Are we seeing similarities that are not present? A literature review; comparing the causative agents that underly hallucinations

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Abstract

This literature review focused on the processes that underly hallucinations. The identification of underlying processes is important because it could lead to a universal treatment. To examine these underlying processes, the four main causative agents of hallucinations were reviewed. The main finding was that there are overarching factors that are shared between causative agents, namely hypoconnectivity between sensory and regulatory regions, overactivity of sensory cortices and altered dopamine activity in the striatum. Other factors that are not shared are sometimes shared between two or three of the causative agents and contribute to the specialization or the onset of hallucinations. Future research should focus on the main pathway that was identified to find a universal cure that can be applied to every patient suffering from hallucinations without adverse side effects.

Introduction

Over the years of evolution, a sophisticated system to perceive the world around us has been developed. A very complex system that allows us to see, hear, smell, feel and taste in order to survive. However, in some cases, perception can go rogue. We call this hallucinating and the lexicon dictionary of the University of Oxford defines it as: “an experience involving the apparent perception of something not present”. Hallucinations are common in patients with Schizophrenia, Charles-Bonnet syndrome, Parkinson’s and psychedelic drug users and can have a big impact on the life of the patient since they are often not distinguishable from reality (1). In order to understand the process of perceiving things that are not present, we must dive into the underlying processes that lead to hallucinations and investigate how different causative agents can result in the same clinical picture.

Research question:

Are the underlying pathways of hallucinations shared between different causative agents or should we refrain from using the word hallucinations as an overarching concept?

Framework:

In order to investigate the differences between the causative agents involved in hallucinations, we must first look at them individually. We will introduce the four main causes of hallucinations and the way they can cause this phenomenon. To conclude, we will compare the different pathways to look at the similarities and differences.

Schizophrenia:

According to the World Health Organization (WHO), the chronic mental disorder called schizophrenia affects at least 20 million people worldwide (2). The disease is characterised by delusions, hallucinations, disorganised speech and behaviour and negative symptoms like diminished emotional expression, according to the DSM-5 criteria (3). About 60-70% of patients suffer from hallucinations, making it one of the most prevalent symptoms of the disorder (4). These problems with perception are mostly in the form of auditory hallucinations (AH) and visual hallucinations (VH). Other types like tactile, gustatory and olfactory hallucinations are more rare but sometimes present (5).

The most prevalent form of hallucinations is a voice or voices in the head of the patient. The voice often has a certain characteristic that does not change and makes it different from that of the patient. In most cases this voice is made up by the brain and never heard in real-life situations. The intensity of the voices can differ due to external auditory input. The intensity will increase in a sound-isolated room and diminish when having a conversation with another person (6). The content of the voices are often comments on the patients' actions, speaking thoughts aloud or arguments (7). The content of visual hallucinations is often about family members, animals and religious figures which often evokes reactions of fear, pleasure or other emotions (8). However, hallucinations of fictional creatures have also been reported (9).

Hallucinations are associated with increased activity in cortical regions. The function of the specific region that is activated defines the content of the hallucination. Loss of a specific region will result in an inability to hallucinate the associated function of that region. For example, a lesion in the region responsible for colour perception, will lead to an inability to hallucinate colours in patients.

When looking at the neurobiological background of schizophrenia, it is often categorised as a disorder of plasticity and brain development (10). The underlying regulator of this disorder is thought to be in the genes since the heritability score is 0.8. However, the specific set of genes responsible for the onset of this disease is still under investigation (11).

Neuroimaging has proven to be helpful in identifying the specific brain regions that are responsible for auditory perception. In order to look at the abnormalities, we must first examine the normal pathways of sound and speech. The primary auditory cortex is responsible for the perception of tone and pitch. The secondary auditory association areas surround the primary auditory cortex and are involved in recognising sequences of sounds, like in speech. There are two language centers in the brain: Wernicke's area, which connects the meaning of words with

objects and Broca's area, which is responsible for language production. The location of the auditory cortices and language areas can be found in figure 1. Additionally, there is the dorsolateral prefrontal cortex which is involved in the regulation of voluntary versus involuntary auditory awareness (12). This concept of auditory awareness might be hard to understand but it can be explained by comparing thoughts with external sensory input. When our name is called, we react to it, this is called involuntary auditory awareness. We cannot choose not to hear our name being called so the nature of this experience is involuntary. However, when we generate thoughts, we are in charge of what we hear inside our heads. We can choose to stop thinking about something, which makes it a voluntary experience.

All of the information that is processed by the auditory system is combined with our expectations to provide an experience. The contribution of the sensory input or the expectation is determined by their reliability. When you are in a novel situation, sensory input is weighted more than prior expectations and vice versa. Hallucinations could therefore be seen as a disbalance in this system, in which prior expectations are given too much weight (13).

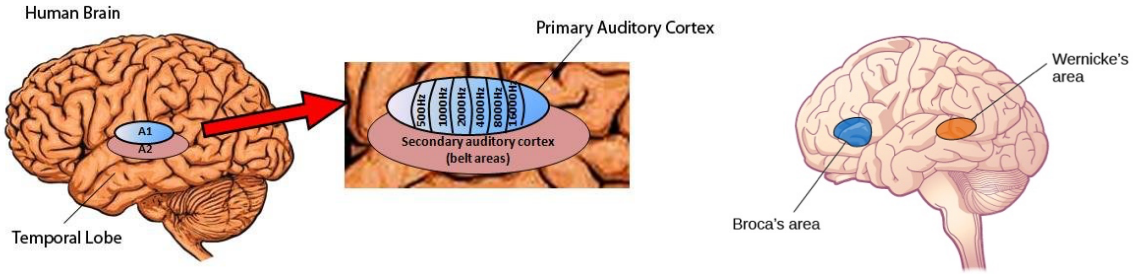

Figure 1. Location of the auditory cortices, Wernicke's and Broca's area

Patients with schizophrenia have been studied to identify the regions responsible for these involuntary auditory hallucinations. Research has shown that patients suffering from auditory hallucinations have a reduced grey matter volume in the superior temporal gyrus, which contains both the primary auditory cortex and secondary auditory association areas (14). Furthermore, a volume reduction in the dorsolateral prefrontal cortex, the area that is responsible for regulation of voluntary versus involuntary auditory awareness, has been shown. This is accompanied by a reduced 5-HT2A serotonin receptor density (15). The reduction in volume could be the cause of hallucinations being involuntary (16). Additionally, fMRI studies have shown an increased activation of the language areas and the primary auditory cortex in patients suffering from auditory hallucinations. Lastly, altered neural connectivity of the brain regions involved in speech was shown in patients with schizophrenia using diffusion tensor imaging (17). All of these brain alterations make it no surprise problems in perception may arise.

The most common treatment of hallucinations in Schizophrenia is however antipsychotics which most of the time influence the dopamine systems (18). So where does dopamine come in to play? Research has shown that patients suffering from Schizophrenia show increased dopamine levels, accompanied by an increase in D2 (dopamine) receptors and an increased releasability of the neurotransmitter (19)(20). These effects are most profound in the striatum and have been associated with a disturbance in the balance between the weight of prior experience versus sensory input, which brings forward problems with perception. PET scans have shown that when this dopamine release in the striatum is inhibited, patients down-weighted the effect of prior expectations and gave more value to the sensory input. In untreated patients, dopamine levels are high and experiments on perception show an inability to reproduce sensory input because too much weight is put on prior expectations. Antipsychotics can inhibit this excessive dopamine release in the striatum and alleviate the hallucinations by regaining the balance between the weight of prior experience and novel sensory input (21).

A popular concept used to explain hallucinations is that patients with schizophrenia misattribute internally generated speech as coming from an external source like a person speaking to them (22). This theory is nicely illustrated by the fact that you cannot tickle yourself because we anticipate a sensory impulse but you can be tickled by somebody else because you are not in control of the stimulus. Healthy individuals are able to distinguish a self-generated tactile stimulus from an externally generated stimulus and generally find the externally generated stimulus more intense (e.g., being tickled by somebody else). However, patients with schizophrenia did not discriminate between the two types of stimuli (23). This phenomenon might arise from the lack of connectivity between brain regions that perform the act and regions that perceive the sensory consequence of that act (24). The lack of connectivity in patients with schizophrenia can be connected to the reduced brain volume and grey matter (25)(26).

Several studies have been performed on this subject and showed that patients with schizophrenia showed reduced frontotemporal connectivity when asked to speak as seen in figure 2. This effect was even more pronounced in patients suffering from auditory hallucinations (27).

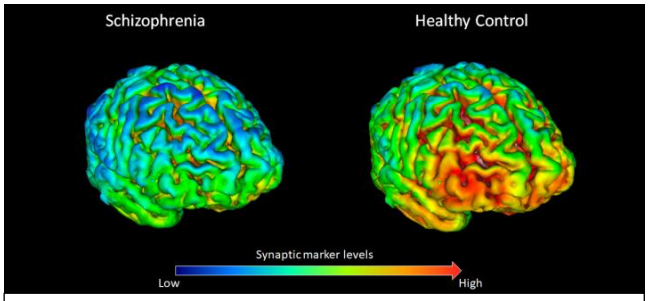

Figure 2. Reduced synaptic density in patients with schizophrenia[1]

To summarise, patients with schizophrenia suffer from decreased grey matter volume. This decrease in grey matter volume leads to reduction in neural connectivity. The areas that are responsible for the production of speech and for identifying whether speech is internal or external are not very well connected because of this reduction. In combination with the increased activation of the language areas and the primary auditory cortex, a volume reduction of the prefrontal cortex with a reduced serotonin receptor density and excessive dopamine activity in the striatum, this leads to internal speech being misattributed to external speech events. Antipsychotics can help by inhibiting striatal dopamine release to regain balance between the weight of prior expectations versus sensory input or by providing agonistic 5-HT2A (serotonin) receptor activity to counter the reduced receptor density in the prefrontal cortex and regain connectivity (28). One of the drugs that provides both dopaminergic antagonism and serotonergic agonism is clozapine, making it the most potent antipsychotic to treat schizophrenic hallucinations.

Charles-Bonnet syndrome:

Charles-Bonnet syndrome causes patients to endure complex visual hallucinations because of deteriorating eyesight. This syndrome is not linked to any other psychological diseases and is present in 0.5% of the world population (29). The visual hallucinations the patient endures are recognised as unreal by the patient in contrast to patients with schizophrenia (30). The patient however has no control over the content of the hallucination (31). The content of the hallucinations often involves a person, small costumed figures and animals (32)(33). Because these visions are very complex and clear, it is in contrast with the blurred perception of reality patients have because of their deteriorated eyesight.

The hallucinations experienced in Charles-Bonnet syndrome are described as "phantom vision" because of deafferentation of the visual association areas (34). There are many theories describing the cause of Charles-Bonnet syndrome but the most supported theory is the Sensory Deprivation Theory. This theory hypothesises that loss of visual input can lead to a change in excitability of the visual association cortex. Ocular pathologies can cause damage to the visual pathways when this occurs and spontaneous neuronal discharge in the visual association cortex is consequently observed. This increase in excitability of the visual association cortex can result in visual hallucinations (35).

Phantom sensations like hallucinations are also found in deprivation of the other senses. Examples of this are phantom pain in amputees and auditory hallucinations in patients with hearing loss.

The physiology of this increased excitability has been described by Yacoub & Ferucci (36). They indicate three main reasons for this increase. Firstly, an increase in the number of neurotransmitters released by the presynaptic neuron due to an increased vesicle size. Secondly, an increase in the number of postsynaptic receptors because of signal deprivation. Finally, they observed changes in the concentration of gamma-aminobutyric acid and glutamatergic N-methyl-d-aspartic acid in the synapse that has been linked to hyperexcitability of the neurons.

fMRI studies have shown that during visual hallucinations, the occipital cortex shows a decreased response to external visual stimuli. This decreased response leads to room for internally generated visual stimuli to be interpreted as external (37). The content of the hallucination is furthermore related to the corresponding region within the ventral occipital lobe, which is specialised for complex visual processing (figure 3.) (38).

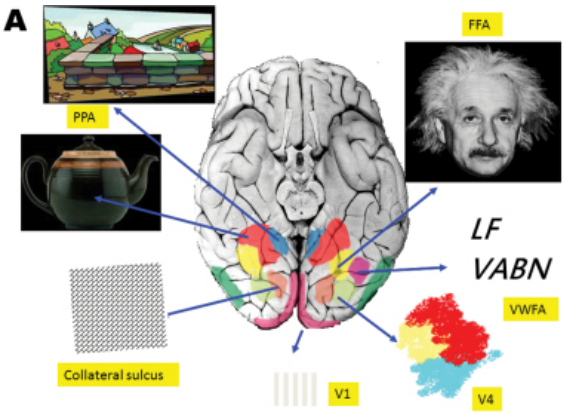

Figure 3. Overview of the specialisation of regions in the ventral occipital lobe, with among others the parahippocampal place area, responsible for landscapes and the fusiform face area, responsible for the recognition of faces (39).

The ventral occipital lobe is located close to the amygdala, the brain region responsible for emotional response. Research has shown that hallucinations are linked to certain emotions in half of the patients who suffer from Charles-Bonnet disease. Of this group, 50% perceived the hallucinations as unpleasant (40). There is currently no treatment for this disease.

To summarise, we have seen that Charles-Bonnet syndrome is a disease that leads to hallucinations in patients with deteriorating eyesight. The hallucinations occur because of sensory deprivation of the visual association cortex. This sensory deprivation leads to an increased excitability. Furthermore, because their vision is deteriorating, the occipital cortex shows a decreased response to external stimuli, leaving room for internally generated visual input to be interpreted as external. Even though there is no treatment currently available for this disease, I propose future research to investigate the suppression of the visual cortex to counter hyperactivity due to deafferentation.

Parkinson's

Parkinson's is a neurodegenerative disorder that affects around 7 to 10 million people worldwide (41). The disorder mainly affects the dopaminergic neurons located in the substantia nigra, which are responsible for dopamine production. The onset of the disease is often hard to identify since the symptoms generally develop slowly. These symptoms include tremor, balance problems, rigidity and sometimes visual hallucinations. The content of the hallucinations often increases in complexity when the disease progresses and ranges from simple flashes of colour to more well-formed images (42). Other types of hallucinations like auditory and olfactory hallucinations are infrequently found and usually linked to visual hallucinations.

Imaging studies have shown brain alterations in patients with Parkinson's disease. Grey matter reductions are found in multiple regions of the brain including the primary and secondary visual cortex (43). Furthermore, functional imaging studies have shown a reduction in activation of the primary visual cortex, accompanied by altered activation of the visual association cortex and the frontal cortex. Additionally, alterations in the ponto-geniculo-occipital system are responsible for a reduced suppression of internally generated images (44).

A variety of fMRI studies have shown a deteriorated connectivity of brain regions in patients with Parkinson's disease. Figure 4 illustrates the synchronisation likelihood, which is used to measure brain connectivity. The higher the synchronisation likelihood, the better the connectivity. Patients with Parkinson's disease who suffer from visual hallucinations show the lowest connectivity of the three investigated groups (45). The global loss of connectivity can be related to attention and perception problems, which is also seen in patients with schizophrenia.

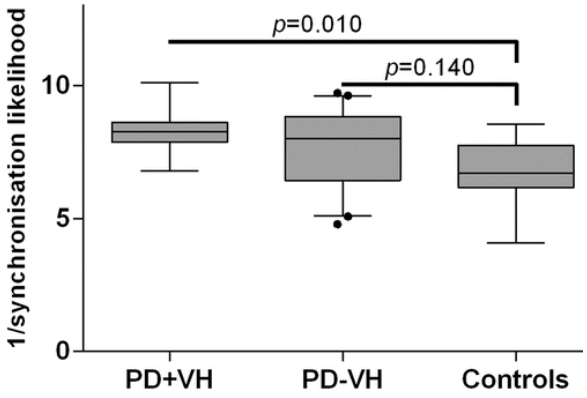

Figure 4. Mean functional connectivity in patients with Parkinson's + visual hallucinations, Parkinson's – visual hallucinations and controls (45).

Another factor that is shared with schizophrenic patients is dopamine alterations in the striatum. We have seen before that sensory input is combined with expectations and when too much weight is put on the expectations, this can lead to hallucinations. Schizophrenic patients

showed an increase in striatal dopamine release. However, studies have shown that patients suffering from Parkinson's with hallucinations show a 17% decreased DAT (striatal dopamine transporter) binding (46). These alterations in dopamine regulation in the striatum can lead to an unbalance between sensory input and prior experiences. Therefore, treatment with selective dopaminergic agonists could form a plausible cure for the effects of deteriorated dopamine signaling in an important area for perception.

In conclusion, we have seen that the destruction of the dopaminergic neurons in the substantia nigra can lead to big changes in brain anatomy and physiology. Grey matter reductions, accompanied by alterations in activity of brain regions involved in perception and deteriorated connectivity, can result in the occurrence of visual hallucinations. Additionally, reduced dopamine signaling in the striatum can lead to a deteriorated balance between sensory input and expectations, supporting hallucinations. Further research must be done to examine the exact pathways that lead to the deterioration of these brain functions in relation to Parkinson's and to develop a cure for this prevalent disease.

Psychedelics (LSD)

Lysergic acid diethylamide is one of the most powerful psychedelic drugs on the market. A small dose can already cause hallucinations that can last for 20 hours. It is often used as a recreational drug or in spiritual settings and the common way of using this drug is by putting a sticker with LSD sprayed on it on your tongue. The drug was discovered in 1938 by Albert Hofmann and became popular in the 1960s as a recreational drug. Hofmann was the first one to experiment with the drug and described the feeling as: "Perceiving an uninterrupted stream of fantastic pictures, extraordinary shapes with intense, kaleidoscopic play of colours."

The trip will end at a certain point for the majority of users, making it a temporary psychotic experience that is described as spiritually life changing in many cases (47), but in some cases LSD use can result in chronic visual hallucinations which is described as hallucinogen persisting perception disorder (HPPD), according to DSM-IV (48). EEG studies in patients with HPPD have shown that when patients close their eyes, the occipital region showed reduced coherence to more distant regions and hypersynchrony within the region. This hypersynchrony and isolation from regulatory brain regions, like the prefrontal cortex, in absence of external visual input can lead to recurring visual hallucinations (49).

But how do these hallucinations occur in the first place, when taking these drugs? LSD acts as an agonist of the 5-HT2A receptor that binds to serotonin. Studies have shown that 5-HT2A receptor antagonists reverse the trip caused by LSD, thereby confirming the effect of the drug (50). Katrin H. Peller et al. (2018) did a study on the role of 5-HT2A receptors in drug induced hallucinations. They compared three groups: a control group, a group that received LSD and a group that received LSD + ketanserin, a 5-HT2A antagonist. They used a global brain connectivity test to examine the effects of the drug. The most significant findings were that LSD induced hyper-connectivity in the sensory areas located in the occipital cortex and hypo-connectivity in cortical areas with associative networks like the prefrontal cortex. These changes were not observed in the control group or the antagonist group (51). The results of this study are depicted in figure 5. Additionally, other studies have shown an increased visual cortex blood flow during an LSD trip and an expanded primary visual cortex (52).

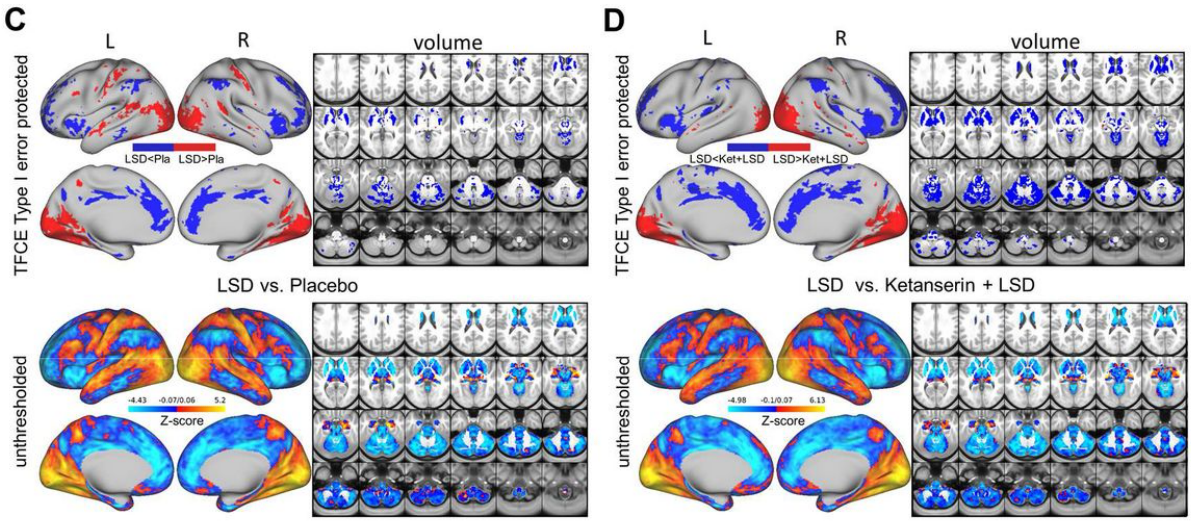

Figure 5. The left part of this figure shows the effects of LSD in comparison with the placebo group. The top panels show the significant areas with increases in global brain connectivity in red and decreases in blue. The bottom panels show the raw Z-scores between groups. The right part shows the same effects but instead of comparing to the placebo group, this part of the figure compares the LSD group to the LSD + antagonist group.

However, LSD does not only act on the serotonergic system; studies have shown that the drug also induces agonistic dopaminergic action. This agonistic effect of LSD on the dopaminergic system was mostly observed in the striatum, an area associated with hallucinations (53). To be more precise, the area that has shown to be important in the regulation of the balance between the weight of sensory input versus expectations. Alterations in striatal dopamine functioning were also described in schizophrenia and Parkinson's and are connected to the occurrence of hallucinations.

To conclude, LSD is a psychedelic drug that works both as a 5-HT2A serotonin receptor agonist and a DAT dopamine receptor agonist. The serotonergic agonistic action results in hypo- and hyperconnectivity within specific regions of the brain. Hyperconnectivity in the sensory areas result in internal image production while hypoconnectivity in association and control areas like the prefrontal cortex results in a failure to interpret the internally generated input. The dopaminergic action results in a disturbance of the balance between sensory input and expectations. The desynchronization between sensory areas and association and control areas in combination with a disbalance between sensory input and expectations can lead to hallucinations. Serotonergic and dopaminergic antagonists could serve as a possible counter to the psychotic effects of this drug, if necessary, in a medical setting.

Analysis

We have seen that the onset of hallucinations can have different backgrounds. Now it is time to start comparing the systems that were identified as responsible for this phenomenon. Figure 6 illustrates the commonalities between the different causative agents. We saw that in schizophrenia, Parkinson's Disease and psychedelic drug users, altered brain connectivity played a major role in the onset of hallucinations. Hypoconnectivity between sensory and regulatory areas can lead to misinterpretation of internally generated sensory experiences. The cause of this deteriorated connectivity is however different between groups. For instance, in patients with Parkinson's, this reduction in connectivity can be linked to the destruction of dopamine producing neurons, while in psychedelic drug users this altered connectivity is due to a change in serotonergic activity.

Another prevalent factor that we have encountered is altered dopaminergic activity in the striatum. This altered activity was observed in schizophrenia, Parkinson's and psychedelics and can additionally be accounted for the onset of hallucinations. Together with altered serotonergic activity in the prefrontal cortex observed in schizophrenic patients and psychedelic drug users, altered neurotransmitter signaling plays a major role in the prevalence of hallucinations.

In most cases the hallucinations are visual, except for patients suffering from Schizophrenia. The reason for this could be that the auditory cortex of schizophrenic patients is damaged more in comparison to other disorders. However, altered activity of sensory cortices can be compared and viewed as a group. The problem does not necessarily lay with altered activation of the sensory cortices but the failure to regulate that activity. The only exception to this statement is Charles-Bonnet syndrome in which only altered activity of the visual cortex was identified. This syndrome is however quite new to the scientific world and future research must be done to examine hallucinations caused by eyesight deterioration. The overactivity of the visual cortex of patients with Charles-Bonnet syndrome is also seen in all of the other causative agents, making it an important aspect of hallucinations.

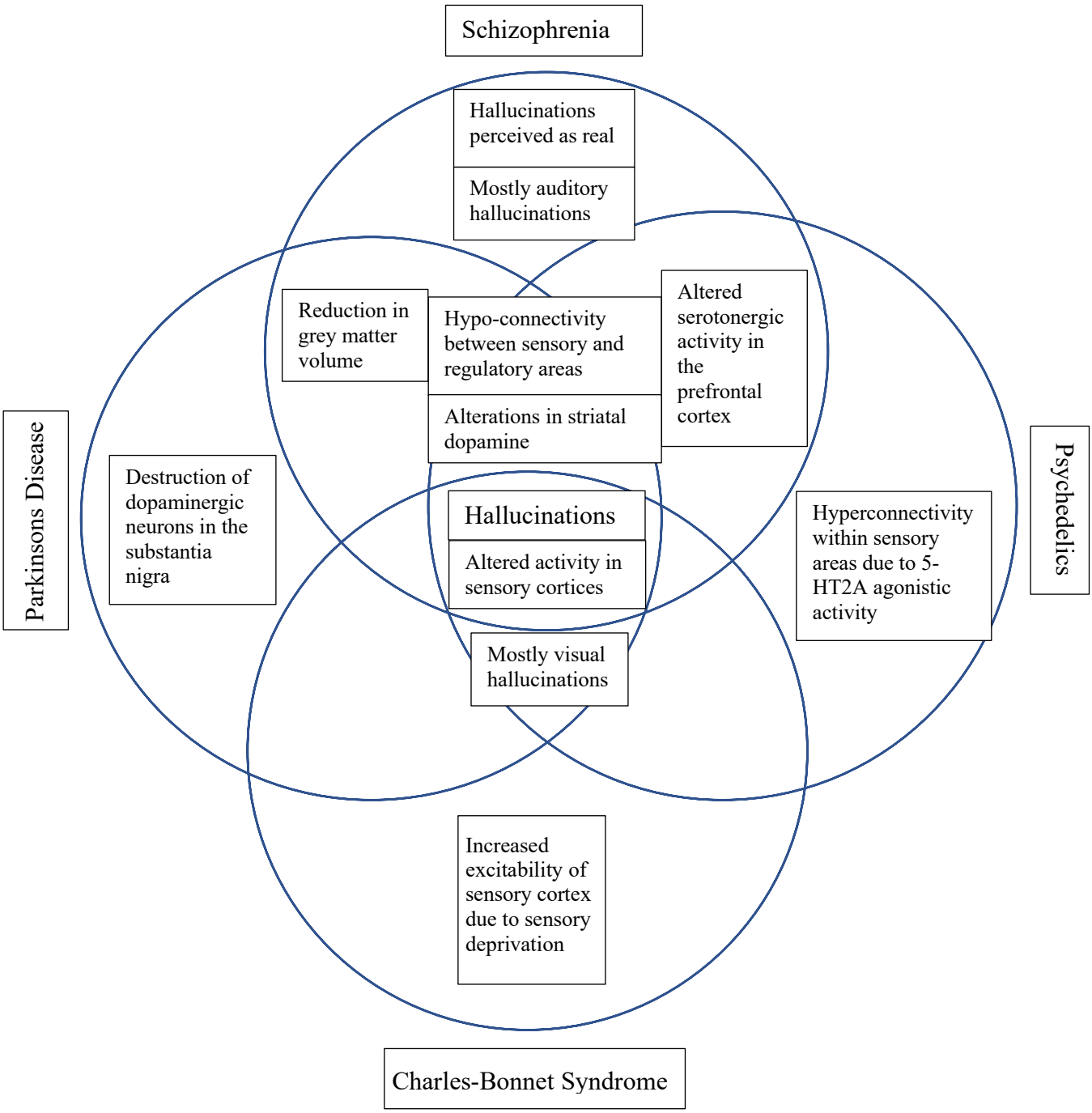

Figure 6. A comparison between the four described causative agents of hallucinations.

Conclusion

From this review we can conclude that there are three main factors when it comes to the generation of hallucinations, namely: Hypoconnectivity between sensory and regulatory regions, overactivity of sensory cortices and alterations in striatal dopamine activity. The causes of these brain alterations can differ greatly and can be chronic or temporal, but the outcome will result in hallucinations for all four described causative agents. Therefore, we can conclude that the term hallucination can be used as an overarching concept. The onset of brain alterations is different between causative agents, but the backbone of brain alterations underlying hallucinations are shared.

Future perspectives

Now we have identified the main processes underlying hallucinations, it is important to look at the future of this subject. First of all, more research has to be done on the underlying processes of Charles-Bonnet syndrome. The literature on this subject is scrappy and there are a lot of speculations and gaps in possible explanations at the moment. If more research is done, patients suffering from Charles-Bonnet syndrome could have more clarity about their disease, a cure might be found and it could form an interesting control in the research on hallucinations. Secondly, the precise mechanisms that are responsible for brain connectivity alterations after dopaminergic destruction in Parkinson's disease should be identified to help understand us the effects of this disease better. Of the three main factors that were identified in this review, only one could serve as a possible location of intervention, namely the neurotransmitter systems. Antipsychotics that work on these systems are already used to treat schizophrenic and sometimes Parkinsonian patients. However, the selectivity of these drugs should improve in the future to minimize side effects that are often observed. My advice for the community would be to start experimenting with selective striatal dopamine a(nta)gonists as a possible antipsychotic and continue researching the mechanisms of brain connectivity alterations and possible treatments for this currently irreversible destructive phenomenon.

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