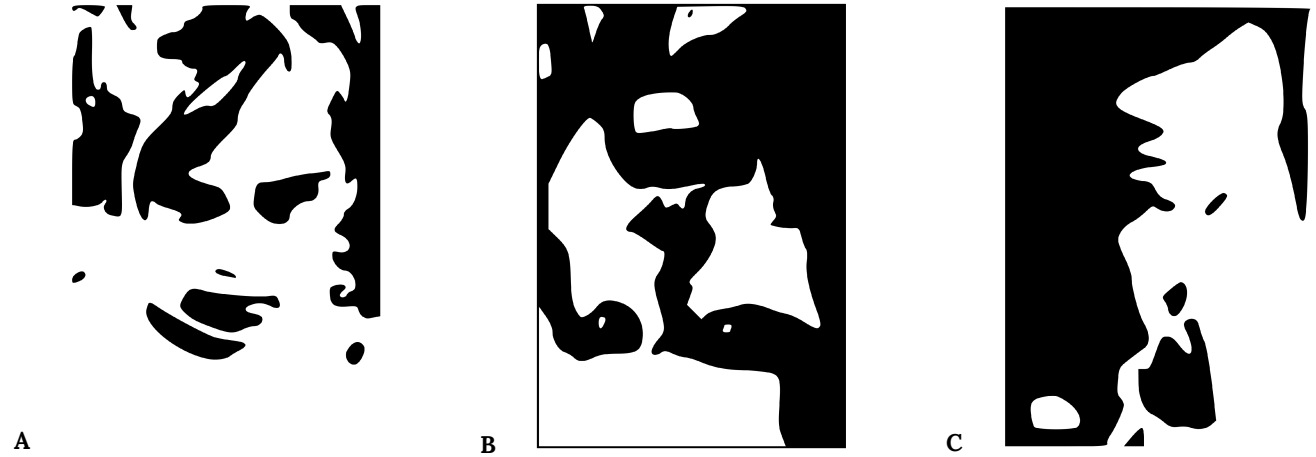


Figure 1. Representative stimuli from the Mooney Faces Test. *The upright Mooney face (A) is typically perceived as a face, whereas the inverted Mooney face (B) is substantially more difficult to recognize due to disruption of holistic face processing. The scrambled image (C) serves as a non-face control stimulus. Stimuli adapted from the dataset of Schwiedrzik et al. (2018) and redrawn as vector graphics for presentation clarity under CC BY 4.0.*

During the experiment conducted by Schwartzman et al., the participants' brain activity was recorded through EEG; specifically, the study focused on ERP components that reflect early visual processes. The components analyzed were the N170, P1 and P2, respectively associated with face recognition, early extraction of information from face stimuli, and finally a higher level of visual processing involving categorization of face stimuli. The interpretation of the stimulus in P2 depends on the reception of information carried out in P1.~~During the experiment conducted by Schwartzman et al., the participants'~~

~~brain activity was recorded through EEG; specifically, the study focused on ERP components that reflect early visual processes. The components analyzed were the N170, P1 and P2, respectively associated with face recognition, early extraction of information from face stimuli, and finally a higher level of visual processing involving categorization of face stimuli. The interpretation of the stimulus in P2 depends on the reception of information carried out in P1.¶~~

The study observed no significant differences in the N170 component, while P1 and P2 showed increased positivity in hallucination-prone individuals. The lack of significant N170 differences suggests that the observed changes in P1 and P2 were not specific to face ~~recognition, but~~recognition but may instead reflect abnormalities in earlier stages of visual processing. Conversely, the increased amplitude registered ~~registered both in P1 and P2 could~~in P1 suggests a dysfunction in the extraction of fine information from visual stimuli, ~~reflected by an increased positivity in P1~~which would in turn ~~. A disrupted extraction of information from the stimulus would also then generate an impaired~~impair the interpretation of the visual information itself, explaining the knock-on effects on P2. Thus, compared with individuals with low hallucination proneness, hallucination-prone participants showed altered stimulus-evoked electrophysiological responses during early visual processing. However, because the study involved healthy participants rather than PD patients with VH, these findings support an association with hallucination susceptibility rather than establishing a PD-specific causal mechanism.¶

~~The study observed a lack of significant differences in the N170 component, while the P1 and P2 both showed an increased positivity in hallucination-prone individuals. The lack of variation in the N170 component between individuals with high and low hallucination proneness suggested that the changes observed in P1 and P2 were not influenced by the object observed—in this case, faces—but rather by an early visual process impairment. Conversely, the increased amplitude registered both in P1 and P2 could suggest a dysfunction in the extraction of fine information from visual stimuli, reflected by an increased positivity in P1. A disrupted extraction of information from the stimulus would also generate an impaired interpretation of the information, explaining the knock-on effects on P2. These findings indicate that hallucinating individuals present an increased amplitude in P1 due to a dysfunction in early visual processes.~~

An earlier study had shown a correlation between P1 ERP component in patients with PD and primary visual processes (Wang et al., 2001). ~~Thus, the early visual dysfunction hypothesis would be supported by hallucinating PD patients presenting increased latency in P1, reflecting an impairment in early stages of visual processing~~Thus, tThe association between P1 and primary visual processing in PD provides a basis for considering abnormal P1 responses as a possible marker of early visual dysfunction in PD-VH.

Although there is evidence that early visual dysfunction is related to VH in PD, it appears to be highly unlikely for VH to be explained as a focal pathology. Instead, a study led by van Ommen et al. (2023) correlated an impairment in primary visual processes to dysfunctions in other visual-related neural networks, proposing a more holistic explanation of VH. ~~Indeed, tThey found that VH might be a result of a dysfunction in the primary visual cortex, V1, which consequently results in an aberrant activation of visual-related networks. A malfunction in the transfer of information between V1 and attention-related networks would eventually result in internally generated stimuli—coming from endogenous neural networks—being perceived as exogenous inputs from V1.~~

~~Van Ommen et al. (2023)~~They aimed to evaluate ~~the an~~a hypothesis previously postulated by Shine et al. (2014), which had

explained VH as a consequence of a disconnection between the primary visual cortex, V1, and higher visual components, inducing a desynchronization between different parts of the visual network. This previous hypothesis was ~~based on~~supported by the reduced activity registered in the primary visual cortex ~~observed~~ in patients with psychotic VH.

In order to evaluate the postulated model from Shine et al. and assess what areas of the brain are involved in psychotic VH, van Ommen et al. (2023) conducted an experiment on hallucinating psychotic individuals, recording their brain activation data during an episode of VH, through functional magnetic resonance imaging (fMRI). The results showed ~~lack of~~reduced a lack of activation in V1 and increased activity across the visual and attention pathways, specifically in the Dorsal Attention Network (DAN), Default mode network (DMN) and Ventral Attention Network (VAN). These are respectively linked to processing external information, interpreting internal stimuli and coordinating memory and finally synchronizing the two networks—DAN and DMN (Van Calster et al., 2017). The results are therefore in line with the hypothesis postulated by Shine et al., 2014, as they show that psychotic VH is not a focal pathology. Instead, it affects a wide range of regions, namely the visual network (VIS)—excluding V1—and vision-related networks involved with memory and attention.

Based on these findings, Van Ommen et al. proposed a ~~refined model~~revisitation refinement of the model postulated by Shine et al., attributing VH in PD to the activation of a loop across the VIS—with the exception of V1—and the DAN, DMN and VAN. ~~to explain~~¶

~~Shine et al. had postulated that an early dysfunction in V1 would cause an incorrect categorization of visual stimuli by relevance in the VAN. As a result, an imbalance between externally and internally generated visual stimuli (in the DAN and DMN) would originate VH. Instead, Van Ommen et al. have proposed a refined model that attributes VH to the activation of a loop across the VIS—with the exception of V1—and the DAN, DMN and VAN. Under~~Under normal circumstances, feed-forward impulses are sent from V1 to the surrounding visual network regions. This flow of information allows the stimulus to be recognized as external. In turn, a feedback inhibitory response is sent from the networks to V1. According to this model, the ability of V1 to provide feed-forward and receive feedback information from the surrounding areas is compromised in psychotic VH. This disruption may cause internally generated information to be misinterpreted as external sensory input, thereby contributing to the generation of VH.~~This eventually causes the brain to misinterpret internally-generated information as external inputs, consequently thus giving rise to~~ creating VH.¶

However, since van Ommen et al. investigated VH in individuals with psychosis rather than specifically in PD patients, the extent to which this network mechanism applies directly to PD-VH remains to be established.

Another piece of evidence in support of the model proposed by van Ommen et al. is given by a study from 2014, led by Yao et al., which investigated DMN activity in resting PD patients, both with (PD-VH) and without VH (PD-non-VH) and in healthy controls. Patients with symptoms of cognitive impairment and dementia were excluded. Resting-state functional magnetic resonance imaging (rsfMRI) data of the part~~t~~icipants were acquired, and the results showed a decreased activity in the DMN in PD patients compared to controls ~~(see Table 1.).~~ Co~~-co~~nversely, PD-VH patients had a greater excitability of the DMN compared to PD-non-VH. Yao et al., therefore, demonstrated that a higher connectivity in the DMN is associated with VH in PD patients, relative to PD-non-VH patients. Showing a correlation between aberrant DMN activity and VH in PD, these data support the model proposed by van Ommen et al.

Thus, while there are findings suggesting that early visual impairment has a role in generating VH in PD, this is treated as one level of a distributed mechanism rather than a complete explanation of the condition. Moreover, ~~the~~ this presented model fails to include the involvement of neurotransmitters in VH in PD. To fully comprehend the underlying neurological mechanisms of VH in PD, it is necessary to adopt a more holistic approach, recognizing the role of neurotransmitters in modulating attention and vision-related networks. Consistent with the model postulated by van Ommen et al., 2023, a second hypothesis attributes VH in PD to an imbalance between external and internal stimuli, and specifically as a consequence of a central cholinergic dysfunction.

3.2 Imbalance Between External and Internal Stimuli due to a Central Cholinergic Dysfunction

The cholinergic model proposes that VH arise partly from impaired cholinergic modulation of attention, contributing to an imbalance between externally driven and internally generated information. Evidence for this model comes from both physiological measures of central cholinergic function and ERP studies of cognitive processing in nondemented PD patients with VH.

A study from 2009, conducted by Manganelli et al., found a correlation between nondemented PD-VH patients and a central cholinergic dysfunction. The research methodology included the use of short-latency afferent inhibition (SAI), a ~~non-invasive protocol thought to reflect central cholinergic activity~~physiological measure commonly used as an indirect marker of central cholinergic function (Martin-Rodriguez ~~et al.~~& Mir, 2020). The participants were 22 non-demented PD patients, both with and without VH (Manganelli et al., 2009). The study found that most PD-VH patients presented aberrant SAI values, unlike PD-non-VH individuals. Therefore, Manganelli et al. concluded that VH in PD could be one of the factors that alter the balance of the cholinergic system. Alternatively, VH would cause a dysfunction between the cholinergic and other neurotransmitter systems. The study also confirmed the hypothesis of a correlation between cholinergic dysfunction and PD patients who are likely to develop dementia. Similarly, VH are considered to be a predictive factor of dementia. Therefore, ~~it is possible that there is a~~there is a possible link between central cholinergic dysfunction and VH in PD.

However, there remains disagreement about the direction of causality, as other later studies consider cholinergic dysfunction as a causal factor of VH in PD. One of these is a study led by Chang et al. (2016).

While aberrant ERP values are considered an indicator of cognitive dysfunction in demented PD patients, their role in nondemented PD patients, both with and without VH, remained unclear. Specifically, some studies had found a correlation between PD-VH patients and impaired P3 responses, a component related to attentional allocation and cognitive processing ~~speed during informative~~of task-relevant stimulus (Kurita ~~xxx~~et al., 2010; Chang et al., 2016). To ~~meet~~address this gap in the literature, Chang et al. compared ERP responses in nondemented PD patients with and without VH,~~To investigate~~ and in healthy controls during a visual target-detection task. They reported that PD-VH individuals showed a prolonged latency of one subcomponent of the P3, namely the P3b component, compared with controls. Since P3b is associated with later cognitive processing and memory updating, this result was interpreted as evidence of altered cognitive processing in PD-VH and was considered compatible with central cholinergic dysfunction (Chang et al., 2016; Polich, 2003).

~~The P3 ERP isERP component is related to attentionalattention allocation and cognitive processing speed of a positive shift when a subject detects anduring informative task-relevant stimulus. It consists of twois composed of mainly two~~

distinct subcomponents, namely P3a and P3b. The latter is associated with later cognitive processing and memory updating (Polich, 2003). Chang et al. found that To The P3 ERP component iThe study wanted to investigate the role of aberrant ERP components in nondemented PD patients with VH.investigate this, Chang et al. , as a follow-up to another investigation that reported , as ¶

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While aberrant ERP values are an indicator of cognitive dysfunction in demented PD patients, increased P3 latency is thought to be correlated with VH in demented PD patients. Moreover, VH is a possible predictor of dementia in PD patients. Therefore, the study aimed to explore the correlation betweenthese ERP abnormalities and in nondemented PD patients. The study compared ERP responses in nondemented PD patients with VH, PD patients without VH, and healthy controls during a visual target-detection task. The analysis focused on several ERP components associated with sensory and cognitive processing, including N1, P2, N2, and P3. The principal finding was a prolonged lateney of the P3b component in PD-VH individuals compared with controls (Chang et al., 2016). Since P3b is associated with later cognitive processing and memory updating, this result was interpreted as evidence of altered cognitive processing in PD-VH and was considered compatible with central cholinergic dysfunction (Chang et al., 2016; Polich, 2003).¶

The research analyzed differences in ERP components in nondemented PD patients with VH, comparing them to PD-non-VH and healthy control individuals. During the experiment, participants were shown different images, which were either target stimuli or nontarget stimuli. Each individual had previously been instructed to identify the target accurately. The participants' task was to respond as quickly as possible by pressing a button when the target stimulus appeared. During the duration of the experiment, the following ERP components were recorded: N1, P2, N2 and P3. Firstly, N1 and P2 are both considered to be related to sensory processing, as well as attention. They are exogenous components, i.e. components primarily driven by the physical properties of external stimuli, related to processing of external stimuli and not influenced by cognitive activity (Donchin et al., 1978). The N2 represents higher visual processing, involving early cognition such as identification of new stimuli, while the P3 responds to detection and categorization of new stimuli, a process involving memory (Chang et al., 2016). Specifically, the P3b occurs from 300 to 700 milliseconds, and it is linked with the update of memory based on new persistent stimuli. It allows the novel context to be stored in memory, and it occurs after the detection of stimulus novelty, reflected by the other part of P3, P3a (Polich, 2003). The results showed a prolonged latency of the P3b component in PD-VH individuals, compared to that of controls (Chang et al., 2016). VH had previously been linked with a cholinergic dysfunction in the pedunculopontine nucleus, and a prolonged P3 ERP component in Alzheimer's disease patients is thought to indicate central cholinergic function. Hence, the study hypothesized that VH in nondemented PD patients might be attributed to a central cholinergic dysfunction and could be indicated by aberrant P3 ERP components. In addition, the study found that neither the N1 nor P2 component presented significant differences among the three groups.¶

TtheThis study also investigated the N1 and P2 components, two endogenousexogenous ERP componentsresponses relatedassociated to with sensory processing and and attentional processing respectively (Chang et al., 2016; Donchin et al., 1978).. Chang et al. reported an absence ofno significant differences in N1 and P2theseein either components across the groups. , two exogenous components related to sensory processing and attention (Chang et al., 2016; Donchin et al., 1978). TheThis finding does not necessarily contradict the visual-network dysfunction model described previously. These ERP components and the DAN, VAN, and DMN reflect different levels of attentionalneural processing, and there is no evidence

that abnormalities in these large-scale networks must be accompanied by altered N1 or P2 responses. The Chang et al. findings therefore add evidence of altered later cognitive processing rather than excluding the involvement of visual and attentional networks.

~~In addition, the study found that neither the N1 nor P2 component presented significant differences among the three groups. This challenges the previously mentioned hypothesis that attributed VH to visual-related network dysfunctions, as both these components are thought to reflect attention-related sensory information. However, N1 and P2 are considered exogenous components, while the earlier stated model focuses on the roles of DAN, VAN and DMN. These also reflect certain cognitive processes and are therefore endogenous neural networks, suggesting that the two factors are independent from each other. Furthermore, there is no evidence that a dysfunction in the DAN, VAN and DMN is reflected by the N1 and P2 components; in turn, aberrant values of N1 and P2 are not necessarily related to these attentional networks. This suggests that the absence of significant findings in the N1 and P2 components does not necessarily contradict the model considered but rather points to a potential direction for further investigation.¶~~

~~3.3~~ Serotonergic Dysfunction, 5-HT2A Receptors, and Brain-State Dynamics

The serotonergic model proposes that altered serotonergic signaling, particularly through 5-HT2A receptors, may contribute to VH by modifying visual processing and the balance between internally and externally driven neural activity. Evidence for this model comes from pharmacological manipulation of 5-HT2A signaling, postmortem receptor analyses in PD, and studies of large-scale brain-state dynamics.

An aberrant density of 5-HT2A receptors in different cortical areas has often been connected to various forms of psychosis, including PDP (Huot, 2018), but the effect of this receptor's activation on VH is left unclear. A study conducted by Kometer et al. (2013) aimed to clarify this connection by investigating the effects that the activation of the 5-HT2A receptor has on parieto-occipital α waves.

α ~~Alpha~~ oscillations, considered to be mostly present in the thalamic regions and visual cortex, ~~have different associations with visual processing and~~ have been correlated with visual processing dysfunctions and impairments (Clayton et al., 2018). Since they are strongly linked to visual processing, they are also ~~influenced by~~associated with visual-related potentials (Kometer et al., 2013). The study presented here hypothesized that α oscillations could ~~mediate the creation of VH~~contribute to the generation of VH. According to their model, activation of 5-HT2A receptors, triggered by the administration of psilocybin, a serotonergic hallucinogen, would alter α ~~-~~ oscillations~~waves would be stimulated by the activation of 5-HT2A receptors, in turn triggered by the administration of psilocybin, a serotonergic hallucinogen~~. A second hypothesis postulated by the study concerned how early visual ERP components—specifically the P1 and N170—~~were~~ would be influenced by psilocybin-induced hallucinations. Thus, the investigation examined the effects of 5-HT2A activation on visual processing in healthy participants by comparing the effects of psilocybin with those observed after pretreatment with the 5-HT2A antagonist ketanserin. EEG responses were recorded during a visual perception task.

~~Seventeen healthy participants were administered a pretreatment and a treatment—respectively: placebo + ketanserin, a 5-HT2A antagonist; placebo + psilocybin—on four different experimental days. After each treatment, the participants were shown some pictures with three "pacman" shapes, which were either arranged in a "Kanizsa," or in a "non-Kanizsa" condition, thus either giving or not the perception of an illusory triangle. The participants' task was to respond as quickly~~

as possible by pressing a button whenever they perceived a triangle. EEGs were recorded during the visual stimulation. After the experiment, the participants completed a self-report questionnaire to state their experience under the effects of the hallucinogen, especially reflecting on any changes felt in their visual perception.¶

Psilocybin increased P1 amplitude over medial parieto-occipital regions, altered N170 responses, and decreased α power. These effects were suppressed by ketanserin pretreatment, supporting their relationship with 5-HT2A activation. Decreased α power waves waswere attributed to an increased cortical excitability especially in the parieto-occipital regions and in visual networks, reflecting thefollowing activation of 5-HT2A receptors. A reduction in α alpha power had already previously been shown associated withto occur during moments of increased visual attention and cortical excitability in the occipital lobe, while an increaseincreased in α alpha oscillations might directly suppress visual functions processing (Clayton et al., 2018). The decreased α power was also related to the increase in P1 medial potentialspotential, which might represent an enhancement in early visual processing (Kometer et al., 2013). ¶

The experiment showed an increase in the amplitudes of the P1 potential over medial parieto-occipital regions in participants after the psilocybin administration, a trend that was inverted following the ketanserin pretreatment. The N170 showed a decreased positivity after psilocybin; conversely, the same component did not show any changes following the ketanserin treatment. Finally, a decrease in α power waves was observed after the psilocybin administration and was later linked to the increased P1 potentials. All the effects detected were suppressed by the ketanserin pretreatment, suggesting that they were caused by psilocybin administration and related to the consequent activation of the 5-HT2A receptors. This coordinated response between the P1 and α power would in turn originate contribute to an imbalance between perception of external and internal stimuli.

Specifically, there is a loss of equilibrium between cortex excitability when external stimuli are perceived and the cortical excitability in the absence of external stimulialtered cortical excitability may reduce the normal distinction between neural activity driven by external visual input and activity occurring in the absence of external stimuli. This corresponds to a change in the activation of brain networks—reflected by decreased α alpha oscillations and enhanced P1 medial potentials—with an increased attention towards internally generated visual stimuli, rather than external stimuli. This model seems to be in line with the hypothesis proposed by van Ommen et al., in(2023), in which VH arise from an altered balance between externally and internally generated signals.

Although the findings suggest that α power waves may have a role in generating elementary psilocybin-induced VH, analytical studies showed little correlation between the two factorsreduced α power and the occurrence of hallucinations, perhaps revealing that the reduction in α power triggered by psilocybin is not sufficient to induce complex VH. Moreover, the study involvesinvolved psilocybin-induced perceptual alterations in healthy participants rather than in the PD population. Therefore, the study does not establishdetermineestablish that the same mechanism causes complex VH in PD. This suggests that other factors contribute to generating VH in PD.¶

Finally, the psilocybin treatment produced a decrease in the N170, which is thought to play a key role in processing meaningful visual stimuli. An alteration in this component is linked associated with altered visual perception, implying that its aberrant values are a consequence of theand may therefore reflect changes produced during psilocybin-induced

hallucinations. Alternatively, the effects on the N170 could be attributed to the increased cortical excitability triggered by the activation of the 5-HT2A receptor, ~~eventually enhancing or originating~~further contributing to an imbalance between external and internal stimuli.

Taken together, the effects of 5-HT2A activation on P1, N170, and α power demonstrate that serotonergic signaling can alter neural processes involved in visual perception and cortical excitability, although these findings do not establish that the same mechanism causes VH in PD.

A previous study had investigated the distribution of 5-HT2A receptors in postmortem PD patients' tissues, postulating a correlation between ~~enhanced levels of this receptor~~increased receptor density and VH in PD (Huot et al., 2010). The results showed an increased density of this receptor in PD tissues with VH, compared to PD-non-VH, therefore ~~substantiating the proposed hypothesis~~providing PD-specific evidence supporting the involvement of 5-HT2A signaling in VH. While an existing postulate attributed the development of psychosis in PD to a polymorphism in the 5-HT2A receptor gene, a study led by Kiferle et al. (2007) refuted this hypothesis, and they concluded that aberrant levels of this receptor are not due to the genetic variations examined.

Huot et al. (2010) proposed a new explanation of the enhanced levels of 5-HT2A receptors in PD patients with psychosis, defining it as a consequence of other neurotransmitter dysfunctions in PD. PD is known to present serotonin (5-HT) dysfunctions; specifically, degeneration in the serotonergic neurons in the brainstem causes a decline in the neurotransmitter levels. ~~This would then result in an increased 5-HT2A density, as a biological attempt to balance the drop of 5-HT in different areas of the brain~~Huot et al. proposed that this may contribute to a compensatory increase in 5-HT2A receptor density, as a biological attempt to balance the drop of 5-HT in different areas of the brain. Enhanced levels of 5-HT2A could also be attributed to the decrease in dopamine (DA) levels, which acts as a partial agonist to the receptor. These two possibilities are likely to be complementary, and this explanation ~~explanation~~ would~~can~~ help explain the late occurrence of VH in the development of PD: the disorder disrupts the dopaminergic system more than ~~it does to~~ the serotonergic system, suggesting that it takes longer for the levels of 5-HT to drop below the threshold level. According to this hypothesis, the resulting serotonergic and receptor-level changes could eventually contribute to the development of VH. This proposed compensatory increase in 5-HT2A receptor density further supports the hypothesis that dysfunction of the serotonergic system, and particularly altered 5-HT2A signaling, may have a role in VH in PD.

A possible limitation of the presented study is the interference of dementia, which was present in four out of the six PD-VH participants. Since dementia is known to cause dysfunctions in many neural networks, such as attention, memory and visual perception (Gratwicke et al., 2015), this factor limits the reliability of the findings and makes it unclear whether they should be attributed to psychosis rather than dementia.

However, there is further evidence that provides support to the hypothesis that the 5-HT2A receptor plays a key role in the development of VH in PD. Specifically, an aberrant density of this receptor was attributed to temporal dysfunctions in transitions between the segregated and integrated states of the brain in hallucinating PD patients (Zarkali et al., 2022). Integrated and segregated states are opposite methods of network organization, although they often coexist in the same functional system (Tononi et al., 1994). Integration means that the different areas of the network are interconnected and there is a fast flow of information among them; each component of the circuit is dependent on the others. Conversely, segregation happens when different regions function relatively independently of one another, with a limited amount of

information flow among the whole system.

~~The study used the definition of these states derived from the network control theory. This is a mathematical framework that identifies states of the brain as "the magnitude of haemodynamic activity across brain regions at a single time point." This framework defines the brain's activation state at a given time as a "linear function of a previous state, the underlying structural connectome and the additional control energy" (Zarkali et al., 2022). The theory also provides a method to estimate the amount of energy used either to switch from state to state or to dwell in a specific state.~~ It is believed that ~~these~~ shifts between integration and segregation ~~in states~~ are controlled by neurotransmitter systems (Zarkali et al., 2022).¶

The study aimed to investigate how temporal dynamics in transitions between integrated and segregated states are affected in PD patients with VH, using rsfMRI. ~~Cognitive levels of all patients were measured through specific tests—e.g. Mini-Mental State Examination (MMSE). Integrated and segregated states were calculated individually for every participant from each group, PD-VH, PD-non-VH and controls. Integrated and segregated states are opposite methods of network organization, although they often coexist in the same functional system (Tononi et al., 1994). Integration means that the different areas of the network are interconnected and there is a fast flow of information among them; each component of the circuit is dependent on the others. Conversely, segregation happens when different regions function relatively independently of one another, with a limited amount of information flow among the whole system.~~

The main difference reported was not the presence of distinct integrated or segregated states, but their temporal dynamics: PD-VH participants spent less time in integrated states, more time in segregates states, and made fewer transition between them than PD-non-VH participants ~~(Zarkali et al., 2022). The results showed no difference between integrated and segregated states themselves but variations in the time frames and number of transitions between these (Zarkali et al., 2022). Specifically, the main finding was that PD-VH participants spent less time in the integrated and therefore a longer time in the segregated state compared to PD-non-VH individuals; moreover, PD-VH showed fewer transitions between the two states.~~.

~~The study attempted to explain this observation by calculating the amount of energy used in transitions between states as well as when persisting in one state, for PD-VH individuals as well as PD-non-VH and controls. The main finding was that the minimum energy needed to transition from the integrated to the segregated was considerably lower in PD-VH compared to PD-non-VH. The study concluded that PD-VH individuals spend more time in the segregated state due to the ease at which they can transition to this state from the integrated one, rather than because persisting in the segregated state itself is less energy-demanding.~~¶

The framework presented by these findings suggests that the DMN and thalamic regions have a role in VH in PD, as these are the nodes responsible for modulating the transitions between integrated and segregated states. Furthermore, the study expanded on these findings, attempting to assess the role of neurotransmitters in the alterations observed. The data gathered by Zarkali et al. provide further evidence ~~to show the key role of the~~for a possible involvement of ~~sercotonergic~~serotonergic ~~singaling~~signaling in ~~5-HT2A receptor in~~ developing VH in PD, as they found significant correlations between regional transition energy and ~~different~~ neurotransmitter receptor~~-densities~~-densit~~i~~y maps~~es~~, including 5-HT2A receptors.

4. Proposal for a Unified Framework

In light of the evidence considered and summarized in Table 21, this study proposes a unified framework to explain the functional changes that occur in PD-VH patients. ~~Indeed, the three existing models present similar characteristics and points of convergence.~~Although the three models emphasize different mechanisms, their findings are not necessarily mutually exclusive. Instead, they may describe abnormalities occurring at different levels of the same distributed perceptual system. The following comparison therefore focuses on points of convergence while distinguishing direct empirical findings from mechanistic links proposed by the present framework.

The first hypothesis, schematized in Figure 2A, attributes VH in PD to an early visual dysfunction. According to this model, an impairment in V1 would cause the activation of a loop across areas of the visual network, with an increased activity in the DMN (Yao et al., 2014) and a dysfunction across the DAN and VAN, resulting in the recognition of internally generated stimuli as external inputs (van Ommen et al., 2023). The original dysfunction in V1 would presumably be reflected by aberrant ERP values in the P1 component (Schwartzman et al., 2008), which in PD patients is correlated to primary visual processes (Wang et al., 2001).

The second hypothesis focuses on the role of a cholinergic dysfunction in PD-VH patients (see Figure 2B). However, there is

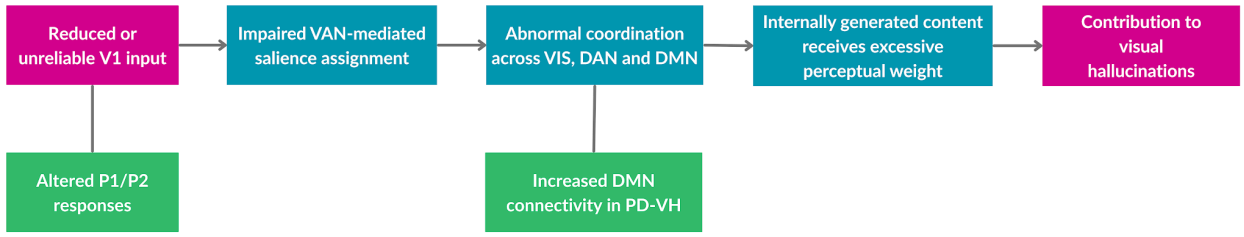
Table 12. Summary of reviewed literature

Hypothesis	Study	Approach	Key finding/relevance
Early visual dysfunction	Schwartzman et al. (2008)	EEG/ERP in hallucination-prone healthy participants	Higher P1/P2 positivity supports altered early visual processing but does not establish PD-specific causality.
	Yao et al. (2014)	Resting-state fMRI in PD-VH, PD-non-VH, and controls	Greater DMN connectivity in PD-VH supports involvement of internally oriented network activity.
	van Ommen et al. (2023)	fMRI during hallucinations in psychosis	Reduced V1 involvement with increased VIS/DAN/DMN/VAN activity supports a distributed network account.
Cholinergic dysfunction	Manganelli et al. (2009)	SAI in nondemented PD patients	Abnormal SAI links PD-VH to central cholinergic dysfunction; direction of causality remains unresolved.
	Chang et al. (2016)	Visual ERP task in nondemented PD groups	Prolonged P3b latency is consistent with altered cholinergic/cognitive processing in PD-VH.

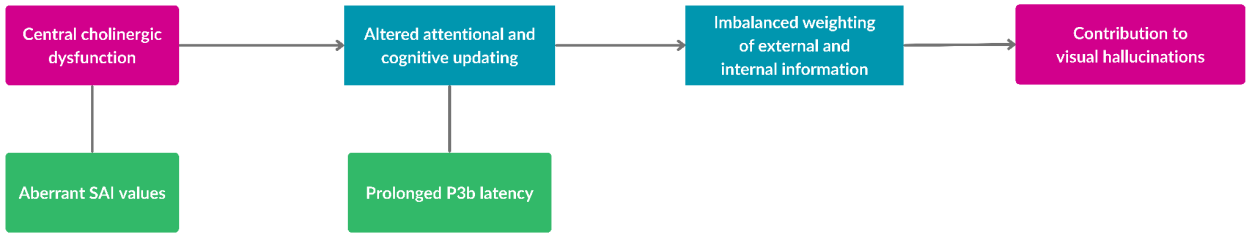
	Kometer et al. (2013)	Psilocybin/ketanserin EEG study in healthy adults	5-HT2A activation altered P1, N170, and αalpha power, providing a mechanistic bridge to visual processingsupporting serotonergic involvement in visual processing and cortical excitability.
Serotonergic/ 5-HT2A	Huot et al. (2010)	Postmortem temporal-cortex receptor analysis	Higher 5-HT2A receptor density in PD-VH supports receptor-level involvement, though dementia is a confound.
	Zarkali et al. (2022)	Resting-state fMRI and network-control analysis	PD-VH showed fewer transitions and longer segregation, linked regionally to neurotransmitter receptor density.

Convergence
A Journal for Young Researchers

A. Early visual dysfunction model



B. Cholinergic dysfunction



C. 5-HT2A receptor dysfunction model

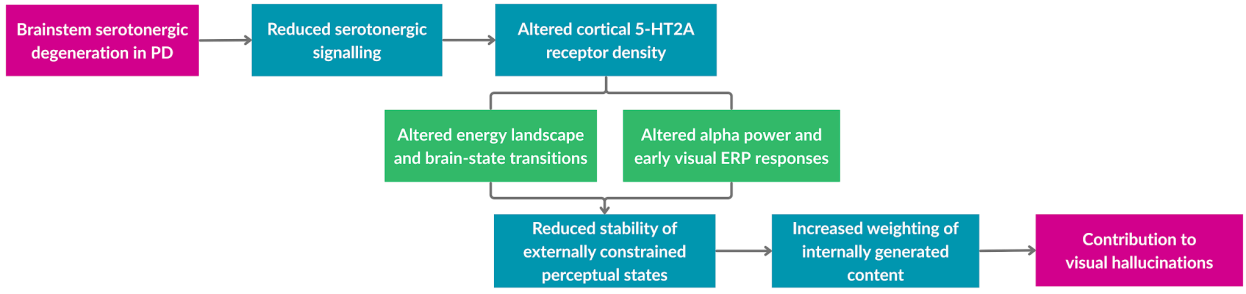


Figure 2. Schematic representations of the three models of visual hallucinations in Parkinson's disease. (A) Early visual dysfunction model. (B) Cholinergic dysfunction model. (C) 5-HT2A receptor dysfunction model. *Color code: key nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships proposed within each model; continuous lines without arrowheads indicate observed associations for which causal direction has not been established.*

divergent evidence regarding whether this is a causing factor of VH or rather a consequence of the condition. Manganelli et al. (2009) postulated the presence of a link between cholinergic dysfunction and VH in PD patients reflected by aberrant SAI values; the direction of causality remains unclear. Conversely, Chang et al. (2016) observed an increased latency of the

P3b component in EEGs of PD-VH patients, hypothesizing that a central cholinergic dysfunction might be an underlying cause of VH in PD.

Lastly, the third hypothesis, outlined in Figure 2C, ~~states~~ suggests that an aberrant density of 5-HT2A receptors in PD-VH patients, possibly due to the dysfunction of the 5-HT system in PD (Huot et al., 2010), ~~would cause a temporal imbalance in the~~ may be associated with altered transitions between integrated and segregated states (Zarkali et al., 2022). Moreover, pharmacological activation of 5-HT2A receptors in healthy participants resulted in increased amplitudes of the P1 potential~~s~~ and decreased α~~alpha~~ power values, providing causal evidence that 5-HT2A activation can alter early visual processing and cortical excitability. These changes may, in turn, contribute to an imbalance between the processing of external and internally generated stimuli (Kometer et al., 2013).

4.1 How Do These Models Relate to Each Other?

The models reviewed above can be related across different levels of processing rather than treated as competing explanations. The early visual model emphasizes altered processing of external sensory information, while the network-level models describe how this information may interact abnormally with internally generated activity. Cholinergic and serotonergic dysfunction may in turn modulate these sensory and network processes.

~~Firstly, it is interesting to note that both the first and third models present the idea that an underlying mechanism of VH in PD consists of an imbalance between internally generated stimuli and external inputs, causing the patient to recognize fictive stimuli as exogenous.¶~~

~~Furthermore, a~~Another significant observation concerns the last hypothesis. While Kometer et al. (2013) observed increased P1 amplitudes ~~P1 potentials~~ and decreased α~~alpha~~ power following pharmacological activation of 5-HT2A receptors, Zarkali et al. (2022) found associations between receptor-density maps and altered brain-state transitions. Specifically, the latter study found that PD-VH patients spend more time in the segregated state rather than the integrated one, compared to PD-non-VH. There is evidence that α ~~alpha~~ power increases during visual integration in various areas of the brain, including early visual cortex and dorsal visual networks (Costa et al., 2024), showing a link between α~~alpha~~ oscillations and states of the brain. Thus, the increased dwelling time in segregated states in PD-VH patients is convergent with the decreased α~~alpha~~ power value identified by Kometer et al. and reflected by increased P1 potentials. However, these findings were obtained using different methods and populations and do not establish that reduced α power directly causes, or indexes, increased network segregation. Their relationship should therefore be considered a testable cross-scale hypothesis.

Additionally, an aberrant value of the P1 ERP component has also been observed by Schwartzman et al. (2008), attributed to primary visual dysfunction and reflecting VH. As previously explained, this last piece of evidence supports the model proposed by van Ommen et al. (2023), according to which VH arise from an early visual dysfunction in V1, involving the DAN, DMN and VAN, and resulting in an imbalance between external and internally generated stimuli.

A further point of convergence between the proposed models is the finding that transitions between segregated and integrated states are highly influenced by the activity of the DMN and thalamic regions (Zarkali et al., 2022), thereby linking ~~the~~ attention- and memory-related networks to altered ~~imbalance of~~ brain-state dynamics.

Drawing on the convergent—but not yet causally unified—evidence considered, the present study proposes a model in which serotonergic dysfunction may act as a central neuromodulatory link, interacting with cholinergic and dopaminergic abnormalities and contributing to downstream changes in visual and attentional networks ~~represent one possible mechanistic link among early visual abnormalities, cholinergic dysfunction, and altered large-scale network dynamics in VH in PD~~ (see Figure 3).

PD is associated with degeneration of serotonergic neurons in the brainstem, leading to reduced 5-HT levels. Huot et al. (2010) proposed that reduced serotonergic signaling may be accompanied by a compensatory increase in 5-HT2A receptor density, which may contribute to abnormal activity in visual and attention-related networks.

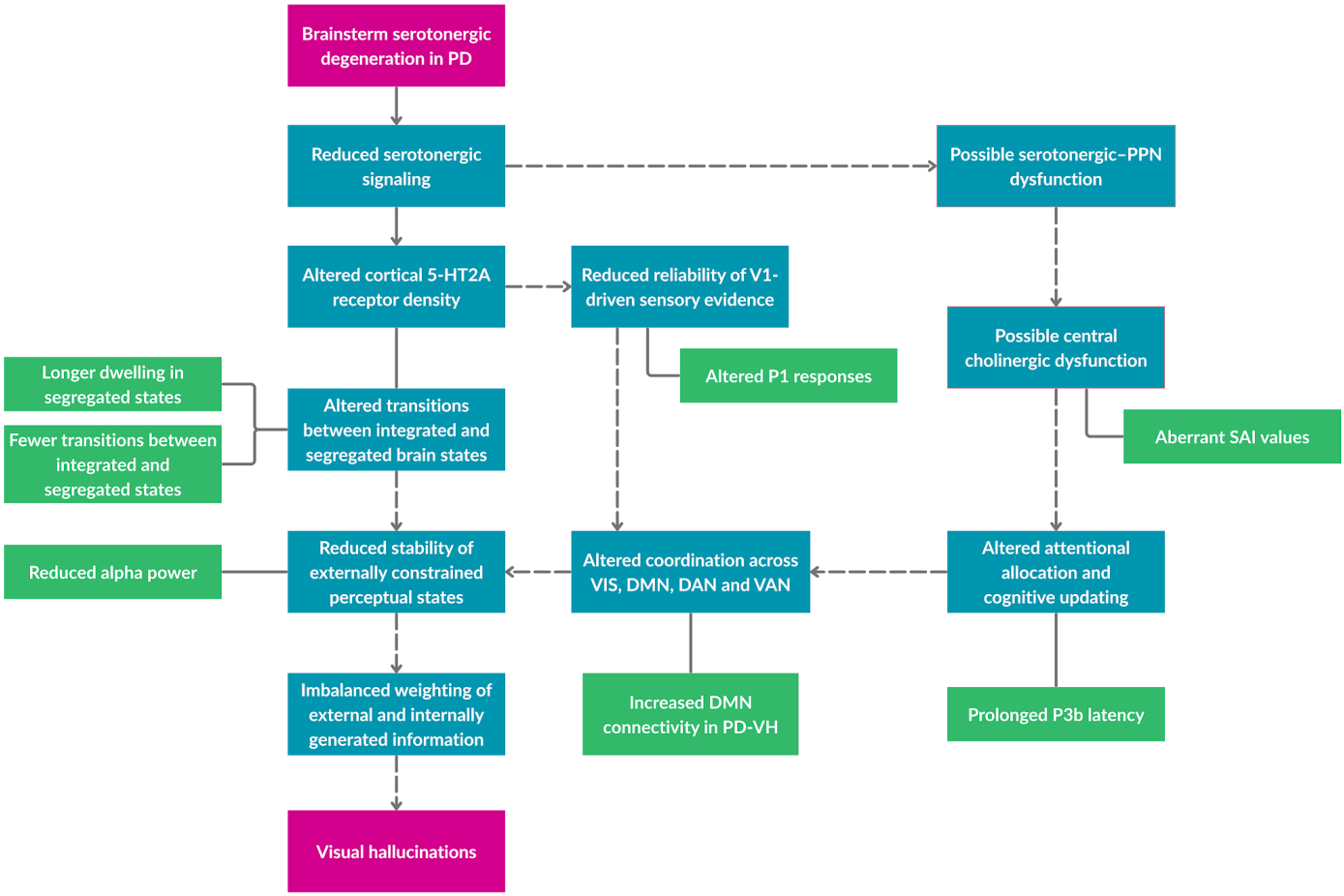


Figure 3. Proposed unified framework for visual hallucinations in Parkinson's disease. *Color code: key framework nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships retained from the reviewed models; continuous lines without arrowheads indicate observed associations for which causal direction has not been established; dashed arrows indicate integrative or unresolved mechanistic links proposed by the unified framework. Red borders identify especially uncertain or indirect components.*

~~Attributing VH in PD to a 5-HT dysfunction~~Within this framework, the comparatively later involvement of the serotonergic system in PD may help explain the delayed emergence of VH, while serotonergic dysfunction may also interact with other neurotransmitter systems and contributes to the downstream cascade of visual, attentional and network abnormalities.

~~explains the late occurrence of this condition in the timeline of the disorder, as the serotonergic system is not as affected as the dopaminergic one in PD.~~ Altered 5-HT2A receptor signaling may contribute to abnormal activity across the VIS and the ~~network of the~~ DAN, DMN and VAN, ~~causing anomalous~~and may be associated with altered α~~alpha~~ power ~~values~~ and~~and~~ impaired transitions between integrated and segregated states, with a prolonged dwelling time in the segregated states and fewer transitions to the integrated state. An increased activity in the DMN found in PD-VH patients (Yao et al., 2014)—and linked with the dysfunction between segregated and integrated states—possibly explains the aberrant P3b values observed by Chang et al. (2016). Indeed, a study conducted by Baumeister et al. (2014) found that increased P3 amplitude is linked to higher excitability in areas related to memory recollection and internal stimuli processing. ~~Therefore, it can be assumed that the P3 ERP component might reflect DMN activity, partly supporting the convergence of the data considered.~~These findings raise the possibility that abnormalities in P3 activity and DMN function reflect overlapping disturbances in internally oriented cognitive processing. However, the available evidence does not establish that P3 directly reflects DMN activity.

The previous models presented by van Ommen et al. (2023) theorized that the activation of the loop giving rise to VH—involving DMN, DAN and VAN—originated from a dysfunction in V1, which would indeed be reflected by the aberrant P1 medial potentials. There are some studies that link serotonin and acetylcholine to V1 functions in animals; for instance, Shimegi et al. (2016) investigated how cholinergic and serotonergic systems modulate visual processing in monkey V1. However, further evidence is necessary to define the underlying mechanisms that activate the loop between the VIS and visual-related networks. It is important to understand how the loop itself begins, whether it arises from dysfunction in V1 or abnormal activity in attentional networks, and to clarify which neurotransmitters are involved.

5. Conclusions

This review proposes that serotonergic dysfunction may ~~provide a~~one possible ~~mechanistic bridge between~~an integrative role in linking early visual abnormalities, altered neuromodulatory signaling, and large-scale network dynamics in PD with VH. ~~In the proposed framework, reduced serotonergic signaling and altered cortical 5-HT2A receptor density may contribute to electrophysiological changes, disrupted transitions between integrated and segregated brain states, and impaired coordination among visual and attention-related networks. A possible serotonergic-PPN-cholinergic pathway may offer an additional connection between these levels, although this component remains indirect and requires specific experimental validation.~~Rather than implying that serotonergic dysfunction represents the single or primary cause of VH, the reviewed evidence supports a model in which multiple sensory, cholinergic, serotonergic, and network-level abnormalities may interact.

The framework should therefore not be interpreted as demonstrating that serotonergic dysfunction is the single cause of VH or that it necessarily precedes cholinergic and network abnormalities. Its principal contribution is to identify testable links among findings that are usually considered separately. Future longitudinal, multimodal, and pharmacological studies will be required to establish causal direction and determine whether these mechanisms represent upstream drivers, interacting contributors, or downstream consequences of VH in PD.

6. Limitations and Future Research Directions

Accordingly, apparent convergence across studies should not be interpreted as evidence that the reported abnormalities belong to a single established causal sequence. In fact, the central limitation of the proposed framework is that it integrates evidence obtained from heterogeneous populations and methods. Some studies involve healthy participants exposed to serotonergic hallucinogens, some examine psychosis outside PD, and some include PD-VH samples affected by dementia.

Future work should therefore test the framework prospectively in carefully phenotyped, nondemented PD cohorts. The strongest design would combine receptor-sensitive imaging, EEG measures of P1/P3b and α~~alpha~~ power, and repeated fMRI measures of DMN–DAN–VAN coupling and integrated–segregated state transitions within the same participants. Longitudinal studies should determine whether serotonergic and cholinergic changes precede hallucination onset, while pharmacological studies should test whether modifying 5-HT2A or cholinergic signaling changes the predicted electrophysiological and network markers. These tests would distinguish correlation from causation and clarify whether the PPN and DRN are upstream drivers, downstream consequences, or interacting modulators of the proposed pathway.

~~A f~~Future studies could also investigate ~~urther possible link between serotonergic and cholinergic dysfunction involves t~~the role of the pedunculopontine nucleus (PPN) in modulating cholinergic and serotonergic dysfunction. The PPN~~, which~~ contains cholinergic neurons and receives serotonergic input from brainstem nuclei including the dorsal raphe nucleus (DRN) (Benarroch, 2013; Michelsen et al., 2007). ~~The PPNIt has also been linked to visual and attentional processing in relation to its prominence in the control of cholinergic neurons and visual cortex, as well as VAN and DAN (Manganelli et al., 2009; Alves et al., 2022). These findings raise the possibility that interactions between serotonergic and cholinergic systems modulated by the PPN could influence visual-attentional networks. However, this pathway remains indirect and has not been demonstrated as a causal mechanism of VH in PD.¶~~

Numerous studies mention the PPN in relation to VH in PD. With its cholinergic neurons, it is linked to attention networks, and it controls the visual cortex (Manganelli et al., 2009). Specifically, it modulates feedforward input to V1, exhibiting its crucial role in visual perception. Moreover, the neurotransmitters synthesized in the PPN modulate both the VAN and the DAN, together with other nuclei in the brainstem (Alves et al., 2022). These findings suggest that there is a connection between the PPN, attentional networks and other structures in the brainstem, especially the DRN, and that these connections are modulated by neurotransmitters. ~~However, t~~ However, the proposed role of the PPN as a link between serotonergic and cholinergic dysfunction and altered visual-attentional processing remains indirect and has not been demonstrated as a causal mechanism of VH in PD. Future studies should therefore determine whether PPN dysfunction contributes to VH by disrupting cholinergic and serotonergic modulation of visual and attentional networks. ~~This pathway remains indirect and has not been demonstrated as a causal mechanism of VH in PD. ; Ffuture research should assessclarify the role of the PPN in VH in PD .¶~~

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9. Author Biography

Redacted for double-blind review.

10. Mentor Contribution Statement

The research mentor provided conceptual guidance, recommended relevant literature, discussed the interpretation of evidence, and offered feedback on the manuscript's organization and argument. The author independently conducted the literature review, developed the proposed unified framework, and wrote and revised the manuscript. The mentor did not collect or analyze original data and is not listed as a co-author.

11. AI Use Statement

Generative AI tools were used for limited editorial support, including assistance with identifying typographical errors and awkward phrasing, checking reference formatting, and improving the organization of flowcharts. The author independently developed the research question, selected and interpreted the literature, constructed the proposed framework, evaluated the scientific claims, and approved all final wording. AI tools were not used to generate original data or conduct data analysis. The author verified the accuracy of all substantive claims, citations, and references and accepts full responsibility for the manuscript.

Cover letters for reviewers

Reviewer 1

Dear Reviewer 1,

Thank you very much for your thoughtful and constructive feedback. I have revised the manuscript substantially in response to your comments, with particular attention to improving clarity and strengthening the synthesis toward the proposed unified framework.

1. **Reduce methodological detail and emphasize interpretation**

I condensed the descriptions of the Schwartzman et al., Chang et al., and Kometer et al. studies, removing procedural details that were not necessary to interpret their findings. I also placed greater emphasis on the key results, limitations, and relevance of each study to the model being discussed.

2. **Strengthen the transition from the literature review to the unified framework.**

I revised the section “How Do These Models Relate to Each Other?” to distinguish more clearly between findings directly demonstrated by the reviewed studies and mechanistic relationships proposed by the present framework. I also clarified throughout that the proposed connections should be interpreted as testable hypotheses rather than established causal relationships.

3. **Make the paper’s conceptual contribution clearer earlier in the manuscript.**

I revised the end of the introductory discussion of the three models to state more explicitly that the paper aims to identify testable links among findings that are usually considered separately.

4. **Increase synthesis relative to study-by-study description.**

Each model section now begins with a short overview of the hypothesis and the type of evidence considered. I also added clearer concluding statements explaining how individual findings support, constrain, or relate to the broader framework.

5. **Preserve the limitations of the framework.**

I retained and expanded the discussion of the heterogeneous populations and methodologies included in the reviewed literature. The revised manuscript emphasizes that the unified framework is a theoretical, testable model rather than a demonstrated causal sequence.

Thank you again for your detailed feedback.

Sincerely,

The Author

Reviewer 2

Dear Reviewer 2,

Thank you very much for your detailed and helpful comments. I revised the manuscript with particular attention to improving clarity, defining technical terms, and making the relationship between the evidence and the three proposed models more explicit.

1. **Clarification of P1, P3b, and brain-state terminology in "Introduction" section.**

I now briefly define P1 as reflecting early visual processing and P3b as being associated with later cognitive processing. I also replaced the vague description of "temporal imbalances" with a more precise explanation that PD-VH participants spend more time in segregated states and make fewer transitions toward integrated states. I made sure to define each key terminology as soon as I identified it to improve the reader's understanding of the content covered.

2. **Introduction and clarification of methodological measures.**

I added a new methods table in the "Methodological Considerations" section. It explains EEG/ERPs, resting-state fMRI, short-latency afferent inhibition (SAI), network-control analysis, and postmortem receptor analysis, including what each method measures and its main limitations.

3. **Early Visual Dysfunction section.**

I added a short introductory paragraph explaining the model and the studies used to assess it. I also revised the Schwartzman et al. discussion to emphasize the pattern of altered neural responses during early visual processing rather than focusing only on P1, and I explicitly acknowledge that the study involved healthy hallucination-prone participants rather than PD-VH patients.

4. **Cholinergic Dysfunction section.**

I added an introductory overview of the evidence considered and defined SAI when it is first introduced. The Chang et al. section was shortened and reorganized so that the prolonged P3b latency and its interpretation receive greater emphasis.

5. **Serotonergic Dysfunction section.**

I reduced procedural detail and strengthened the synthesis of the Kometer, Huot, and Zarkali findings. I also revised the language throughout (in "Introduction", "Proposal for a Unified Framework" and "Conclusion" sections) so that serotonergic dysfunction is

presented as a possible integrative neuromodulatory factor rather than as the single or primary cause of VH.

6. **Relationship among the three models.**

I revised the synthesis section to state explicitly that cholinergic, serotonergic, dopaminergic, visual, and network-level abnormalities are not necessarily mutually exclusive and may interact at different levels of the same distributed perceptual system.

7. **Pedunculopontine nucleus (PPN).**

I removed the PPN from the main proposed framework and moved its discussion to the “Limitations” and “Future Research Directions” section. It is now presented as a possible avenue for future investigation rather than as an established component of the model.

Thank you again for your detailed and constructive feedback.

Sincerely,

The Author

The revised manuscript is significantly improved overall. The author has clearly put a great deal of thought into addressing provided feedback and editing suggestions, notably in the development of a helpful methodological overview and more consistently presenting the unified framework as a testable hypothesis rather than an established causal model. The manuscript now also better acknowledges the heterogeneity of the populations and methods represented in the cited literature.

There are several areas that would benefit from further clarification before publication:

1. Method and Scope Section: should provide greater transparency regarding study selection. Author states that targeted searches of PubMed, Google Scholar, and reference lists were performed, but does not indicate when the searches were conducted, the approximate date range covered, the criteria used to include or exclude studies, or approximately how many studies were ultimately included. Very briefly providing this information would help readers understand the scope of the literature reviewed and reduce the appearance of selective study inclusion.

2. Some mechanistic connections are still more strongly stated than the evidence supports. For example, reduced α power following psilocybin administration and increased time spent in segregated brain states in PD-VH are described as "convergent." While these findings may both be compatible with the proposed framework, they come from different populations, use different methods, and measure distinct neurophysiological phenomena. This relationship may be better presented as a cross-scale hypothesis requiring simultaneous EEG and fMRI testing in patients with PD-VH.

3. A similar issue (as #2) applies to the discussion of P3b abnormalities and DMN activity. Chang et al. reported prolonged P3b latency, whereas Baumeister et al. discuss P3 amplitude and regional excitability. Because latency and amplitude are distinct ERP properties, the current evidence does not clearly support the suggestion that increased DMN activity "possibly explains" the Chang et al. finding. The author should either provide more direct evidence connecting P3b latency with DMN dysfunction or avoid implying a direct mechanistic relationship.

4. The discussion of P1 and V1 could be more precise. Abnormal P1 potentials may support altered early visual processing, but scalp-recorded ERPs do not specifically localize dysfunction to V1. Additionally, Schwartzman et al. studied healthy hallucination-prone individuals rather than patients with PD-VH. P1 should therefore be described as a marker of altered early visual processing rather than direct evidence of V1 dysfunction.

5. The cholinergic section remains somewhat ambiguous regarding directionality. The author should clarify whether cholinergic dysfunction is proposed to contribute to VH, develops as a consequence of VH or disease progression, or occurs in parallel with VH as part of another underlying process.

6. The organization of the framework could also be more consistent. The manuscript refers to “three models,” but network-state dysfunction is sometimes presented within the serotonergic model and elsewhere as a separate explanatory level. The author would do well to clarify whether altered network dynamics represent a distinct model or a mechanism through which serotonergic and cholinergic abnormalities may operate and apply this terminology consistently throughout the manuscript.

7. Additional tightening would improve readability. The conclusion repeats qualifications already discussed elsewhere and could be consolidated for a more decisive ending. Awkward phrases such as “a causing factor,” “provides support to the hypothesis,” and “the effects that they have on the overall health of the patient” could also be revised to be more in active voice and/or more straightforward and concise. Table 1’s duplicated title should be corrected during final formatting.

Overall, these remaining concerns are targeted and can be addressed without reconceptualizing the manuscript’s central contribution.

Fantastic job thus far to the Author!

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Proposal for a Unified Framework to Understand the Functional Changes That Occur in Visual Hallucinations in Parkinson's Disease

Abstract

Visual hallucinations in Parkinson's disease are often viewed as isolated symptoms of neurodegeneration. However, growing evidence suggests that they reflect deeper disruptions in how the brain constructs perception. This paper reviews three major hypotheses—early visual dysfunction, cholinergic dysfunction, and serotonergic dysfunction—and proposes a unified framework linking these mechanisms across multiple levels of brain organization. By integrating electrophysiological, neurochemical, and network-level findings, this study argues that hallucinations arise from an imbalance between internally generated and externally driven signals. Specifically, serotonergic dysfunction, through alterations in 5-HT2A receptor density, may be a mechanistic bridge linking early sensory processing with large-scale network dynamics, including impaired transitions between brain states. Understanding these mechanisms provides insight not only into Parkinson's disease, but also into the fundamental nature of perception as an active and dynamic process. More broadly, this work highlights the importance of approaching neurodegeneration as a distributed, multilevel phenomenon, with implications for developing more integrated and effective therapeutic strategies.

Keywords: Parkinson's disease; visual hallucinations; serotonin; 5-HT2A receptor; visual processing; attention networks; brain-state dynamics

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder attributed to a dysfunction in the dopaminergic system (Lew, 2007). The main symptoms of PD and those that serve as a diagnosis are motor, but patients often show a spectrum of various non-motor symptoms as well. Moreover, it is possible for PD patients to develop dementia or psychotic symptoms. This last condition is known as Parkinson's disease psychosis (PDP) (Friedman, 2010), and its main symptom is visual hallucinations (VH).

VH can present in different forms, and they are commonly classified as elementary and complex. Elementary VH generally

consist of geometric patterns, such as lines, curves or spots (Billock & Tsou, 2012). These can also have additional features such as color or motion. Conversely, complex VH feature a variety of different contents, often depicting animal or human figures in absurd or unrealistic contexts (Manford & Andermann, 1998). Patients who suffer from a psychotic disorder often encounter both elementary and complex VH, but most PD patients recall having experienced complex VH (van Ommen et al., 2023).

It was initially believed that VH and PDP were a collateral effect of dopaminergic treatments, administered to alleviate the motor symptoms of the disorder; however, some PD patients develop PDP without medications (Friedman, 2010). This suggests that PDP is a progression of PD itself. Indeed, while dopamine is the main neurotransmitter attributed to PD motor symptoms, it is believed that the disorder also displays dysfunctions in other neurotransmitter systems and in the interactions between those; many motor and non-motor symptoms of the disease have been attributed to neurotransmitters such as serotonin, acetylcholine, glutamate and γ-aminobutyric acid (GABA) (Barone, 2010).

PD is the second most prevalent neurodegenerative disorder in the world population, and VH has a prevalence range of 8%–40% in PD patients (Barone, 2010; Manganelli et al., 2009). Moreover, there are a variety of correlates linking VH and PD. For example, VH in PD are associated with aberrant event-related potential (ERP) components, including alterations in P1, which reflects early visual processing, and P3b, associated with later cognitive processing of stimuli. Moreover, some PD-VH patients present anomalous neural network behavior, including enhanced excitability in the default mode network and in attention-related networks, as well as longer periods in segregated brain states and fewer transitions toward integrated states. Nevertheless, the underlying mechanisms giving rise to VH are largely unknown.

A complicating factor to this phenomenon is the high occurrence of dementia in PD, known to cause cognitive impairment and dysfunctions in many neural networks, namely in attention, memory and visual perception pathways, sometimes resulting in VH itself (Gratwicke et al., 2015). Since dementia and psychosis often coexist in PD patients, it is difficult to discern the distinct effects that the two conditions have on neural networks in PD, as well as to identify their respective causal factors.

At present there remains no unified framework able to explain how and which neural networks are involved in VH among nondemented PD patients. Investigating the functional changes that occur in VH in PD can offer new insights into visual processing and stimuli interpretation. Moreover, it may enhance treatments to alleviate VH, improving patients' quality of life. This is clinically relevant as VH in PD are associated with an increased risk of dementia and mortality (Manganelli et al., 2009).

The present study reviews three existing hypotheses of VH in PD, namely early visual, cholinergic, and serotonergic, and examines how evidence from these hypotheses may interact rather than represent mutually exclusive explanations. In particular, it proposes that serotonergic dysfunction may provide one possible integrative bridge between these abnormalities.

2. Method and Scope of the Review

This paper is a focused narrative review and theoretical synthesis. It compares evidence from electroencephalography, neuroimaging, pharmacological studies, network-control approaches and postmortem receptor analyses (see Table 1).

76 ***Table 1. Methods Used to Characterize Neural Dysfunction in Visual Hallucinations***

Method	What it measures	Main strength	Main limitation
Electroencephalography (EEG) and Event-Related Potentials (ERPs)	EEG records electrical activity from the scalp; ERPs isolate activity time-locked to specific stimuli or events (Fabiani et al., 2007; Beres, 2017).	Excellent temporal resolution, allowing neural responses to be tracked on the millisecond scale (Beres, 2017).	Limited ability to precisely localize the neural source of the recorded activity (Beres, 2017).
Resting-state fMRI (rsfMRI)	Measures spontaneous fluctuations in the blood-oxygen-level-dependent (BOLD) signal at rest and their correlations across brain regions, allowing functional connectivity to be estimated (Van Den Heuvel & Pol, 2010).	Allows investigation of large-scale functional networks across the brain.	BOLD is an indirect measure of neural activity and has relatively poor temporal resolution because of the delayed haemodynamic response.
Short-latency afferent inhibition (SAI)	A neurophysiological measure of sensorimotor inhibition that is used as a putative marker of central cholinergic function (Martin-Rodriguez & Mir, 2020).	Provides a non-invasive physiological measure associated with cholinergic function in humans.	It is an indirect marker rather than a direct measurement of acetylcholine, and it can be influenced by factors such as disease duration and dopaminergic medication (Martin-Rodriguez & Mir, 2020).
Network-control analysis	Uses structural and functional brain-network data to estimate transitions between brain states and the control energy required for those transitions (Zarkali et al., 2022).	Can characterize dynamic differences in integrated and segregated brain states.	The inferred transitions and energy values depend on the assumptions of the mathematical model used and do not directly measure neurotransmitter activity.

Postmortem receptor analysis	Uses receptor-binding techniques in brain tissue to quantify receptor density; Huot et al. (2010), for example, measured 5-HT2A receptor binding in cortical tissue from PD patients.	Provides direct anatomical evidence of receptor-level differences in human brain tissue.	It is cross-sectional and cannot establish whether receptor changes precede or result from VH.

Relevant studies were identified between June and August 2025 through targeted searches of PubMed, Google Scholar, and reference lists of key reviews using combinations of terms related to PD, VH, visual processing, cholinergic dysfunction, serotonin, 5-HT2A receptors, and brain-state dynamics. Studies were selected for their relevance to three recurring explanatory levels: early visual processing, cholinergic modulation, and serotonergic dysfunction. The final bibliography comprised 36 sources published between 1978 and 2024, although older sources were primarily included for methodological or conceptual background. Most cited literature (31 of 36 sources) was published between 2007 and 2024. Eight core empirical studies, published between 2008 and 2023, were selected for detailed comparison because they directly examined evidence relevant to the three explanatory models considered in this review and provided findings pertinent to the overall synthesis. Studies were prioritized when they directly examined VH, relevant electrophysiological or network abnormalities, or cholinergic/serotonergic mechanisms pertinent to the proposed framework; studies used only to define methods, neural processes, or broader PD background were treated as supporting literature rather than empirical evidence. Where findings were inconsistent with, or did not fully support, the proposed hypotheses, these were discussed explicitly rather than excluded from consideration. Because the included studies differ substantially in population, task, and measurement method, and several do not examine nondemented PD patients directly, the proposed framework should be interpreted as a testable integrative hypothesis rather than a demonstrated causal model.

3. Literature Review on Visual Hallucinations in Parkinson's Disease

Several models have been proposed to explain the functional changes associated with VH in PD. The present study focuses on three frameworks that emphasize different but potentially interacting levels of dysfunction. The first hypothesis focuses on early visual dysfunction (Schwartzman et al., 2008; van Ommen et al., 2023), while the second and third present a broader explanation of VH involving an imbalance between external and internal stimuli and the modulation of visual and attentional networks. The distinguishing factor between the last two models lies in the type of neurotransmitters involved: the second emphasizes central cholinergic dysfunction (Manganelli et al., 2009), whereas the third focuses on serotonergic dysfunction and altered 5-HT2A receptor density (Kometer et al., 2013).

3.1 Early Visual Dysfunction

The early visual dysfunction model proposes that abnormalities in the initial processing of visual information may contribute to VH and, through disrupted communication with higher-order visual and attentional networks, lead to the misinterpretation of internally generated information as external. Evidence for this model comes from studies examining

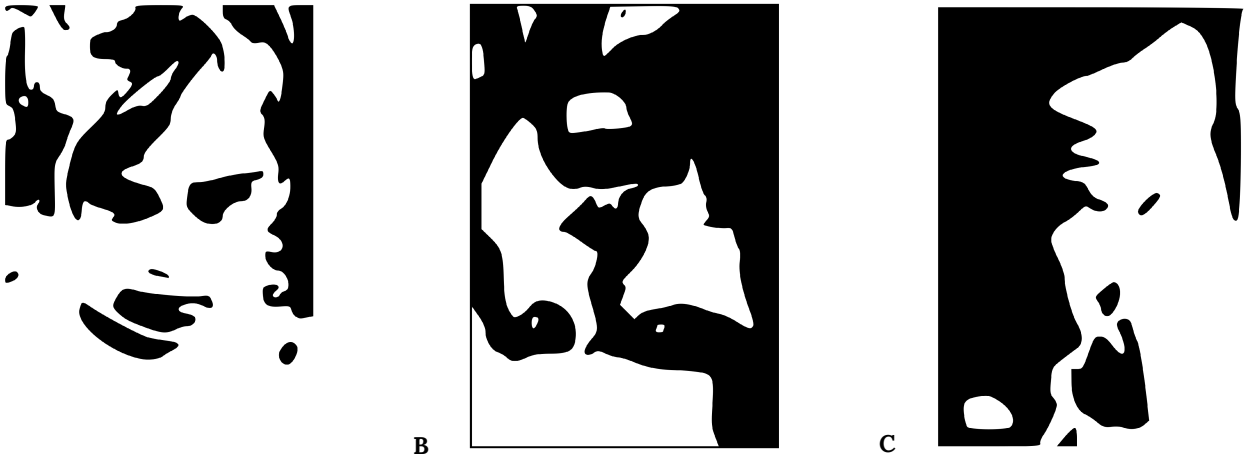


Figure 1. Representative stimuli from the Mooney Faces Test. *The upright Mooney face* (A) *is typically perceived as a face, whereas the inverted Mooney face* (B) *is substantially more difficult to recognize due to disruption of holistic face processing. The scrambled image* (C) *serves as a non-face control stimulus. Stimuli adapted from the dataset of Schwiedrzik et al.* (2018) *and redrawn as vector graphics for presentation clarity under CC BY 4.0.*

both early electrophysiological responses to visual stimuli and the interaction between primary visual processing and broader visual-attentional networks.

A study conducted by Schwartzman et al. (2008) evaluated the hypothesis that aberrant early visual ERP components reflect individuals' proneness to hallucinate. While early visual disruption had been previously associated with various psychological and neurological disorders that present VH—e.g. PD, schizophrenia—it remained unclear whether an early impairment of visual processes was a key factor in the development of VH or rather a mere outcome of the disorder itself.

In order to reduce the possibly confounding influence of cognitive decline, the study analyzed electroencephalogram (EEG) recordings from healthy individuals divided according to their proneness to hallucinate. Hallucination proneness was assessed using a questionnaire, after which participants completed a face-perception task involving photographs, Mooney faces, and scrambled Mooney faces (see Figure 1). The Mooney Faces Test (MFT) evaluates an individual's ability to perceive human faces in two-dimensional, black and white pictures, shown both upright and upside down (Silverstein et al., 2021).

During the experiment conducted by Schwartzman et al., the participants' brain activity was recorded through EEG; specifically, the study focused on ERP components that reflect early visual processes. The components analyzed were the N170, P1 and P2, respectively associated with face recognition, early extraction of information from face stimuli, and finally a higher level of visual processing involving categorization of face stimuli. The interpretation of the stimulus in P2 depends on the reception of information carried out in P1.

The study observed no significant differences in the N170 component, while P1 and P2 showed increased positivity in hallucination-prone individuals. The lack of significant N170 differences suggests that the observed changes in P1 and P2 were not specific to face recognition but may instead reflect abnormalities in earlier stages of visual processing.

Conversely, the increased amplitude registered in P1 suggests a dysfunction in the extraction of fine information from visual stimuli, which would in turn impair the interpretation of the visual information itself, explaining the knock-on effects on P2. Thus, compared with individuals with low hallucination proneness, hallucination-prone participants showed altered stimulus-evoked electrophysiological responses during early visual processing. However, because the study involved healthy participants rather than PD patients with VH, these findings support an association with hallucination susceptibility rather than establishing a PD-specific causal mechanism.

An earlier study had shown a correlation between P1 ERP component in patients with PD and primary visual processes (Wang et al., 2001). The association between P1 and primary visual processing in PD provides a basis for considering abnormal P1 responses as a possible marker of early visual dysfunction in PD-VH.

Although early visual dysfunction is associated with VH in PD, existing evidence does not support a purely focal explanation. Instead, a study led by van Ommen et al. (2023) correlated an impairment in primary visual processes to dysfunctions in other visual-related neural networks, proposing a more holistic explanation of VH.

They aimed to evaluate a hypothesis previously postulated by Shine et al. (2014), which had explained VH as a consequence of a disconnection between the primary visual cortex, V1, and higher visual components, inducing a desynchronization between different parts of the visual network. This previous hypothesis was supported by the reduced activity registered in the primary visual cortex in patients with psychotic VH.

In order to evaluate the postulated model from Shine et al. and assess what areas of the brain are involved in psychotic VH, van Ommen et al. (2023) conducted an experiment on hallucinating psychotic individuals, recording their brain activation data during an episode of VH, through functional magnetic resonance imaging (fMRI). The results showed a lack of activation in V1 and increased activity across the visual and attention pathways, specifically in the Dorsal Attention Network (DAN), Default mode network (DMN) and Ventral Attention Network (VAN). These are respectively linked to processing external information, interpreting internal stimuli and coordinating memory and finally synchronizing the two networks—DAN and DMN (Van Calster et al., 2017). The results are therefore in line with the hypothesis postulated by Shine et al., 2014, as they show that psychotic VH is not a focal pathology. Instead, it affects a wide range of regions, namely the visual network (VIS)—excluding V1—and vision-related networks involved with memory and attention.

Based on these findings, Van Ommen et al. proposed a refinement of the model postulated by Shine et al., attributing VH in PD to the activation of a loop across the VIS—with the exception of V1—and the DAN, DMN and VAN. Under normal circumstances, feed-forward impulses are sent from V1 to the surrounding visual network regions. This flow of information allows the stimulus to be recognized as external. In turn, a feedback inhibitory response is sent from the networks to V1. According to this model, the ability of V1 to provide feed-forward and receive feedback information from the surrounding areas is compromised in psychotic VH. This disruption may cause internally generated information to be misinterpreted as external sensory input, thereby contributing to the generation of VH.

However, since van Ommen et al. investigated VH in individuals with psychosis rather than specifically in PD patients, the extent to which this network mechanism applies directly to PD-VH remains to be established.

Additional evidence comes from Yao et al. (2014), who investigated DMN activity in resting PD patients, both with (PD-VH) and without VH (PD-non-VH) and in healthy controls. Patients with symptoms of cognitive impairment and dementia were

excluded. Resting-state functional magnetic resonance imaging (rsfMRI) data of the participants were acquired, and the results showed a decreased activity in the DMN in PD patients compared to controls. Conversely, PD-VH patients had a greater connectivity in the DMN compared to PD-non-VH. Yao et al., therefore, demonstrated that a higher connectivity in the DMN is associated with VH in PD patients, relative to PD-non-VH patients. Showing a correlation between aberrant DMN activity and VH in PD, these data support the model proposed by van Ommen et al.

Thus, while there are findings suggesting that early visual impairment has a role in generating VH in PD, this is treated as one level of a distributed mechanism rather than a complete explanation of the condition. Moreover, this presented model fails to include the involvement of neurotransmitters in VH in PD. To fully comprehend the underlying neurological mechanisms of VH in PD, it is necessary to adopt a more holistic approach, recognizing the role of neurotransmitters in modulating attention and vision-related networks. Consistent with the model postulated by van Ommen et al., 2023, a second hypothesis attributes VH in PD to an imbalance between external and internal stimuli associated with central cholinergic dysfunction.

3.2 Imbalance Between External and Internal Stimuli and Central Cholinergic Dysfunction

The cholinergic model proposes an association between impaired cholinergic modulation of attention and the imbalance between externally driven and internally generated information observed in VH in PD. Nevertheless, the available evidence, coming from both physiological measures of central cholinergic function and ERP studies of cognitive processing in nondemented PD patients with VH, does not fully establish the direction of this relationship. There remains disagreement whether cholinergic dysfunction directly contributes to VH, develops alongside VH as part of PD progression, or arises secondarily in association with the condition.

A study from 2009, conducted by Manganelli et al., found a correlation between nondemented PD-VH patients and a central cholinergic dysfunction. The research methodology included the use of short-latency afferent inhibition (SAI), a physiological measure commonly used as an indirect marker of central cholinergic function (Martin-Rodriguez & Mir, 2020). The participants were 22 non-demented PD patients, both with and without VH (Manganelli et al., 2009). The study found that most PD-VH patients presented aberrant SAI values, unlike PD-non-VH individuals. Therefore, Manganelli et al. concluded that VH in PD could be one of the factors that alter the balance of the cholinergic system. Alternatively, VH would cause a dysfunction between the cholinergic and other neurotransmitter systems. The study also confirmed the hypothesis of a correlation between cholinergic dysfunction and PD patients who are likely to develop dementia. Similarly, VH are considered to be a predictive factor of dementia. Therefore, there is a possible link between central cholinergic dysfunction and VH in PD.

However, there remains disagreement about the direction of causality, as other later studies consider cholinergic dysfunction as a causal factor of VH in PD. One of these is a study led by Chang et al. (2016).

While aberrant ERP values are considered an indicator of cognitive dysfunction in demented PD patients, their role in nondemented PD patients, both with and without VH, remained unclear. Specifically, some studies had found a correlation between PD-VH patients and impaired P3 responses, a component related to attentional allocation and cognitive processing of task-relevant stimulus (Kurita et al., 2010; Chang et al., 2016). To address this gap in the literature, Chang et al. compared ERP responses in nondemented PD patients with and without VH, and in healthy controls during a visual

target-detection task. They reported that PD-VH individuals showed a prolonged latency of one subcomponent of the P3, namely the P3b component, compared with controls. Since P3b is associated with later cognitive processing and memory updating, this result was interpreted as evidence of altered cognitive processing in PD-VH and was considered compatible with central cholinergic dysfunction (Chang et al., 2016; Polich, 2003).

This study also investigated N1 and P2, two exogenous ERP responses associated with sensory and attentional processing respectively (Chang et al., 2016; Donchin et al., 1978). Chang et al. reported no significant differences in either component across the groups. This finding does not necessarily contradict the visual-network dysfunction model described previously. These ERP components and the DAN, VAN, and DMN reflect different levels of neural processing, and there is no evidence that abnormalities in these large-scale networks must be accompanied by altered N1 or P2 responses. The Chang et al. findings therefore add evidence of altered later cognitive processing rather than excluding the involvement of visual and attentional networks.

Overall, the findings reviewed support an association between central cholinergic dysfunction and VH in PD; yet they do not establish its direction of causality. Consequently, the present framework treats cholinergic dysfunction as a potentially interacting contributor to VH rather than as a demonstrated upstream cause or downstream consequence.

3.3 Serotonergic Dysfunction, 5-HT2A Receptors, and Brain-State Dynamics

The serotonergic model proposes that altered serotonergic signaling, particularly through 5-HT2A receptors, may contribute to VH by modifying visual processing and the balance between internally and externally driven neural activity. Evidence for this model comes from pharmacological manipulation of 5-HT2A signaling, postmortem receptor analyses in PD, and studies of large-scale brain-state dynamics.

An aberrant density of 5-HT2A receptors in different cortical areas has often been connected to various forms of psychosis, including PDP (Huot, 2018), but the effect of this receptor's activation on VH is left unclear. A study conducted by Kometer et al. (2013) aimed to clarify this connection by investigating the effects that the activation of the 5-HT2A receptor has on parieto-occipital α waves.

Alpha oscillations, considered to be mostly present in the thalamic regions and visual cortex, have been correlated with visual processing dysfunctions and impairments (Clayton et al., 2018). Since they are strongly linked to visual processing, they are also associated with visual-related potentials (Kometer et al., 2013). The study presented here hypothesized that α oscillations could contribute to the generation of VH. According to their model, activation of 5-HT2A receptors, triggered by the administration of psilocybin, a serotonergic hallucinogen, would alter α oscillations. A second hypothesis postulated by the study concerned how early visual ERP components—specifically the P1 and N170—would be influenced by psilocybin-induced hallucinations. Thus, the investigation examined the effects of 5-HT2A activation on visual processing in healthy participants by comparing the effects of psilocybin with those observed after pretreatment with the 5-HT2A antagonist ketanserin. EEG responses were recorded during a visual perception task.

Psilocybin increased P1 amplitude over medial parieto-occipital regions, altered N170 responses, and decreased α power. These effects were suppressed by ketanserin pretreatment, supporting their relationship with 5-HT2A activation. Decreased α power was attributed to increased cortical excitability especially in the parieto-occipital regions and visual

networks, following activation of 5-HT2A receptors. A reduction in α power had previously been associated with increased visual attention and cortical excitability in the occipital lobe, while increased α oscillations might directly suppress visual processing (Clayton et al., 2018). The decreased α power was also related to the increase in P1 medial potential, which might represent an enhancement in early visual processing (Kometer et al., 2013). This coordinated response between the P1 and α power would in turn contribute to an imbalance between perception of external and internal stimuli.

Specifically, altered cortical excitability may reduce the normal distinction between neural activity driven by external visual input and activity occurring in the absence of external stimuli. This corresponds to a change in the activation of brain networks—reflected by decreased α oscillations and enhanced P1 medial potentials—with an increased attention towards internally generated visual stimuli, rather than external stimuli. This model seems to be in line with the hypothesis proposed by van Ommen et al. (2023), in which VH arise from an altered balance between externally and internally generated signals.

Although the findings suggest that α power waves may have a role in psilocybin-induced VH, analytical studies showed little correlation between reduced α power and the occurrence of hallucinations, perhaps revealing that the reduction in α power triggered by psilocybin is not sufficient to induce complex VH. Moreover, the study involved psilocybin-induced perceptual alterations in healthy participants rather than in the PD population. Therefore, the study does not establish that the same mechanism causes complex VH in PD.

Finally, the psilocybin treatment produced a decrease in the N170, which is thought to play a key role in processing meaningful visual stimuli. An alteration in this component is associated with altered visual perception and may therefore reflect changes produced during psilocybin-induced hallucinations. Alternatively, the effects on the N170 could be attributed to the increased cortical excitability triggered by the activation of the 5-HT2A receptor, further contributing to an imbalance between external and internal stimuli.

Taken together, the effects of 5-HT2A activation on P1, N170, and α power demonstrate that serotonergic signaling can alter neural processes involved in visual perception and cortical excitability, although these findings do not establish that the same mechanism causes VH in PD.

A previous study had investigated the distribution of 5-HT2A receptors in postmortem PD patients' tissues, postulating a correlation between increased receptor density and VH in PD (Huot et al., 2010). The results showed an increased density of this receptor in PD tissues with VH, compared to PD-non-VH, therefore providing PD-specific evidence supporting the involvement of 5-HT2A signaling in VH. While an existing postulate attributed the development of psychosis in PD to a polymorphism in the 5-HT2A receptor gene, a study led by Kiferle et al. (2007) refuted this hypothesis, and they concluded that aberrant levels of this receptor are not due to the genetic variations examined.

Huot et al. (2010) proposed a new explanation of the enhanced levels of 5-HT2A receptors in PD patients with psychosis, defining it as a consequence of other neurotransmitter dysfunctions in PD. PD is known to present serotonin (5-HT) dysfunctions; specifically, degeneration in the serotonergic neurons in the brainstem causes a decline in the neurotransmitter levels. Huot et al. proposed that this may contribute to a compensatory increase in 5-HT2A receptor density, as a biological attempt to balance the drop of 5-HT in different areas of the brain. Enhanced levels of 5-HT2A could also be attributed to the decrease in dopamine (DA) levels, which acts as a partial agonist to the receptor. These two

possibilities are likely to be complementary, and this explanation would help explain the late occurrence of VH in the development of PD: the disorder disrupts the dopaminergic system more than the serotonergic system, suggesting that it takes longer for the levels of 5-HT to drop below the threshold level. According to this hypothesis, the resulting serotonergic and receptor-level changes could eventually contribute to the development of VH. This proposed compensatory increase in 5-HT2A receptor density further supports the hypothesis that dysfunction of the serotonergic system, and particularly altered 5-HT2A signaling, may have a role in VH in PD.

A possible limitation of the presented study is the interference of dementia, which was present in four out of the six PD-VH participants. Since dementia is known to cause dysfunctions in many neural networks, such as attention, memory and visual perception (Gratwicke et al., 2015), this factor limits the reliability of the findings and makes it unclear whether they should be attributed to psychosis rather than dementia.

Additional evidence suggests an association between 5-HT2A and altered brain-state dynamics in PD-VH. Specifically, an aberrant density of this receptor was attributed to temporal dysfunctions in transitions between the segregated and integrated states of the brain in hallucinating PD patients (Zarkali et al., 2022). Integrated and segregated states are opposite methods of network organization, although they often coexist in the same functional system (Tononi et al., 1994). Integration means that the different areas of the network are interconnected and there is a fast flow of information among them; each component of the circuit is dependent on the others. Conversely, segregation happens when different regions function relatively independently of one another, with a limited amount of information flow among the whole system.

It is believed that shifts between integration and segregation are controlled by neurotransmitter systems (Zarkali et al., 2022). The study aimed to investigate how temporal dynamics in transitions between integrated and segregated states are affected in PD patients with VH, using rsfMRI.

The main difference reported was not the presence of distinct integrated or segregated states, but their temporal dynamics: PD-VH participants spent less time in integrated states, more time in segregated states, and made fewer transitions between them than PD-non-VH participants.

The framework presented by these findings suggests that the DMN and thalamic regions have a role in VH in PD, as these are the nodes responsible for modulating the transitions between integrated and segregated states. Furthermore, the study expanded on these findings, attempting to assess the role of neurotransmitters in the alterations observed. The data gathered by Zarkali et al. provide further evidence for a possible involvement of serotonergic signaling in developing VH in PD, as they found significant correlations between regional transition energy and neurotransmitter receptor-density maps, including 5-HT2A receptors.

4. Proposal for a Unified Framework

4.1 Summary of Reviewed Literature

The first hypothesis, schematized in Figure 2A, attributes VH in PD to early visual dysfunction. According to this model, an impairment in V1 would cause the activation of a loop across areas of the visual network, with an increased activity in the DMN (Yao et al., 2014) and a dysfunction across the DAN and VAN, resulting in the recognition of internally generated stimuli as external inputs (van Ommen et al., 2023). Aberrant P1 responses may reflect altered early visual processing, although they do not specifically localize this dysfunction to V1 (Schwartzman et al., 2008; Wang et al., 2001).

The second hypothesis focuses on the role of a cholinergic dysfunction in PD-VH patients (see Figure 2B). However, the available evidence does not establish whether this directly contributes to VH or rather develops as a consequence of the condition. Manganelli et al. (2009) postulated the presence of a link between cholinergic dysfunction and VH in PD patients reflected by aberrant SAI values; the direction of causality remains unclear. Conversely, Chang et al. (2016) observed an increased latency of the P3b component in EEGs of PD-VH patients, hypothesizing that a central cholinergic dysfunction might be an underlying cause of VH in PD. Accordingly, the unified framework does not assign a fixed causal position to cholinergic dysfunction.

Lastly, the third hypothesis, outlined in Figure 2C, suggests that an aberrant density of 5-HT2A receptors in PD-VH patients, possibly due to the dysfunction of the 5-HT system in PD (Huot et al., 2010), may be associated with altered transitions between integrated and segregated states (Zarkali et al., 2022). Moreover, pharmacological activation of 5-HT2A receptors in healthy participants resulted in increased amplitudes of the P1 potential and decreased α power values, providing causal evidence that 5-HT2A activation can alter early visual processing and cortical excitability (Kometer et al., 2013). These changes may, in turn, contribute to an imbalance between the processing of external and internally generated stimuli.

4.2 How Do These Models Relate to Each Other?

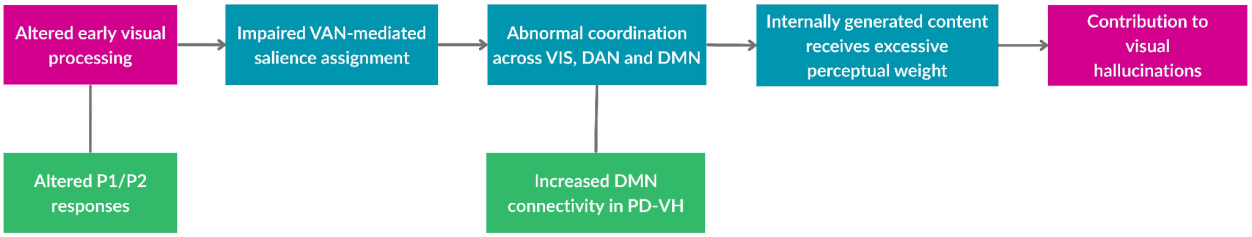
In light of the evidence considered and summarized in Table 2, this study proposes a unified framework to explain the functional changes that occur in PD-VH patients. Although the three models emphasize different mechanisms, their findings are not necessarily mutually exclusive. Instead, they may describe abnormalities occurring at different levels of the same distributed perceptual system. The following comparison therefore focuses on points of convergence while distinguishing direct empirical findings from mechanistic links proposed by the present framework.

Firstly, both the first and third models propose that an underlying mechanism of VH in PD may involve an imbalance between internally generated stimuli and external inputs, leading patients to misattribute internally generated stimuli as exogenous. While an early visual dysfunction might alter the processing of external sensory information, network-level abnormalities may describe how this information interacts abnormally with internally generated activity (Schwartzman et al., 2008; van Ommen et al., 2023). Cholinergic and serotonergic dysfunction may in turn modulate these sensory and network processes (Chang et al., 2016; Kometer et al., 2013).

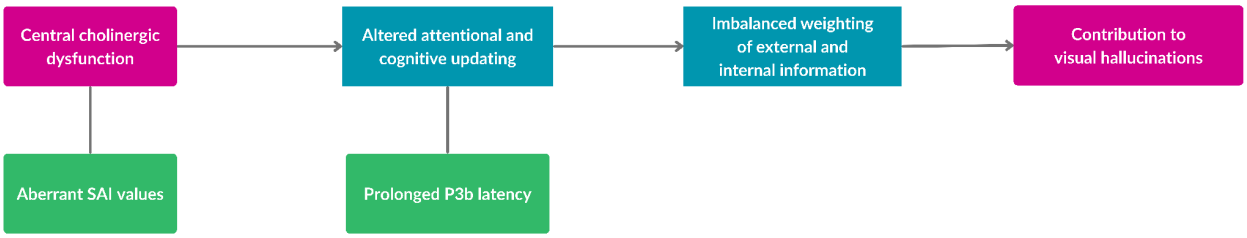
Additionally, aberrant P1 values observed in hallucination-prone individuals (Schwartzman et al., 2008) may be compatible with the explanatory model proposed by van Ommen et al. (2023). Schwartzman et al. (2008) interpreted P1 abnormalities

as reflecting altered early visual processing, while van Ommen et al. proposed that psychotic VH involve a dysfunction in V1,

A. Early visual dysfunction model



B. Cholinergic dysfunction



C. 5-HT2A receptor dysfunction model

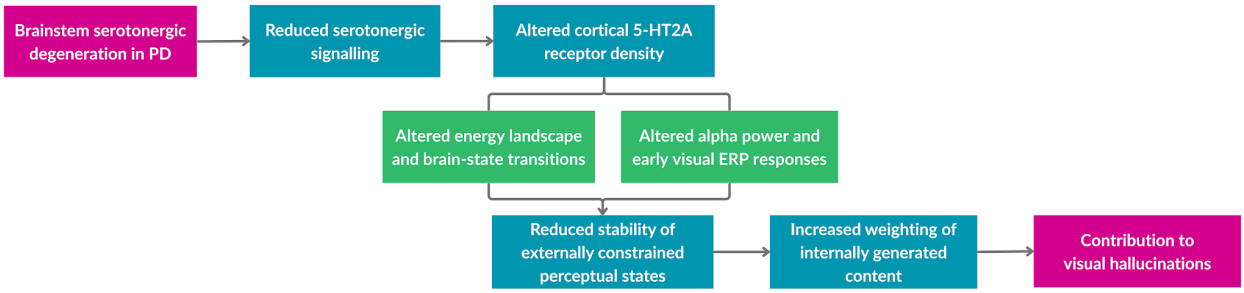


Figure 2. Schematic representations of the three models of visual hallucinations in Parkinson's disease. (A) Early visual dysfunction model. (B) Cholinergic dysfunction model. (C) 5-HT2A receptor dysfunction model. *Color code: key nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships proposed within each model; continuous lines without arrowheads indicate observed associations for which causal direction has not been established.*

Table 2. Summary of reviewed literature

Hypothesis	Study	Approach	Key finding/relevance
Early visual dysfunction	Schwartzman et al. (2008)	EEG/ERP in hallucination-prone healthy participants	Higher P1/P2 positivity supports altered early visual processing but does not establish PD-specific causality.
	Yao et al. (2014)	Resting-state fMRI in PD-VH, PD-non-VH, and controls	Greater DMN connectivity in PD-VH supports involvement of internally oriented network activity.
	van Ommen et al. (2023)	fMRI during hallucinations in psychosis	Reduced V1 involvement with increased VIS/DAN/DMN/VAN activity supports a distributed network account.
Cholinergic dysfunction	Manganelli et al. (2009)	SAI in nondemented PD patients	Abnormal SAI links PD-VH to central cholinergic dysfunction; direction of causality remains unresolved.
	Chang et al. (2016)	Visual ERP task in nondemented PD groups	Prolonged P3b latency is consistent with altered cholinergic/cognitive processing in PD-VH.
Serotonergic/ 5-HT2A	Kometer et al. (2013)	Psilocybin/ketanserin EEG study in healthy adults	5-HT2A activation altered P1, N170, and α power, supporting serotonergic involvement in visual processing and cortical excitability.
	Huot et al. (2010)	Postmortem temporal-cortex receptor analysis	Higher 5-HT2A receptor density in PD-VH supports receptor-level involvement, though dementia is a confound.
	Zarkali et al. (2022)	Resting-state fMRI and network-control analysis	PD-VH showed fewer transitions and longer segregation, linked regionally to 5-HT2A receptor density.

together with the DAN, DMN and VAN, resulting in an imbalance between external and internally generated stimuli. This evidence suggests that altered early visual processing reflected by P1 and dysfunction in V1 in psychotic VH may potentially represent related features of the same broader perceptual disturbance. However, Schwartzman et al. investigated healthy individuals prone to hallucinate, and P1 measurements do not specifically localize dysfunction to V1. Thus, studies examining P1 responses alongside measures of V1 activity and network function in a PD-VH population are necessary to determine whether these abnormalities are mechanistically related.

Another possible point of convergence in the reviewed literature is that the decreased α power reported by Kometer et al. and the altered brain-state dynamics observed by Zarkali et al may reflect a common underlying neural dysfunction. Kometer et al. (2013) observed increased P1 amplitudes and decreased α power following pharmacological activation of 5-HT2A receptors, while Zarkali et al. (2022) found associations between 5-HT2A receptor-density maps and altered brain-state transitions. Specifically, the latter study found that PD-VH patients spent more time in the segregated state rather than the integrated one, compared to PD-non-VH patients. There is evidence that α power increases during visual integration in various areas of the brain, including early visual cortex and dorsal visual networks (Costa et al., 2024). This raises the possibility that increased dwelling time in segregated states in PD-VH patients and the decreased α power observed by Kometer et al., alongside increased P1 potentials, may reflect different manifestations of a common underlying imbalance in neural integration associated with VH. Nevertheless, the findings derive from distinct populations and methods, and measure different neurophysiological phenomena. Specifically, Kometer et al. investigated psilocybin-induced changes in healthy participants, whereas Zarkali et al. examined brain-state dynamics in patients with PD-VH. Therefore, whether these findings reflect a common underlying mechanism remains to be established through further studies combining EEG and fMRI in patients with PD-VH.

Additional support for the proposed unified framework comes from the finding that transitions between segregated and integrated states are highly influenced by the activity of the DMN and thalamic regions (Zarkali et al., 2022), thereby linking attention- and memory-related networks to altered brain-state dynamics.

In addition, increased activity in the DMN observed in PD-VH patients (Yao et al., 2014) may be related to the aberrant P3b latency reported by Chang et al. (2016). As the P3b component reflects top-down attentional processing of visual stimuli, and the DAN is involved in directing attention toward salient information (Shine et al., 2014; Van Calster et al., 2017), the abnormal P3b values reported by Chang et al. may reflect a dysfunction in visual attention allocation involving visual and attentional networks—DAN, VAN and DMN. Since DAN activity is typically negatively correlated with DMN activity within this attentional network pathway, dysfunction involving the DAN may also be associated with the increased DMN connectivity reported by Yao et al. This raises the possibility that abnormalities in P3b activity and DMN function reflect overlapping disturbances in attentional allocation and internally oriented processing of visual information. Nevertheless, this remains a speculative cross-scale hypothesis. Future studies combining EEG and fMRI are needed to determine whether P3b abnormalities are associated with dysfunction within attentional and visual networks, particularly the DMN.

Drawing on the convergent, but not yet causally unified, evidence considered, the present study proposes a framework in

which abnormalities in early visual processing, neuromodulatory function, attentional networks, and brain-state dynamics may represent interacting levels of the same distributed perceptual disturbance (see Figure 3). Serotonergic dysfunction may act as one integrative neuromodulatory factor, interacting with cholinergic and dopaminergic abnormalities rather than functioning as an isolated or necessarily upstream cause.

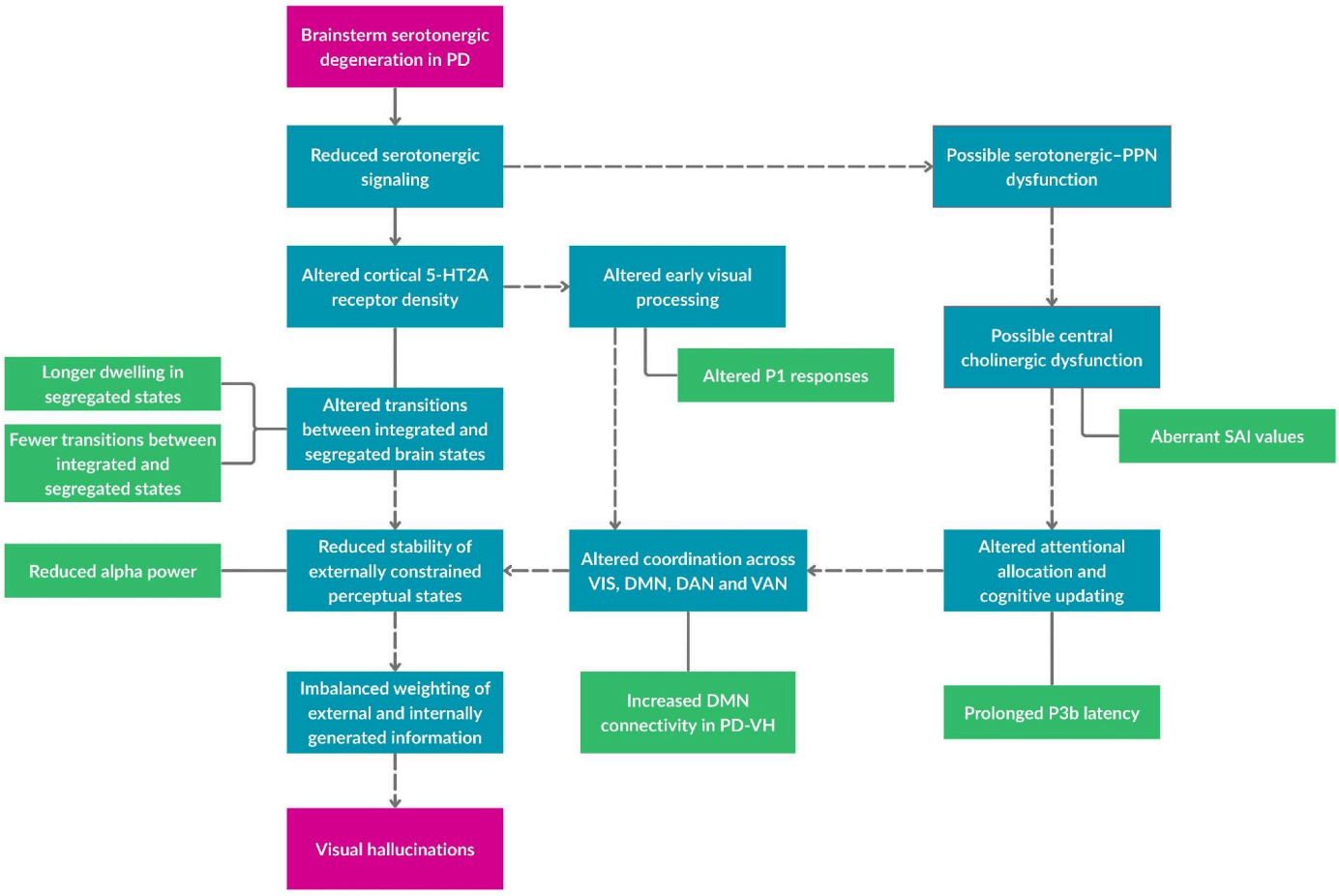


Figure 3. Proposed unified framework for visual hallucinations in Parkinson's disease. *Color code: key framework nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships retained from the reviewed models; continuous lines without arrowheads indicate observed associations for which causal direction has not been established; dashed arrows indicate integrative or unresolved mechanistic links proposed by the unified framework.*

PD is associated with degeneration of serotonergic neurons in the brainstem, leading to reduced 5-HT levels. Huot et al. (2010) proposed that reduced serotonergic signaling may be accompanied by a compensatory increase in 5-HT2A receptor density. Altered 5-HT2A signaling may in turn be, directly or indirectly, associated with changes in visual processing, α

oscillations, attentional-network activity, and brain-state dynamics. Cholinergic dysfunction may additionally affect attentional allocation and the balance between externally and internally generated information, although its causal position relative to VH remains unresolved. Together, these abnormalities could contribute to a perceptual system in which internally generated information is more readily misattributed as external.

Within this framework, the comparatively later involvement of the serotonergic system in PD may help explain the delayed emergence of VH, while serotonergic dysfunction may also interact with other neurotransmitter systems and contribute to the downstream cascade of visual, attentional and network abnormalities.

Van Ommen et al. (2023) proposed that the loop involving the DMN, DAN and VAN and contributing to VH may originate from a dysfunction in V1. Some studies link serotonin and acetylcholine to V1 functions in animals; for instance, Shimegi et al. (2016) investigated how cholinergic and serotonergic systems modulate visual processing in monkey V1. However, the available evidence does not establish specifically where dysfunction within visual and attentional networks originates, nor which neurotransmitter systems are most directly involved. Determining the temporal and mechanistic relationships among early visual abnormalities, altered attentional-network activity, and neuromodulatory dysfunction will require studies combining electrophysiological, neurochemical, and functional-network measures within a well-characterized PD-VH population.

5. Conclusions

This review proposes that serotonergic dysfunction may play an integrative role in linking early visual abnormalities, altered neuromodulatory signaling, and large-scale network dynamics in PD with VH. By identifying testable links among abnormalities measured at different levels of the perceptual system, the proposed framework provides a basis for longitudinal and multimodal studies aimed at determining how these correlates interact, which changes occur earlier in the disease process, and how they contribute to the neural mechanisms underlying VH in PD.

6. Limitations and Future Research Directions

Accordingly, apparent convergence across studies should not be interpreted as evidence that the reported abnormalities belong to a single established causal sequence. In fact, the central limitation of the proposed framework is that it integrates evidence obtained from heterogeneous populations and methods. Some studies involve healthy participants exposed to serotonergic hallucinogens, some examine psychosis outside PD, and some include PD-VH samples affected by dementia.

Future work should therefore test the framework prospectively in carefully phenotyped, nondemented PD cohorts. The strongest design would combine receptor-sensitive imaging, EEG measures of P1/P3b and α power, and repeated fMRI measures of DMN–DAN–VAN coupling and integrated–segregated state transitions within the same participants. Longitudinal studies should determine whether serotonergic and cholinergic changes precede hallucination onset, while pharmacological studies should test whether modifying 5-HT2A or cholinergic signaling changes the predicted electrophysiological and network markers. These tests would distinguish correlation from causation and clarify whether the PPN and DRN are upstream drivers, downstream consequences, or interacting modulators of the proposed pathway.

Future studies could also investigate the role of the pedunculopontine nucleus (PPN) in modulating cholinergic and

serotonergic dysfunction. The PPN contains cholinergic neurons and receives serotonergic input from brainstem nuclei including the dorsal raphe nucleus (DRN) (Benarroch, 2013; Michelsen et al., 2007). Numerous studies mention the PPN in relation to VH in PD. With its cholinergic neurons, it is linked to attention networks, and it controls the visual cortex (Manganelli et al., 2009). Specifically, it modulates feedforward input to V1, exhibiting its crucial role in visual perception. Moreover, the neurotransmitters synthesized in the PPN modulate both the VAN and the DAN, together with other nuclei in the brainstem (Alves et al., 2022). These findings suggest that there is a connection between the PPN, attentional networks and other structures in the brainstem, especially the DRN, and that these connections are modulated by neurotransmitters. However, the proposed role of the PPN as a link between serotonergic and cholinergic dysfunction and altered visual-attentional processing remains indirect and has not been demonstrated as a causal mechanism of VH in PD. Future studies should therefore determine whether PPN dysfunction contributes to VH by disrupting cholinergic and serotonergic modulation of visual and attentional networks.

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9. Author Biography

Redacted for double-blind review.

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The research mentor provided conceptual guidance, recommended relevant literature, discussed the interpretation of evidence, and offered feedback on the manuscript's organization and argument. The author independently conducted the literature review, developed the proposed unified framework, and wrote and revised the manuscript. The mentor did not collect or analyze original data and is not listed as a co-author.

11. AI Use Statement

Generative AI tools were used for limited editorial support, including assistance with identifying typographical errors and awkward phrasing, checking reference formatting, and improving the organization of flowcharts. The author independently developed the research question, selected and interpreted the literature, constructed the proposed framework, evaluated the scientific claims, and approved all final wording. AI tools were not used to generate original data or conduct data analysis. The author verified the accuracy of all substantive claims, citations, and references and accepts full responsibility for the manuscript.

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Proposal for a Unified Framework to Understand the Functional Changes That Occur in Visual Hallucinations in Parkinson's Disease

Abstract

Visual hallucinations in Parkinson's disease are often viewed as isolated symptoms of neurodegeneration. However, growing evidence suggests that they reflect deeper disruptions in how the brain constructs perception. This paper reviews three major hypotheses—early visual dysfunction, cholinergic dysfunction, and serotonergic dysfunction—and proposes a unified framework linking these mechanisms across multiple levels of brain organization. By integrating electrophysiological, neurochemical, and network-level findings, this study argues that hallucinations arise from an imbalance between internally generated and externally driven signals. Specifically, serotonergic dysfunction, through alterations in 5-HT2A receptor density, may be a mechanistic bridge linking early sensory processing with large-scale network dynamics, including impaired transitions between brain states. Understanding these mechanisms provides insight not only into Parkinson's disease, but also into the fundamental nature of perception as an active and dynamic process. More broadly, this work highlights the importance of approaching neurodegeneration as a distributed, multilevel phenomenon, with implications for developing more integrated and effective therapeutic strategies.

Keywords: Parkinson's disease; visual hallucinations; serotonin; 5-HT2A receptor; visual processing; attention networks; brain-state dynamics

1. Introduction

Parkinson's disease (PD) is a neurodegenerative disorder attributed to a dysfunction in the dopaminergic system (Lew, 2007). The main symptoms of PD and those that serve as a diagnosis are motor, but patients often show a spectrum of various non-motor symptoms as well. Moreover, it is possible for PD patients to develop dementia or psychotic symptoms. This last condition is known as Parkinson's disease psychosis (PDP) (Friedman, 2010), and its main symptom is visual hallucinations (VH).

VH can present in different forms, and they are commonly classified as elementary and complex. Elementary VH generally

consist of geometric patterns, such as lines, curves or spots (Billock & Tsou, 2012). These can also have additional features such as color or motion. Conversely, complex VH feature a variety of different contents, often depicting animal or human figures in absurd or unrealistic contexts (Manford & Andermann, 1998). Patients who suffer from a psychotic disorder often encounter both elementary and complex VH, but most PD patients recall having experienced complex VH (van Ommen et al., 2023).

It was initially believed that VH and PDP were a collateral effect of dopaminergic treatments, administered to alleviate the motor symptoms of the disorder; however, some PD patients develop PDP without medications (Friedman, 2010). This suggests that PDP is a progression of PD itself. Indeed, while dopamine is the main neurotransmitter attributed to PD motor symptoms, it is believed that the disorder also displays dysfunctions in other neurotransmitter systems and in the interactions between those; many motor and non-motor symptoms of the disease have been attributed to neurotransmitters such as serotonin, acetylcholine, glutamate and γ-aminobutyric acid (GABA) (Barone, 2010).

PD is the second most prevalent neurodegenerative disorder in the world population, and VH has a prevalence range of 8%–40% in PD patients (Barone, 2010; Manganelli et al., 2009). Moreover, there are a variety of correlates linking VH and PD. For example, VH in PD are associated with aberrant event-related potential (ERP) components, including alterations in P1, which reflects early visual processing, and P3b, associated with later cognitive processing of stimuli. Moreover, some PD-VH patients present anomalous neural network behavior, including enhanced excitability in the default mode network and in attention-related networks, as well as longer periods in segregated brain states and fewer transitions toward integrated states. Nevertheless, the underlying mechanisms giving rise to VH are largely unknown.

A complicating factor to this phenomenon is the high occurrence of dementia in PD, known to cause cognitive impairment and dysfunctions in many neural networks, namely in attention, memory and visual perception pathways, sometimes resulting in VH itself (Gratwicke et al., 2015). Since dementia and psychosis often coexist in PD patients, it is difficult to discern the distinct effects that the two conditions have on neural networks in PD, as well as to identify their respective causal factors.

At present there remains no unified framework able to explain how and which neural networks are involved in VH among nondemented PD patients. Investigating the functional changes that occur in VH in PD can offer new insights into visual processing and stimuli interpretation. Moreover, it may enhance treatments to alleviate VH, ~~perhaps reducing the effects that they have on the overall health of the patient.~~ improving patients' quality of life. This is clinically relevant as VH in PD are associated with an increased risk of ~~VH are indeed linked with both a greater~~ dementia ~~chance of developing dementia~~ and ~~a higher risk of~~ mortality (Manganelli et al., 2009). ~~Eventually, having a better understanding of the neural networks involved in VH in PD can lead to improvements in the quality of life of the patients.~~

The present study reviews three existing hypotheses of VH in PD, namely ~~and examines how findings from~~ early visual, cholinergic, and serotonergic~~, and~~, and examines how evidence from these hypotheses may ~~network-level models may~~ interact rather than represent mutually exclusive explanations. In particular, it proposes that serotonergic dysfunction may provide one possible integrative bridge between these abnormalities.

2. Method and Scope of the Review

This paper is a focused narrative review and theoretical synthesis. It compares evidence from electroencephalography, neuroimaging, pharmacological studies, network-control approaches and postmortem receptor analyses (see Table 1).

Table 1. Methods Used to Characterize Neural Dysfunction in Visual Hallucinations

Method	What it measures	Main strength	Main limitation
Electroencephalography (EEG) and Event-Related Potentials (ERPs)	EEG records electrical activity from the scalp; ERPs isolate activity time-locked to specific stimuli or events (Fabiani et al., 2007; Beres, 2017).	Excellent temporal resolution, allowing neural responses to be tracked on the millisecond scale (Beres, 2017).	Limited ability to precisely localize the neural source of the recorded activity (Beres, 2017).
Resting-state fMRI (rsfMRI)	Measures spontaneous fluctuations in the blood-oxygen-level-dependent (BOLD) signal at rest and their correlations across brain regions, allowing functional connectivity to be estimated (Van Den Heuvel & Pol, 2010).	Allows investigation of large-scale functional networks across the brain.	BOLD is an indirect measure of neural activity and has relatively poor temporal resolution because of the delayed haemodynamic response.
Short-latency afferent inhibition (SAI)	A neurophysiological measure of sensorimotor inhibition that is used as a putative marker of central cholinergic function (Martin-Rodriguez & Mir, 2020).	Provides a non-invasive physiological measure associated with cholinergic function in humans.	It is an indirect marker rather than a direct measurement of acetylcholine, and it can be influenced by factors such as disease duration and dopaminergic medication (Martin-Rodriguez & Mir, 2020).

Network-control analysis	Uses structural and functional brain-network data to estimate transitions between brain states and the control energy required for those transitions (Zarkali et al., 2022).	Can characterize dynamic differences in integrated and segregated brain states.	The inferred transitions and energy values depend on the assumptions of the mathematical model used and do not directly measure neurotransmitter activity.
Postmortem receptor analysis	Uses receptor-binding techniques in brain tissue to quantify receptor density; Huot et al. (2010), for example, measured 5-HT2A receptor binding in cortical tissue from PD patients.	Provides direct anatomical evidence of receptor-level differences in human brain tissue.	It is cross-sectional and cannot establish whether receptor changes precede or result from VH.

Relevant studies were identified between June and August 2025 through targeted searches of PubMed, Google Scholar, and reference lists of key reviews using combinations of terms related to PD, VH, visual processing, cholinergic dysfunction, serotonin, 5-HT2A receptors, and brain-state dynamics. Studies were selected for their relevance to three recurring explanatory levels: early visual processing, cholinergic modulation, and serotonergic ~~/network-state~~ dysfunction. The final bibliography comprised 3~~8~~6 sources published between 1978 and 2024, although older sources were primarily included for methodological or conceptual background. Most cited literature (3~~2~~1 of ~~38~~36 sources) was published between 2007 and 2024. Eight core empirical studies, published between 2008 and 2023, were selected for detailed comparison because they directly examined evidence relevant to the three explanatory models considered in this review and provided findings pertinent to the overall synthesis. Studies were prioritized when they directly examined VH, relevant electrophysiological or network abnormalities, or cholinergic/serotonergic mechanisms pertinent to the proposed framework; studies used only to define methods, neural processes, or broader PD background were treated as supporting literature rather than empirical evidence ~~to support the hypotheses~~. Where findings were inconsistent with, or did not fully support, the proposed hypotheses, these were discussed explicitly rather than excluded from consideration. Because the included studies differ substantially in population, task, and measurement method, and several do not examine nondemented PD patients directly, the proposed framework should be interpreted as a testable integrative hypothesis rather than a demonstrated causal model.

3. Literature Review on Visual Hallucinations in Parkinson's Disease

~~There are s~~Several models ~~that try~~have been proposed to explain the functional changes ~~that occur in PD patients causing~~associated with VH in PD. The present study focuses on three frameworks that emphasize different but potentially

interacting levels of dysfunction. The first hypothesis focuses on early visual dysfunction (Schwartzman et al., 2008; van Ommen et al., 2023), while the second and third present a broader explanation of VH involving an imbalance between external and internal stimuli and the modulation of visual and attentional networks. The distinguishing factor between the last two models lies in the type of neurotransmitters involved: the second emphasizes central cholinergic dysfunction (Manganelli et al., 2009), whereas the third focuses on serotonergic dysfunction and altered 5-HT2A receptor density (Kometer et al., 2013).

3.1 Early Visual Dysfunction

The early visual dysfunction model proposes that abnormalities in the initial processing of visual information may contribute to VH and, through disrupted communication with higher-order visual and attentional networks, lead to the misinterpretation of internally generated information as external. Evidence for this model comes from studies examining

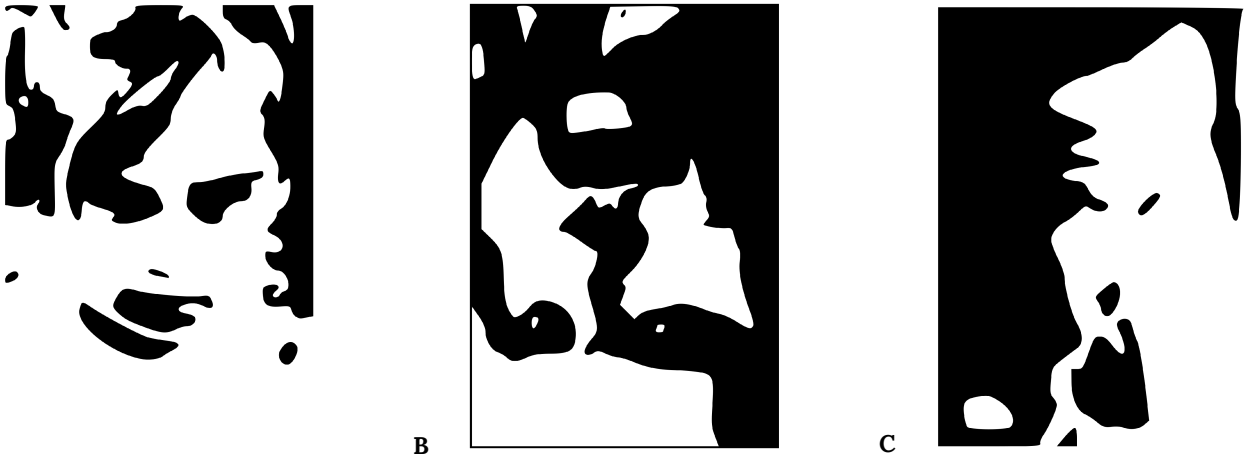


Figure 1. Representative stimuli from the Mooney Faces Test. *The upright Mooney face (A) is typically perceived as a face, whereas the inverted Mooney face (B) is substantially more difficult to recognize due to disruption of holistic face processing. The scrambled image (C) serves as a non-face control stimulus. Stimuli adapted from the dataset of Schwiedrzik et al. (2018) and redrawn as vector graphics for presentation clarity under CC BY 4.0.*

both early electrophysiological responses to visual stimuli and the interaction between primary visual processing and broader visual-attentional networks.

A study conducted by Schwartzman et al. (2008) evaluated the hypothesis that aberrant early visual ERP components reflect individuals' proneness to hallucinate. While early visual disruption had been previously associated with various psychological and neurological disorders that present VH—e.g. PD, schizophrenia—it remained unclear whether an early impairment of visual processes was a key factor in the development of VH or rather a mere outcome of the disorder itself.

In order to reduce the possibly confounding influence of cognitive decline, the study analyzed electroencephalogram (EEG) recordings from healthy individuals divided according to their proneness to hallucinate. Hallucination proneness was

assessed using a questionnaire, after which participants completed a face-perception task involving photographs, Mooney faces, and scrambled Mooney faces (see Figure 1). The Mooney Faces Test (MFT) evaluates an individual's ability to perceive human faces in two-dimensional, black and white pictures, shown both upright and upside down (Silverstein et al., 2021).

During the experiment conducted by Schwartzman et al., the participants' brain activity was recorded through EEG; specifically, the study focused on ERP components that reflect early visual processes. The components analyzed were the N170, P1 and P2, respectively associated with face recognition, early extraction of information from face stimuli, and finally a higher level of visual processing involving categorization of face stimuli. The interpretation of the stimulus in P2 depends on the reception of information carried out in P1.

The study observed no significant differences in the N170 component, while P1 and P2 showed increased positivity in hallucination-prone individuals. The lack of significant N170 differences suggests that the observed changes in P1 and P2 were not specific to face recognition but may instead reflect abnormalities in earlier stages of visual processing. Conversely, the increased amplitude registered in P1 suggests a dysfunction in the extraction of fine information from visual stimuli, which would in turn impair the interpretation of the visual information itself, explaining the knock-on effects on P2. Thus, compared with individuals with low hallucination proneness, hallucination-prone participants showed altered stimulus-evoked electrophysiological responses during early visual processing. However, because the study involved healthy participants rather than PD patients with VH, these findings support an association with hallucination susceptibility rather than establishing a PD-specific causal mechanism.

An earlier study had shown a correlation between P1 ERP component in patients with PD and primary visual processes (Wang et al., 2001). The association between P1 and primary visual processing in PD provides a basis for considering abnormal P1 responses as a possible marker of early visual dysfunction in PD-VH.

Although ~~there is evidence that~~ early visual dysfunction is ~~related~~ associated with~~to~~ VH in PD, existing evidence does not support a purely focal explanation ~~it appears to be highly unlikely for VH to be explained as a focal pathology~~. Instead, a study led by van Ommen et al. (2023) correlated an impairment in primary visual processes to dysfunctions in other visual-related neural networks, proposing a more holistic explanation of VH.

They aimed to evaluate a hypothesis previously postulated by Shine et al. (2014), which had explained VH as a consequence of a disconnection between the primary visual cortex, V1, and higher visual components, inducing a desynchronization between different parts of the visual network. This previous hypothesis was supported by the reduced activity registered in the primary visual cortex in patients with psychotic VH.

In order to evaluate the postulated model from Shine et al. and assess what areas of the brain are involved in psychotic VH, van Ommen et al. (2023) conducted an experiment on hallucinating psychotic individuals, recording their brain activation data during an episode of VH, through functional magnetic resonance imaging (fMRI). The results showed a lack of activation in V1 and increased activity across the visual and attention pathways, specifically in the Dorsal Attention Network (DAN), Default mode network (DMN) and Ventral Attention Network (VAN). These are respectively linked to processing external information, interpreting internal stimuli and coordinating memory and finally synchronizing the two networks—DAN and DMN (Van Calster et al., 2017). The results are therefore in line with the hypothesis postulated by Shine et al., 2014, as they show that psychotic VH is not a focal pathology. Instead, it affects a wide range of regions, namely the

visual network (VIS)—excluding V1—and vision-related networks involved with memory and attention.

Based on these findings, Van Ommen et al. proposed a refinement of the model postulated by Shine et al., attributing VH in PD to the activation of a loop across the VIS—with the exception of V1—and the DAN, DMN and VAN. Under normal circumstances, feed-forward impulses are sent from V1 to the surrounding visual network regions. This flow of information allows the stimulus to be recognized as external. In turn, a feedback inhibitory response is sent from the networks to V1. According to this model, the ability of V1 to provide feed-forward and receive feedback information from the surrounding areas is compromised in psychotic VH. This disruption may cause internally generated information to be misinterpreted as external sensory input, thereby contributing to the generation of VH.

However, since van Ommen et al. investigated VH in individuals with psychosis rather than specifically in PD patients, the extent to which this network mechanism applies directly to PD-VH remains to be established.

~~Another piece of evidence~~Additional evidence comes ~~in support of the model proposed by van Ommen et al. is given by from a study from 2014, led by~~ Yao et al. (2014)~~.~~, ~~who which~~ investigated DMN activity in resting PD patients, both with (PD-VH) and without VH (PD-non-VH) and in healthy controls. Patients with symptoms of cognitive impairment and dementia were excluded. Resting-state functional magnetic resonance imaging (rsfMRI) data of the participants were acquired, and the results showed a decreased activity in the DMN in PD patients compared to controls. Conversely, PD-VH patients had a greater ~~excitability~~ connectivity~~of~~ in the DMN compared to PD-non-VH. Yao et al., therefore, demonstrated that a higher connectivity in the DMN is associated with VH in PD patients, relative to PD-non-VH patients. Showing a correlation between aberrant DMN activity and VH in PD, these data support the model proposed by van Ommen et al.

Thus, while there are findings suggesting that early visual impairment has a role in generating VH in PD, this is treated as one level of a distributed mechanism rather than a complete explanation of the condition. Moreover, this presented model fails to include the involvement of neurotransmitters in VH in PD. To fully comprehend the underlying neurological mechanisms of VH in PD, it is necessary to adopt a more holistic approach, recognizing the role of neurotransmitters in modulating attention and vision-related networks. Consistent with the model postulated by van Ommen et al., 2023, a second hypothesis attributes VH in PD to an imbalance between external and internal stimuli~~, and specifically as a consequence of a~~ associated with central cholinergic dysfunction.

3.2 Imbalance Between External and Internal Stimuli ~~due to a~~and Central Cholinergic Dysfunction

The cholinergic model proposes ~~that VH arise partly from~~an association between impaired cholinergic modulation of attention and the imbalance between ~~, contributing to an~~¶
~~imbalance between~~ externally driven and internally generated information observed in VH in PD. ~~Evidence~~Nevertheless, the available evidence, ~~for this model comes~~coming from both physiological measures of central cholinergic function and ERP studies of cognitive processing in nondemented PD patients with VH, does not fully establish the direction of this relationship. There remains disagreement whether cholinergic dysfunction directly contributes to VH, develops alongside VH as part of PD progression, or arises secondarily in association with the condition.~~Thus,~~

A study from 2009, conducted by Manganelli et al., found a correlation between nondemented PD-VH patients and a

central cholinergic dysfunction. The research methodology included the use of short-latency afferent inhibition (SAI), a physiological measure commonly used as an indirect marker of central cholinergic function (Martin-Rodriguez & Mir, 2020). The participants were 22 non-demented PD patients, both with and without VH (Manganelli et al., 2009). The study found that most PD-VH patients presented aberrant SAI values, unlike PD-non-VH individuals. Therefore, Manganelli et al. concluded that VH in PD could be one of the factors that alter the balance of the cholinergic system. Alternatively, VH would cause a dysfunction between the cholinergic and other neurotransmitter systems. The study also confirmed the hypothesis of a correlation between cholinergic dysfunction and PD patients who are likely to develop dementia. Similarly, VH are considered to be a predictive factor of dementia. Therefore, there is a possible link between central cholinergic dysfunction and VH in PD.

However, there remains disagreement about the direction of causality, as other later studies consider cholinergic dysfunction as a causal factor of VH in PD. One of these is a study led by Chang et al. (2016).

While aberrant ERP values are considered an indicator of cognitive dysfunction in demented PD patients, their role in nondemented PD patients, both with and without VH, remained unclear. Specifically, some studies had found a correlation between PD-VH patients and impaired P3 responses, a component related to attentional allocation and cognitive processing of task-relevant stimulus (Kurita et al., 2010; Chang et al., 2016). To address this gap in the literature, Chang et al. compared ERP responses in nondemented PD patients with and without VH, and in healthy controls during a visual target-detection task. They reported that PD-VH individuals showed a prolonged latency of one subcomponent of the P3, namely the P3b component, compared with controls. Since P3b is associated with later cognitive processing and memory updating, this result was interpreted as evidence of altered cognitive processing in PD-VH and was considered compatible with central cholinergic dysfunction (Chang et al., 2016; Polich, 2003).

This study also investigated N1 and P2, two exogenous ERP responses associated with sensory and attentional processing respectively (Chang et al., 2016; Donchin et al., 1978). Chang et al. reported no significant differences in either component across the groups. This finding does not necessarily contradict the visual-network dysfunction model described previously. These ERP components and the DAN, VAN, and DMN reflect different levels of neural processing, and there is no evidence that abnormalities in these large-scale networks must be accompanied by altered N1 or P2 responses. The Chang et al. findings therefore add evidence of altered later cognitive processing rather than excluding the involvement of visual and attentional networks.

Overall, the findings reviewed support an association between central cholinergic dysfunction and VH in PD; yet they do not establish its direction of causality. Consequently, the present framework treats cholinergic dysfunction as a potentially interacting contributor to VH rather than as a demonstrated upstream cause or downstream consequence.

3.3 Serotonergic Dysfunction, 5-HT2A Receptors, and Brain-State Dynamics

The serotonergic model proposes that altered serotonergic signaling, particularly through 5-HT2A receptors, may contribute to VH by modifying visual processing and the balance between internally and externally driven neural activity. Evidence for this model comes from pharmacological manipulation of 5-HT2A signaling, postmortem receptor analyses in PD, and studies of large-scale brain-state dynamics.

An aberrant density of 5-HT2A receptors in different cortical areas has often been connected to various forms of psychosis, including PDP (Huot, 2018), but the effect of this receptor's activation on VH is left unclear. A study conducted by Kometer et al. (2013) aimed to clarify this connection by investigating the effects that the activation of the 5-HT2A receptor has on parieto-occipital α waves.

α Alpha oscillations, considered to be mostly present in the thalamic regions and visual cortex, have been correlated with visual processing dysfunctions and impairments (Clayton et al., 2018). Since they are strongly linked to visual processing, they are also associated with visual-related potentials (Kometer et al., 2013). The study presented here hypothesized that α oscillations could contribute to the generation of VH. According to their model, activation of 5-HT2A receptors, triggered by the administration of psilocybin, a serotonergic hallucinogen, would alter α oscillations. A second hypothesis postulated by the study concerned how early visual ERP components—specifically the P1 and N170—would be influenced by psilocybin-induced hallucinations. Thus, the investigation examined the effects of 5-HT2A activation on visual processing in healthy participants by comparing the effects of psilocybin with those observed after pretreatment with the 5-HT2A antagonist ketanserin. EEG responses were recorded during a visual perception task.

Psilocybin increased P1 amplitude over medial parieto-occipital regions, altered N170 responses, and decreased α power. These effects were suppressed by ketanserin pretreatment, supporting their relationship with 5-HT2A activation. Decreased α power was attributed to increased cortical excitability especially in the parieto-occipital regions and visual networks, following activation of 5-HT2A receptors. A reduction in α power had previously been associated with increased visual attention and cortical excitability in the occipital lobe, while increased α oscillations might directly suppress visual processing (Clayton et al., 2018). The decreased α power was also related to the increase in P1 medial potential, which might represent an enhancement in early visual processing (Kometer et al., 2013). This coordinated response between the P1 and α power would in turn contribute to an imbalance between perception of external and internal stimuli.

Specifically, altered cortical excitability may reduce the normal distinction between neural activity driven by external visual input and activity occurring in the absence of external stimuli. This corresponds to a change in the activation of brain networks—reflected by decreased α oscillations and enhanced P1 medial potentials—with an increased attention towards internally generated visual stimuli, rather than external stimuli. This model seems to be in line with the hypothesis proposed by van Ommen et al. (2023), in which VH arise from an altered balance between externally and internally generated signals.

Although the findings suggest that α power waves may have a role in psilocybin-induced VH, analytical studies showed little correlation between reduced α power and the occurrence of hallucinations, perhaps revealing that the reduction in α power triggered by psilocybin is not sufficient to induce complex VH. Moreover, the study involved psilocybin-induced perceptual alterations in healthy participants rather than in the PD population. Therefore, the study does not establish that the same mechanism causes complex VH in PD.

Finally, the psilocybin treatment produced a decrease in the N170, which is thought to play a key role in processing meaningful visual stimuli. An alteration in this component is associated with altered visual ~~perception, and~~perception and may therefore reflect changes produced during psilocybin-induced hallucinations. Alternatively, the effects on the N170 could be attributed to the increased cortical excitability triggered by the activation of the 5-HT2A receptor, further contributing to an imbalance between external and internal stimuli.

Taken together, the effects of 5-HT2A activation on P1, N170, and α power demonstrate that serotonergic signaling can alter neural processes involved in visual perception and cortical excitability, although these findings do not establish that the same mechanism causes VH in PD.

A previous study had investigated the distribution of 5-HT2A receptors in postmortem PD patients' tissues, postulating a correlation between increased receptor density and VH in PD (Huot et al., 2010). The results showed an increased density of this receptor in PD tissues with VH, compared to PD-non-VH, therefore providing PD-specific evidence supporting the involvement of 5-HT2A signaling in VH. While an existing postulate attributed the development of psychosis in PD to a polymorphism in the 5-HT2A receptor gene, a study led by Kiferle et al. (2007) refuted this hypothesis, and they concluded that aberrant levels of this receptor are not due to the genetic variations examined.

Huot et al. (2010) proposed a new explanation of the enhanced levels of 5-HT2A receptors in PD patients with psychosis, defining it as a consequence of other neurotransmitter dysfunctions in PD. PD is known to present serotonin (5-HT) dysfunctions; specifically, degeneration in the serotonergic neurons in the brainstem causes a decline in the neurotransmitter levels. Huot et al. proposed that this may contribute to a compensatory increase in 5-HT2A receptor density, as a biological attempt to balance the drop of 5-HT in different areas of the brain. Enhanced levels of 5-HT2A could also be attributed to the decrease in dopamine (DA) levels, which acts as a partial agonist to the receptor. These two possibilities are likely to be complementary, and this explanation would help explain the late occurrence of VH in the development of PD: the disorder disrupts the dopaminergic system more than the serotonergic system, suggesting that it takes longer for the levels of 5-HT to drop below the threshold level. According to this hypothesis, the resulting serotonergic and receptor-level changes could eventually contribute to the development of VH. This proposed compensatory increase in 5-HT2A receptor density further supports the hypothesis that dysfunction of the serotonergic system, and particularly altered 5-HT2A signaling, may have a role in VH in PD.

A possible limitation of the presented study is the interference of dementia, which was present in four out of the six PD-VH participants. Since dementia is known to cause dysfunctions in many neural networks, such as attention, memory and visual perception (Gratwicke et al., 2015), this factor limits the reliability of the findings and makes it unclear whether they should be attributed to psychosis rather than dementia.

~~However, there is further evidence that provides support to the hypothesis that the~~Additional evidence suggests an association between 5-HT2A ~~receptor plays a key role in the development of VH in PD~~and altered brain-state dynamics in PD-VH. Specifically, an aberrant density of this receptor was attributed to temporal dysfunctions in transitions between the segregated and integrated states of the brain in hallucinating PD patients (Zarkali et al., 2022). Integrated and segregated states are opposite methods of network organization, although they often coexist in the same functional system (Tononi et al., 1994). Integration means that the different areas of the network are interconnected and there is a fast flow of information among them; each component of the circuit is dependent on the others. Conversely, segregation happens when different regions function relatively independently of one another, with a limited amount of information flow among the whole system.

It is believed that shifts between integration and segregation are controlled by neurotransmitter systems (Zarkali et al., 2022). The study aimed to investigate how temporal dynamics in transitions between integrated and segregated states are affected in PD patients with VH, using rsfMRI.

The main difference reported was not the presence of distinct integrated or segregated states, but their temporal dynamics: PD-VH participants spent less time in integrated states, more time in segregated states, and made fewer transitions between them than PD-non-VH participants.

The framework presented by these findings suggests that the DMN and thalamic regions have a role in VH in PD, as these are the nodes responsible for modulating the transitions between integrated and segregated states. Furthermore, the study expanded on these findings, attempting to assess the role of neurotransmitters in the alterations observed. The data gathered by Zarkali et al. provide further evidence for a possible involvement of serotonergic signaling in developing VH in PD, as they found significant correlations between regional transition energy and neurotransmitter receptor-density maps, including 5-HT2A receptors.

4. Proposal for a Unified Framework

4.1 Summary of Reviewed Literature

The first hypothesis, schematized in Figure 2A, attributes VH in PD to early visual dysfunction. According to this model, an impairment in V1 would cause the activation of a loop across areas of the visual network, with an increased activity in the DMN (Yao et al., 2014) and a dysfunction across the DAN and VAN, resulting in the recognition of internally generated stimuli as external inputs (van Ommen et al., 2023). ~~This~~The ~~original dysfunction~~ ~~disruption~~Aberrant P1 responses may reflect altered ~~in~~ ~~V1~~ early visual processing, although they do not specifically localize this dysfunction to V1 ~~would presumably be reflected by aberrant ERP values in the P1 component~~ (Schwartzman et al., 2008~~;), which in PD patients is correlated to primary visual processes (~~Wang et al., 2001).

The second hypothesis focuses on the role of a cholinergic dysfunction in PD-VH patients (see Figure 2B). However, ~~there is divergent~~ the available evidence ~~regarding whether this is a causing factor~~ does not establish whether this directly contributes to~~of~~ VH or rather develops as a consequence of the condition. Manganelli et al. (2009) postulated the presence of a link between cholinergic dysfunction and VH in PD patients reflected by aberrant SAI values; the direction of causality remains unclear. Conversely, Chang et al. (2016) observed an increased latency of the P3b component in EEGs of PD-VH patients, hypothesizing that a central cholinergic dysfunction might be an underlying cause of VH in PD. Accordingly, the unified framework does not assign a fixed causal position to cholinergic dysfunction.

Lastly, the third hypothesis, outlined in Figure 2C, suggests that an aberrant density of 5-HT2A receptors in PD-VH patients, possibly due to the dysfunction of the 5-HT system in PD (Huot et al., 2010), may be associated with altered transitions between integrated and segregated states (Zarkali et al., 2022). Moreover, pharmacological activation of 5-HT2A receptors in healthy participants resulted in increased amplitudes of the P1 potential and decreased α power values, providing causal evidence that 5-HT2A activation can alter early visual processing and cortical excitability (Kometer et al., 2013). These changes may, in turn, contribute to an imbalance between the processing of external and internally generated stimuli ~~(Kometer et al., 2013)~~.

4.2 How Do These Models Relate to Each Other?

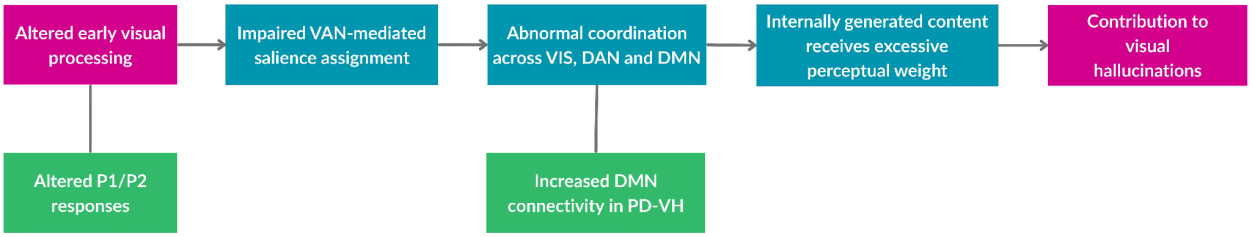
In light of the evidence considered and summarized in Table 2, this study proposes a unified framework to explain the functional changes that occur in PD-VH patients. Although the three models emphasize different mechanisms, their findings are not necessarily mutually exclusive. Instead, they may describe abnormalities occurring at different levels of the same distributed perceptual system. The following comparison therefore focuses on points of convergence while distinguishing direct empirical findings from mechanistic links proposed by the present framework.

Firstly, both the first and third models propose that an underlying mechanism of VH in PD may involve an imbalance between internally generated stimuli and external inputs, leading patients to misattribute internally generated stimuli as exogenous. ~~The~~While an early visual ~~model~~ dysfunction ~~hypothesis emphasizes~~might alter the~~ed~~ processing of external sensory information, ~~while the~~ network-level ~~empirical~~abnormalities ~~models measures~~ may describe how this information ~~may~~ interacts abnormally with internally generated activity (Schwartzman et al., 2008; van Ommen et al., 2023). Cholinergic and serotonergic dysfunction may in turn modulate these sensory and network processes (Chang et al., 2016; Kometer et al., 2013).

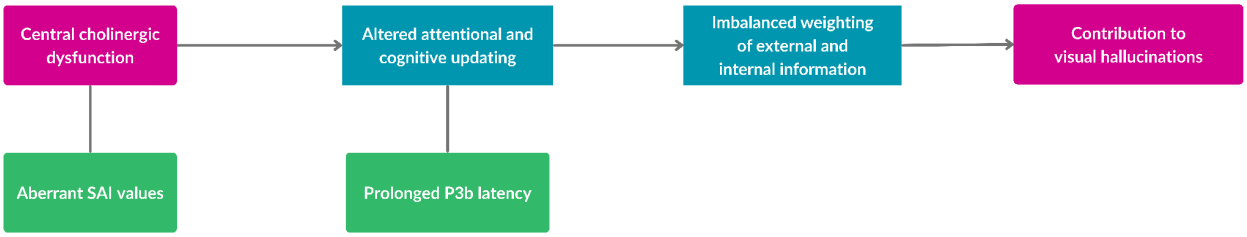
Additionally, aberrant P1 values observed in hallucination-prone individuals (Schwartzmann et al., 2008) may be compatible with the explanatory model proposed by van Ommen et al. (2023). Schwartzman et al. (2008) interpreted P1 abnormalities as reflecting altered early visual processing, while van Ommen et al. proposed that psychotic VH involve a dysfunction in V1,

A. Early visual dysfunction model

~~Early visual dysfunction model¶~~



B. Cholinergic dysfunction



C. 5-HT2A receptor dysfunction model

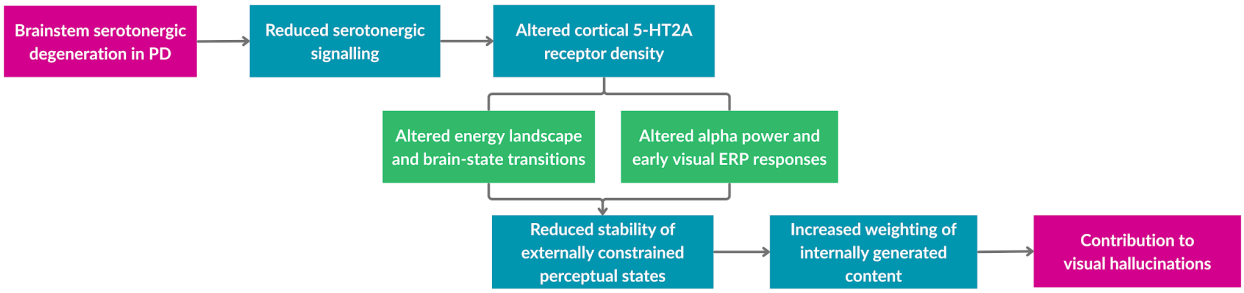


Figure 2. Schematic representations of the three models of visual hallucinations in Parkinson's disease. (A) Early visual dysfunction model. (B) Cholinergic dysfunction model. (C) 5-HT2A receptor dysfunction model. *Color code: key nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate*

directional relationships proposed within each model; continuous lines without arrowheads indicate observed associations for which causal direction has not been established.

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378 *Table 2. Summary of reviewed literature*

Hypothesis	Study	Approach	Key finding/relevance
Early visual dysfunction	Schwartzman et al. (2008)	EEG/ERP in hallucination-prone healthy participants	Higher P1/P2 positivity supports altered early visual processing but does not establish PD-specific causality.
	Yao et al. (2014)	Resting-state fMRI in PD-VH, PD-non-VH, and controls	Greater DMN connectivity in PD-VH supports involvement of internally oriented network activity.
	van Ommen et al. (2023)	fMRI during hallucinations in psychosis	Reduced V1 involvement with increased VIS/DAN/DMN/VAN activity supports a distributed network account.
Cholinergic dysfunction	Manganelli et al. (2009)	SAI in nondemented PD patients	Abnormal SAI links PD-VH to central cholinergic dysfunction; direction of causality remains unresolved.
	Chang et al. (2016)	Visual ERP task in nondemented PD groups	Prolonged P3b latency is consistent with altered cholinergic/cognitive processing in PD-VH.
Serotonergic/ 5-HT2A	Kometer et al. (2013)	Psilocybin/ketanserin EEG study in healthy adults	5-HT2A activation altered P1, N170, and α power, supporting serotonergic involvement in visual processing and cortical excitability.
	Huot et al. (2010)	Postmortem temporal-cortex receptor analysis	Higher 5-HT2A receptor density in PD-VH supports receptor-level involvement, though dementia is a confound.

	Zarkali et al. (2022)	Resting-state fMRI and network-control analysis	PD-VH showed fewer transitions and longer segregation, linked regionally to ~~neurotransmitter~~ 5-HT2A receptor density.

together with the DAN, DMN and VAN, resulting in an imbalance between external and internally generated stimuli. This evidence suggests that altered early visual processing reflected by P1 and dysfunction in V1 in psychotic VH may potentially represent related features of the same broader perceptual disturbance. However, Schwartzman et al. investigated healthy ~~evidence suggests that altered early visual processing reflected by P1 and dysfunction in V1 in psychotic VH may potentially represent related features of the same broader perceptual disturbance. However, Schwartzman et al. investigated healthy~~ individuals prone to hallucinate, and P1 measurements do not specifically localize dysfunction to V1. Thus, studies examining P1 ~~potentials~~responses alongside measures of V1 activity and network function in a PD-VH population are necessary to determine whether these abnormalities are mechanistically related.

~~Additionally, an aberrant values of the P1 ERP component has also beenwas observed by Schwartzman et al. (2008) were , attributed to primary early visual dysfunction and reflecting VH. As previously explained, this last piece of evidence supports the model proposed by van Ommen et al. (2023), according to which VH arise from an early visual dysfunction in V1, involving the DAN, DMN and VAN, and resulting in an imbalance between external and internally generated stimuli.¶~~

~~distinctThus, the increased dwelling time in segregated states in PD-VH patients is convergent with the decreased α power value identified by Kometer et al. and reflected by increased P1 potentials. However, these findings were obtained using different methods and populations and do not establish that reduced α power directly causes, or indexes, increased network segregation. Their relationship should therefore be considered a testable cross-scale hypothesis.¶~~

Another ~~significant observation concerns the last hypothesis~~possible point of convergence in the reviewed literature ~~regards~~is that the decreased α power reported by Kometer et al. and the altered brain-state dynamics ~~reported by Kometer et al. and~~observed by Zarkali et al may reflect a common underlying neural dysfunction~~, respectively~~. ~~While~~ Kometer et al. (2013) observed increased P1 amplitudes and decreased α power following pharmacological activation of 5-HT2A receptors, while Zarkali et al. (2022) ~~found associations~~~~attributed~~found associations between ~~altered brain-state transitions~~ between ~~to receptor~~5-HT2A receptor-density maps and altered brain-state transitions ~~and altered brain-state transitions~~. Specifically, the latter study found that PD-VH patients ~~spend~~ spent more time in the segregated state rather than the integrated one, compared to PD-non-VH patients. There is evidence that α power increases during visual integration in various areas of the brain, including early visual cortex and dorsal visual networks (Costa et al., 2024). This ~~, showing a link~~~~suggestsing~~raises the possibility ~~a relationship between~~~~that~~that ~~both the~~ increased dwelling time in segregated states in PD-VH patients and the decreased α power ~~value~~ observed by Kometer et al., alongside increased P1 potentials, ~~the the reported findings on α oscillations and states of the brain~~~~brain-states organization might~~may reflect different manifestations of ~~an~~a common underlying ~~the same inherent neural dysfunction~~imbalance in neural integration~~,~~ associated with VH. ~~Thus, both the increased dwelling time in segregated states in PD-VH patients and the decreased α power value~~

identifiedobserved by Kometer et al. and reflected by, alongside increased P1 potentials, may be compatible with the proposed framework. Nevertheless, the findings regardderive from distinct populations and methods, and they measure different neurophysiological phenomena. Specifically, Zarkali et al.Kometer et al. investigated healthy controls under psylocybinpsilocybin-induced changes in healthy participantsadministration, rather than PD population itselfwhereas Zarkali et al. examined brain-state dynamics in patients thewith PD-VH population. Therefore, the extent to whichwhether these findings from Zarkali et al. and Kometer et al. are convergent needsreflect a common underlying mechanism remains to be established withthrough further studies combining EEG and fMRI testing ofin patients with PD-VH.

Further evidence that supportsAdditional support for the proposed unified framework risescomes from A further point of convergence between the proposed models is the finding that transitions between segregated and integrated states are highly influenced by the activity of the DMN and thalamic regions (Zarkali et al., 2022), thereby linking attention- and memory-related networks to altered brain-state dynamics.

In addition, Aan increased activity in the DMN foundobserved in PD-VH patients (Yao et al., 2014) and linked with the dysfunction between segregated and integrated states may be related to the aberrant P3b latency valuesobservedreported by Chang et al. (2016). As the P3b component reflects top-down attribution of visualattentional processing of visual stimuli, and the DAN is responsibleinvolved in directing for top-down direction of attention toward salient stimuliinformation (Shine et al., 2014; Van Calster et al., 2017), the aberrantabnormal P3b values reported by Chang et al. mightmay reflect theaa dysfunction in visual attention allocation processes within theinvolving visual and attentional networks—DAN, VAN and DMN. Since theDAN activity of the DANis typically correlates negatively correlated with the DMN activity within this attentional network in the context of the DMN, DAN and VAN looppathway, aberrant activity in thedysfunction involving the DAN could explain may also be associated with the increasedthe higher DMN excitabilityconnectivity DMN reported by Yao et al. This reasoning raises the possibility that abnormalities in P3b activity and DMN function reflect overlapping disturbances in internally orientedattentional allocation and internally oriented cognitive processing of visual stimuliinformation. Nevertheless, thesethis remains a speculative cross-scale hypothesesshypothesis. Future studies should combineing EEG studies and fMRI analysesare needed to determine the mechanistic interplay between whether P3b abnormalities andare associated with dysfunction within attentional and visual networks dysfunctions, and specificallyparticularly focusing on the DMN.

Furthermore, a study conducted by Baumeister et al. (2014) found that increased P3 amplitude is linked to higher excitability in areas related to memory recollection and internal stimuli processing. However, further studies should be conducted investigating fMRI and EEG correlations in PD patients the available evidence does not establish that P3 directly reflects DMN activity.¶

Drawing on the convergent, but not yet causally unified, evidence considered, the present study proposes a model framework in which abnormalities in early visual processing, neuromodulatory function, attentional networks, and brain-state dynamics may represent interacting levels of the same distributed perceptual disturbance serotonergic dysfunction may act as a central neuromodulatory link, interacting with cholinergic and dopaminergic abnormalities and contributing to downstream changes in visual and attentional networks (see Figure 3). Serotonergic dysfunction may act as one integrative neuromodulatory factor, interacting with cholinergic and dopaminergic abnormalities rather than functioning as an isolated or necessarily upstream cause.

PD is associated with degeneration of serotonergic neurons in the brainstem, leading to reduced 5-HT levels. Huot et al. (2010) proposed that reduced serotonergic signaling may be accompanied by a compensatory increase in 5-HT2A receptor density. Altered 5-HT2A signaling , which may contribute to abnormal activity in visual and attention-related networks. may in turn be, directly or indirectly, associated with changes in ¶

Aaltered 5-HT2A receptor signaling may contribute to abnormal activity across thevisual processing, VIS and the DAN, DMN and VAN, and may be associated with altered α poweroscillations, attentional network activity, and brain state dynamics. and impaired transitions between integrated and segregated states, with a prolonged dwelling time in the segregated states and fewer transitions to the integrated state. Aberrant activity within visual and attentional pathways in the attention allocation and internal processing of visual stimuli, together with altered brain states dynamics would ultimately cause an imbalance between internally and externally generated information, giving rise to VH would be reflected by Add aberrant pP3b values;. A plethora of EEG and fMRI measures would each reflect dysfunctions in a part of the loop, but eventually convergent with the overall perceptual system imbalance.Cholinergic dysfunction may additionally affect

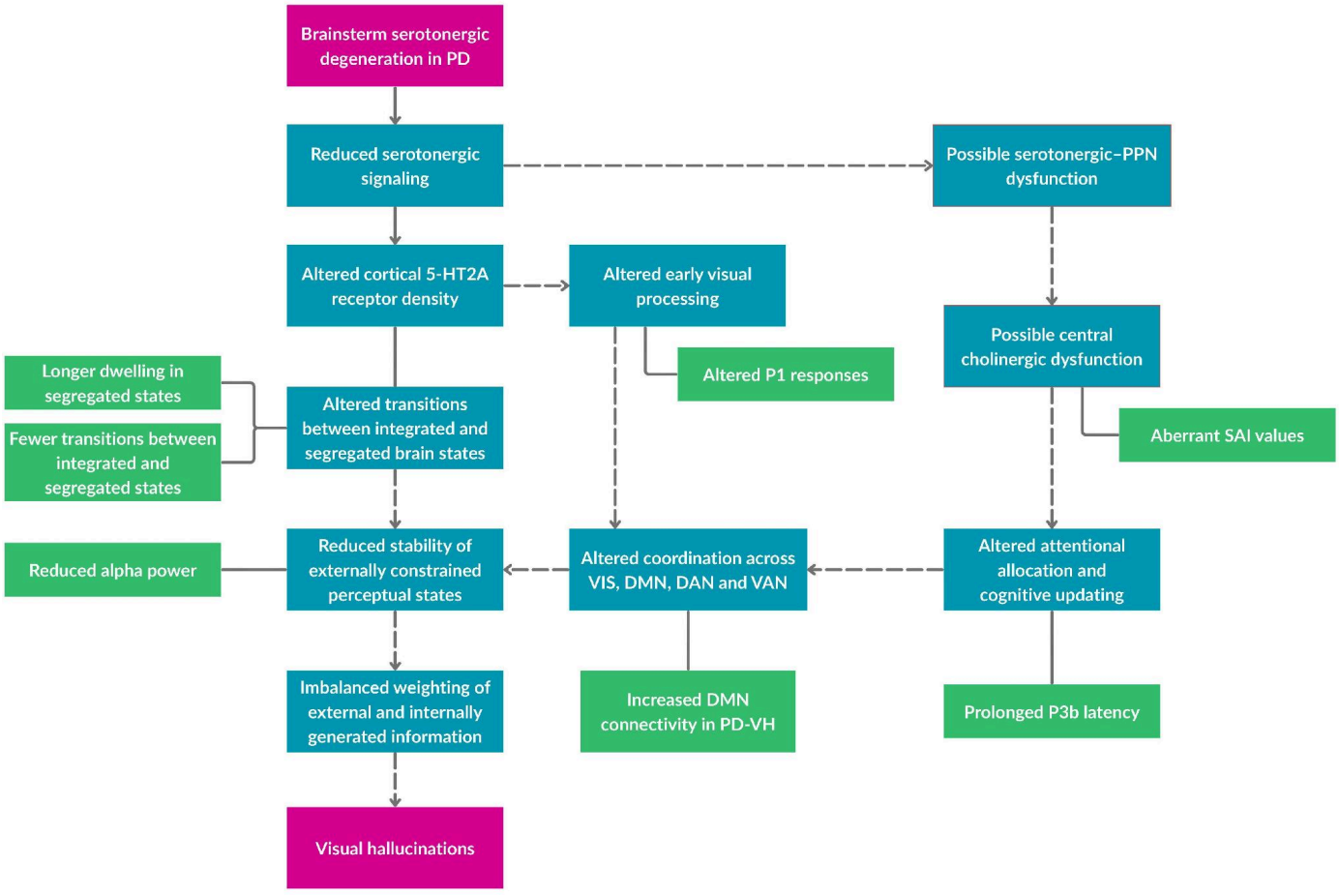


Figure 3. Proposed unified framework for visual hallucinations in Parkinson's disease. *Color code: key framework nodes in pink; intermediate mechanistic steps in blue; supporting empirical observations in green. Line code: continuous arrows indicate directional relationships retained from the reviewed models; continuous lines without arrowheads indicate observed associations for which causal direction has not been established; dashed arrows indicate integrative or unresolved mechanistic links proposed by the unified framework. ~~Red borders identify especially uncertain or indirect components.~~*

PD is associated with degeneration of serotonergic neurons in the brainstem, leading to reduced 5-HT levels. Huot et al. (2010) proposed that reduced serotonergic signaling may be accompanied by a compensatory increase in 5-HT2A receptor density. Altered 5-HT2A signaling may in turn be, directly or indirectly, associated with changes in visual processing, α oscillations, attentional-network activity, and brain-state dynamics. Cholinergic dysfunction may additionally affect attentional allocation and the balance between externally and internally generated information, although its causal position relative to VH remains unresolved. Together, these abnormalities could contribute to a perceptual system in which internally generated information is more readily misattributed as external. ~~DMN <-> integration~~

Within this framework, the comparatively later involvement of the serotonergic system in PD may help explain the delayed emergence of VH, while serotonergic dysfunction may also interact with other neurotransmitter systems and contribute to the downstream cascade of visual, attentional and network abnormalities.

~~Altered 5-HT2A receptor signaling may contribute to abnormal activity across the VIS and the DAN, DMN and VAN, and may be associated with altered α power and impaired transitions between integrated and segregated states, with a prolonged dwelling time in the segregated states and fewer transitions to the integrated state. An increased activity in the DMN found in PD-VH patients (Yao et al., 2014) and linked with the dysfunction between segregated and integrated states may be related to the aberrant P3b lateney values observed by Chang et al. (2016). As the P3b component reflects top-down attribution of visual processing, and the DAN is responsible for top-down direction of attention to salient stimuli (Shine et al., 2014; Van Calster et al., 2017), the aberrant P3b values reported by Chang et al. might reflect a dysfunction in in the DANvisual attention allocation processes within the visual and attentional networks – DAN, VAN and DMN. Since the activity of the DAN correlates negatively with the DMN in the context of the DMN, DAN and VAN loop, aberrant activity in the DAN could explain the higher excitability DMN reported by Yao et al. These findingsThis reasoning raises the possibility that abnormalities in P3 activity and DMN function reflect overlapping disturbances in internally oriented cognitive processing Nevertheless, these remain speculative cross-scale hypotheses. Future studies should combine EEG studies and fMRI analyses to determine the interplay between P3b abnormalities and attentional and visual networks dysfunctions, and specifically the DMN.¶~~

~~Furthermore, a study conducted by Baumeister et al. (2014) found that increased P3 amplitude is linked to higher excitability in areas related to memory recollection and internal stimuli processing. However, further studies should be conducted investigating fMRI and EEG correlations in PD patients the available evidence does not establish that P3 directly reflects DMN activity.¶~~

~~The previous models presented by van~~Van Ommen et al. (2023) ~~theorized~~ proposed that the ~~activation of the~~ loop ~~giving rise to VH –~~ involving the DMN, DAN and VAN and contributing to VH may ~~–originat~~originate~~ed~~ from a dysfunction in V1. ~~ThisThe consequent early visual dysfunction, which in early visual processing would indeed then be reflected by the aberrant P1 medial potentialsAltered P1 responses may independently indicate abnormalities in early visual processing, but~~

the available evidence does not establish that these responses originate specifically from V1 dysfunction. There are someSome studies that link serotonin and acetylcholine to V1 functions in animals; for instance, Shimegi et al. (2016) investigated how cholinergic and serotonergic systems modulate visual processing in monkey V1. However, further the available evidence does not establish specifically where this dysfunction within al process begins: early visual abnormalities, altered attentional-network activity, and neuromodulatory dysfunction may represent interacting contributors rather than a single linear causal sequencein visual and attentional networks beginsoriginates, nor whatwhich neurotransmitter systems are most directly involvedis the main contributor. Determining theirthe temporal and mechanistic relationships between among early visual abnormalities, altered attentional-network activity, and neuromodulatory dysfunctions will require studies combining electrophysiological, neurochemical, and functional-network measures within a controlledwell-characterized PD-VH population.gins: early visual abnormalities, alteredis necessary to define the underlying mechanisms that activate the loop between the VIS and visual-related networks. It is important to understand how the loop itself begins, whether it arises from dysfunction in V1 or abnormal activity in attentional networks, and to clarify which neurotransmitters are involved.

5. Conclusions

This review proposes that serotonergic dysfunction may play an integrative role in linking early visual abnormalities, altered neuromodulatory signaling, and large-scale network dynamics in PD with VH. By identifying testable relationshipslinks among abnormalities measured at different levels of the perceptual system, the proposed framework provides a basis for longitudinal and multimodal studies aimed at establishing their temporal and mechanistic relationshipsassociationsdetermining how these correlates interact, which changes occur earlier in the disease process, and how they contribute to eventually have a clear outline of to the neural networksmechanisms that underlyingie VH in PD. Eventually, altered 5-HT2A receptor density would originate dysfunctions that would propagate across different perceptual levels – networ-level, brain-states dynamics, alpha power waves, EEG potentials – contributes to the interpretation of internally generated stimuli as external, giving rise to VH. Rather than implying that serotonergic dysfunction represents the single or primary cause of VH, the reviewed evidence supports a model in which multiple sensory, cholinergic, serotonergic, and network-level abnormalities may interact.¶

The framework should therefore not be interpreted as demonstrating that serotonergic dysfunction is the single cause of VH or that it necessarily precedes cholinergic and network abnormalities. Its principal contribution is to identify testable links among findings that are usually considered separately. Future longitudinal, multimodal, and pharmacological studies will be required to establish causal direction and determine whether these mechanisms represent upstream drivers, interacting contributors, or downstream consequences of VH in PD.

6. Limitations and Future Research Directions

Accordingly, apparent convergence across studies should not be interpreted as evidence that the reported abnormalities belong to a single established causal sequence. In fact, the central limitation of the proposed framework is that it integrates evidence obtained from heterogeneous populations and methods. Some studies involve healthy participants exposed to serotonergic hallucinogens, some examine psychosis outside PD, and some include PD-VH samples affected by dementia.

Future work should therefore test the framework prospectively in carefully phenotyped, nondemented PD cohorts. The

strongest design would combine receptor-sensitive imaging, EEG measures of P1/P3b and α power, and repeated fMRI measures of DMN–DAN–VAN coupling and integrated–segregated state transitions within the same participants. Longitudinal studies should determine whether serotonergic and cholinergic changes precede hallucination onset, while pharmacological studies should test whether modifying 5-HT2A or cholinergic signaling changes the predicted electrophysiological and network markers. These tests would distinguish correlation from causation and clarify whether the PPN and DRN are upstream drivers, downstream consequences, or interacting modulators of the proposed pathway.

Future studies could also investigate the role of the pedunculopontine nucleus (PPN) in modulating cholinergic and serotonergic dysfunction. The PPN contains cholinergic neurons and receives serotonergic input from brainstem nuclei including the dorsal raphe nucleus (DRN) (Benarroch, 2013; Michelsen et al., 2007). Numerous studies mention the PPN in relation to VH in PD. With its cholinergic neurons, it is linked to attention networks, and it controls the visual cortex (Manganelli et al., 2009). Specifically, it modulates feedforward input to V1, exhibiting its crucial role in visual perception. Moreover, the neurotransmitters synthesized in the PPN modulate both the VAN and the DAN, together with other nuclei in the brainstem (Alves et al., 2022). These findings suggest that there is a connection between the PPN, attentional networks and other structures in the brainstem, especially the DRN, and that these connections are modulated by neurotransmitters. However, the proposed role of the PPN as a link between serotonergic and cholinergic dysfunction and altered visual-attentional processing remains indirect and has not been demonstrated as a causal mechanism of VH in PD. Future studies should therefore determine whether PPN dysfunction contributes to VH by disrupting cholinergic and serotonergic modulation of visual and attentional networks.

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9. Author Biography

Redacted for double-blind review.

10. Mentor Contribution Statement

The research mentor provided conceptual guidance, recommended relevant literature, discussed the interpretation of evidence, and offered feedback on the manuscript's organization and argument. The author independently conducted the literature review, developed the proposed unified framework, and wrote and revised the manuscript. The mentor did not collect or analyze original data and is not listed as a co-author.

11. AI Use Statement

Generative AI tools were used for limited editorial support, including assistance with identifying typographical errors and

awkward phrasing, checking reference formatting, and improving the organization of flowcharts. The author independently developed the research question, selected and interpreted the literature, constructed the proposed framework, evaluated the scientific claims, and approved all final wording. AI tools were not used to generate original data or conduct data analysis. The author verified the accuracy of all substantive claims, citations, and references and accepts full responsibility for the manuscript.

Dear Reviewer,

Thank you very much for your careful review and for the additional suggestions. I have revised the manuscript accordingly, as depicted below.

1. Method and Scope
   The Method and Scope section has been expanded to specify when the literature searches were conducted, the publication range of the sources, the approximate number of sources and core empirical studies considered, and the criteria used to distinguish corer empirical evidence from supporting methodological or background literature. I also clarified that findings inconsistent with, or not fully supportive of, the proposed hypotheses were considered rather than excluded, to avoid bias.

2. Alpha power and brain-state dynamics
   I revised this discussion so that decreased alpha power and altered brain-state dynamics are no longer presented as established convergent mechanisms. Their possible relationship is now explicitly described as a cross-scale hypothesis, while acknowledging the differences in populations, methods, and neurophysiological measures. I also added a clearer topic sentence introducing this proposed point of convergence and state that combined EEG and fMRI studies in PD-VH patients would be required to test whether or not the findings do reflect a common underlying mechanism.

3. P3b and DMN activity
   I removed the Baumeister et al. amplitude evidence from this comparison because it did not directly address the prolonged P3b latency reported by Chang et al. The revised discussion now presents the possible relationship between P3b abnormalities and DMN activity as a speculative cross-scale hypothesis. The paragraph was also given a clearer topic sentence.

4. P1 and V1
   I revised the manuscript throughout to distinguish abnormal P1 responses from direct evidence of V1 dysfunction. P1 is now describes as a marker of altered early visual processing, and the manuscript explicitly states that scalp-recorded P1 responses do not specifically localize dysfunction to V1. The first box in the early visual dysfunction schematic (Fig. 2A) and the box relating to V1

dysfunction in Figure 3 were also edited to avoid implying a direct association between P1 abnormalities and V1 dysfunction.

5. Cholinergic directionality
   I removed causal language that could imply a fixed direction between cholinergic dysfunction and VH, instead explicitly stating that the available evidence does not establish direction of causality.

6. Organization and consistency of the framework
   I clarified that the manuscript covers three principal hypotheses, namely early visual dysfunction, cholinergic dysfunction and serotonergic dysfunction, avoiding confusion with network-state abnormalities. The “Proposal of a Unified Framework” section was divided into two paragraph, “Summary of Reviewed Literature” and “How Do These Models Relate to Each Other?” to help the reader understand the logic of the discussion. The latter section was expanded to explain more clearly how comparisons and testable hypotheses are presented, and to distinguish empirical findings from mechanistic links proposed by the framework. Topic sentences introducing the different points of convergence were made more explicit, and the concluding part was reordered to improve logical progression and reduce repetition.

7. Readability and final formatting
   I tightened the wording throughout the manuscript, including the phrases identified by the reviewer. The “Conclusion” section was also trimmed to avoid overlap with the “Limitations and Future Directions” section, while effectively summarizing the contributions of the paper. Table 1 was reviewed and its title checked to ensure that it only appears once in the revised manuscript.

Thank you so much again for the thoughtful and constructive feedback. I am truly grateful to have been given the opportunity to revise my manuscript to help clarify causal links, improve organization of the unified framework and make the distinction between empirical findings and testable hypotheses more explicit.

Sincerely,
The Author