Review Article

Underlying Similarities Between Psychedelic and Schizophrenia Hallucinations

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ABSTRACT

Though distinctly different in their effects, hallucinations occurring from schizophrenia (SCZ) symptoms and psychedelic drug action can appear similar. To investigate how different mechanisms underlie these effects, this paper highlights similarities at the molecular and anatomical network level and identifies potential new therapeutic applications and directions for research. This paper explores the 1950s-1960s studies involving schizophrenic patients, hallucinogenic drugs, and their historical significance. Next, the paper dives into overlaps between schizophrenic and psychedelic hallucinations– from molecular to cellular levels. The paper's overlaps section starts with Neuroplasticity overlaps between SCZ and Psychedelics; then is followed by the cortico-striatal-thalamo-cortical (CSTC) theory in psychedelics and schizophrenia's hallucinations; serotonin (5-HT) mediated hallucinations and psychotic effects; triple network disconnectivity in psychopathology and schizophrenia pathology; and finally, synaptic disconnections role in neuropharmacology of hallucinations seen by computational modeling. The paper includes a final section of how the drug, nicotine, impacts SCZ patients. This paper aims to clarify the neuropharmacological overlap between these phenomena to call for further research in developing targeted treatments.

Keywords: Schizophrenia; Hallucinogens; Neuroplasticity; 5-HT2A; Neuropharmacology

INTRODUCTION

Hallucinogens are used worldwide for various purposes, including recreation, therapy, and spiritual experiences. In fact, one in every ten American adults have reported using these drugs at least once in their lifetime (1). Society often stigmatizes hallucinogens due to their hallucinogenic effects, leading to widespread disapproval of their use. However, in rare cases, hallucinogens' unique effects have a high probability of being functional treatments in a medical context. Research suggests that the medical use of hallucinogens may have potential therapeutic benefits for various mental health conditions, including major depressive disorder, post-traumatic stress disorder, and schizophrenia. Despite their poorly defined pharmacology, hallucinogens' function is important to know so that it can be used in medical settings properly.

At the same time, schizophrenia research has grown rapidly because of its life-altering symptoms that, as

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of now, scientists know very little about. This causes many to have immense determination in identifying the cause of onset, symptoms, and possible treatments/cure of schizophrenia. Hallucinogens and schizophrenia on the surface seem to have very similar symptoms. Some symptoms are the various types of hallucinations detected in both. Neuroscientists have observed this neurological disorder and hallucinogenic drugs and have taken the unique opportunity to observe them both separately and combined (Table 1). This allows the neuroscience community to further strengthen the knowledge they have of the functions of the brain.

Schizophrenia

While schizophrenia (SCZ) remains incompletely understood, scientists continually strive to piece together the puzzle of this complex disorder to improve understanding and develop better treatments. The symptoms can be split into three categories: positive, negative, and cognitive symptoms (2). Positive symptoms are categorized as any symptoms that cause an increase in brain activity. These symptoms include hallucinations, delusions, and disorganized speech and thought. Negative symptoms are related to blunted affect (absence of emotional expression), alogia (when one speaks less or speaks minimal words in reply to others), avolition (the inability to engage in purposeful behaviors), reduced experience of pleasure, and withdrawal from social settings. Cognitive symptoms include decreased processing speed, attention deficits, verbal learning impairments, and decreased sense of reasoning and problem-solving. Patients with SCZ often have working memory deficits that occur from a reduction in information processing efficiency in the dorsal prefrontal cortex. Working memory deficits relate heavily to cognitive symptoms. The most common positive symptom in SCZ patients is auditory hallucinations (3).

The cause of onset for SCZ is not yet entirely known. However, many prominent hypotheses are emergent. SCZ is a neural development disorder likely resulting from both genetic background and environmental factors. Though many neurotransmitters play a role in the pathophysiology of SCZ, the neurotransmitter dopamine has proved to be a large factor in psychosis. The dopamine hypothesis proposes that dysfunction in the brain's reward system occurs during the conversion of electrical signals to chemical signals. Dopaminergic dysfunction starts at a presynaptic level before dopamine is released. Psychosis in SCZ can occur from this abnormal hyperactivity in dopaminergic transmission in limbic pathways. Neurons in limbic pathways have been shown to release an inordinate amount of dopamine from abnormal function from glutamate circuits: proving to be a strong theory for positive symptoms.

Negative symptoms, however, could be caused by hypodopaminergic functioning in the frontal structures of the brain (4).

Another prominent hypothesis is the serotonergic hypothesis which observes how stress-induced serotonergic overdrive from the dorsal raphe nucleus disrupts cortical neuron function. This means that the brain's response to chronic stress induces serotonergic stimulation causing cortical neuron dysfunction. This along with the hyperactivity of 5HT receptors in the cerebral cortex is a leading theory in the cause of SCZ. The glutamate hypothesis is newer but has key points to make it a dominant theory in the field of neuroscience. It states that positive symptoms come from the excessive release of dopamine from the mesolimbic pathway because of abnormal function from the neurocircuit loop in which glutamate ultimately disinhibits DA. Negative and cognitive symptoms on the other hand can be caused by not enough dopamine in the mesocortical region from the neurocircuit that ultimately inhibits dopamine. These changes in glutamate signaling relate to the dysfunction of glutamatergic receptors, which happen to be schizophrenia risk genes. Negative and cognitive symptom development

Table 1. The differences and similarities between hallucinogen induced hallucinations and schizophrenia's symptoms of hallucinations in regard to the modality, brain regions, and neurotransmitters involved in each hallucination

	Schizophrenia	Hallucinogens
Modality	Most commonly auditory (3)	Dependent, but usually visual (10)
Brain Regions Affected	Cerebral cortex, thalamus, hippocampus, and cerebellum (25)	Cortex, thalamus, brain stem, and basal ganglia (12)
Neurotransmitters involved	Dopamine, 5-HT2A, glutamate, mGlu2 (4,6,9)	Primarily 5-HT2A and mGlu2 (11)

can occur from the loss of too many glutamatergic inputs around cortical neurons that disrupt excitation and inhibition balance (5). While these theories are adequate in providing possible reasons for the cause of different symptoms seen in SCZ, different SCZ risk genes reflect each of these different hypotheses. The dopamine receptor D2 has been suggested to be a SCZ risk gene. Specifically, a DRD2 variant, S311C, has been proposed to take a role in SCZ's highly disorganized symptomatology (6). Variants of the genes that make up glutamate receptors such as NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) subunit genes, have also been found to correlate to SCZ risk (7). The proper function of glutamate genes is necessary because of their association with brain morphology and cognition.

In first and second-generation antipsychotics a complete suspension of positive symptoms takes place but very often cognitive and negative symptoms are not well improved. As a result, researchers are turning their efforts to finding a treatment that is effective for all categories of symptoms. These efforts have led to the discovery of the important receptors 5-HT2A and mGlu2. In schizophrenia, the density of the 5-HT2A and mGlu2 heteromeric complex in the cortex is dysregulated. A heteromeric complex is composed of at least two receptors that hold biochemical properties that allow the two receptors to communicate uniquely. The 5-HT2A and mGlu2 heteromeric complex comprises G-coupled proteins (Gi and Go) that allow the receptors to communicate with one another via signal transduction. In a healthy human brain the serotonin receptor 5-HT2A (5-hydroxytryptamine) and glutamate receptor mGlu2/3 (metabotropic glutamate 2/3) cross-talk in an antagonistic manner. This crosstalk facilitates synaptic mechanisms, downstream or regulation effectors, and genetic factors that result from the receptor's heteromeric complex. The correlation between the inhibitory Gi-coupled protein mGlu2 and excitatory Gq-coupled protein 5-HT2A receptor causes inverse cross-signaling. This means that each receptor's antagonists signal to the opposite receptor and agonists suppress signals to the partner receptor (Figure 1). This cross-talk allows for the heteromeric structure of 5-HT2A and mGlu2 receptors to process antipsychotic drugs and psychedelic actions through the G proteins' connecting loop (9). For instance, mGlu2 knockout mice were unaffected by the common neurological effects in response to hallucinogens. This suggests that atypical antipsychotics – such as those that are antagonists to the 5-HT2A receptor– will inhibit the effects 5HT-2a has on the mGlu2 receptor, occluding hallucinogenic effects (Boczek *et al*., 2021) (5). Additionally, mGlu2 activation causes a higher probability of the 5-HT2A agonists finding a receptor, hence producing hallucinogenic effects and indicating that the complex is necessary for responses from psilocybin-like drugs. Some atypical antipsychotics, such as clozapine and risperidone, have a high probability of causing a loop of dysregulation via histone deacetylase 2 (HDAC2) binding to the *mGluR2* promoter. This downregulation can lead to synaptic structure and behavioral plasticity decline, which is a common symptom in schizophrenic patients. Therefore, a potential SCZ therapeutic should target both the 5-HT2A serotonin receptor and the mGlu2 receptor for potentially more efficacious results (9).

Hallucinogens

Another place where the 5-HT2A receptor is activated is with the use of hallucinogens. Hallucinogens come in different chemical structures, and all have different effects on the brain. Psilocybin, a serotonergic hallucinogen, causes many similar symptoms compared to schizophrenia. Alterations in mood, delay in thought process, and perceptions are altered. Hallucinations, a

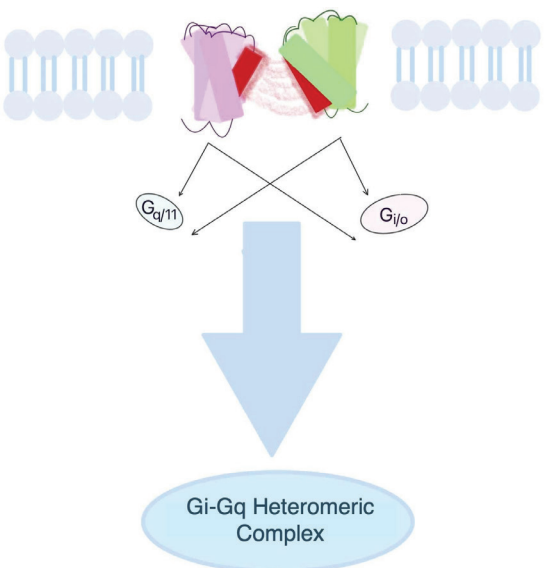

Figure 1. The relationship between the receptors mGlu2 and 5-HT2A communicating in a heteromeric complex. The excitatory 5-HT2A and inhibitory mGlu2 receptors communicate through their Gi and Gq proteins. Their unique communication style is hypothesized to relate to mechanisms behind hallucinations in SCZ and psychedelics.

large characteristic of schizophrenic symptoms, also occur when one is under the effect of a hallucinogenic. These hallucinations differ from schizophrenic hallucinations because the ones that occur in psychedelic states are mostly euphoric visual hallucinations. There are three different classes of psychedelics: phenethylamines, tryptamines (psilocybin class), and ergolines. These drugs can be derived from plants or can be semisynthetic. Examples of hallucinogens that are relevant to the paper are Lysergic acid diethylamide (LSD), psilocybin ('magic' mushrooms), and N-dimethyl-tryptamine (DMT) (10). Additionally, when serotonergic hallucinogens act on the brain, the 5-HT2A receptor is hypothesized to activate G-protein Coupled Receptor (GPCR) signaling pathways that regulate excitatory-secretion coupling. It is believed that the 5-HT2A receptor is linked to the action of hallucinogenic drugs because when the 5-HT2A antagonist ketanserin is co-administered, effects from LSD and psilocybin are blocked in humans (11).

Brain regions affected by psychedelics (as observed through FMRI studies)

Receptors that are agonists of hallucinogens are loaded heavily in areas where the performance of motor tasks, judgment, and social appropriateness; the hippocampus; which is involved in memory, learning, and emotion; the thalamus; an information relay station; and the basal ganglia: that's used for motor learning, behavior, and emotions. In the frontal cortex, these serotonin receptors are found on the dendrites of excitatory glutamatergic pyramidal neurons. However, brain regions affected by hallucinogens can be seen in a variety of ways. A study was performed to determine the shared and distinct brain regions activated through hallucinogens–specifically, ketamine and psilocybin— using c-fos gene expression seen in light sheet microscopy and serial two-photon microscopy. C-Fos is a protein released by the Fos gene that arises in response to neuronal activity. Therefore, c-Fos protein is used as a marker to determine activated brain regions. After multiple trials, 296 regions were proven during

drug-evoked changes to have a high percent increase in c-Fos cells and differences in regional c-Fos density. The cortex, thalamus, and brainstem were marked to have considerable differences. The largest change in c-Fos expression was in the dorsal regions and the ventral anterior cingulate cortex. Ketamine and psilocybin were discovered to have different escalations of c-Fos in the dorsal agranular insular area and the piriform. However, depression of c-Fos expression also occurred. Both ketamine and psilocybin suppressed expression in the gigantocellular reticular nucleus and the raphe nuclei (12).

Psychedelics in SCZ patients in the 1950s and 60s

Following the discovery of Lysergic acid diethylamide (LSD) in 1938, human trials began within a decade. LSD and psilocybin in the 1950s and 60s were used frequently as recreational drugs but also in medical settings to test their psychological effects. At the time, technology in neuroscience was not advanced causing the main source of data to be from human recollection of memories. Because patients were intoxicated, the conclusions of each test have a high probability of being inaccurate. After the ban of psychedelics in 1968 and the exclusion of SCZ patients from psychedelic testing because of the hallucinogenic properties, no recent data on the combination has been collected. The papers reviewed in the present paper relate to how psychedelics interact with schizophrenic patients. However, results from schizophrenia and psychedelic studies in the 1950s, revealed that negative symptoms in schizophrenic patients improved and psychosis was not exacerbated.[13] Recently, advances in neuroscience have allowed researchers to look back at this work and analyze the findings. Today, researchers attribute the effects of psychedelics observed in schizophrenia patients in the 1950s to the following process: they propose that schizophrenia causes a reduction in synaptic neuroplasticity. When psychedelics are introduced, the 5-HT2A agonists promote plasticity through a hypothetical stimulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors. This results in a positive feedback loop that enhances neuroplasticity in SCZ patients, leading to improvements in negative symptoms that were previously observed. Psychedelics increase long-term dendritic arbor complexity, promote dendritic spine growth, stimulate synapse formation, and increase neurotrophin levels. In SCZ patients gray matter decreases, neurotrophin levels decline, and synaptic proteins are lost. Therefore, hypotheses concluded that with a combination of antipsychotics and psychedelics, more therapeutic effects can be admitted in SCZ patients.[14] Recent studies with new technology in neuroscience research allow scientists to study schizophrenia and psychedelics separately, but link their findings. Because at network levels schizophrenia and psychedelics share interesting similarities and differences, studies have continued to arise. Functional magnetic resonance imaging (fMRI) capture studies compare ON and OFF phases of hallucinations, specifically finding phasic neural changes in hallucinatory ON periods. In

SCZ patients' studies, a part for modality-dependent associative cortex overactivations in hallucinations was suggested. The onset of hallucinations has been found to relate to various activation and deactivation patterns: specifically, hyperactivity in the hippocampal complex and hallucinatory-related cortices. In the psychedelic hallucination trials, the outcomes were not as direct because the study investigated all neural changes after psychedelic intoxication. However, in visual hallucinations a cerebral blood flow increase was noted, along with decreased associative processing in visual areas accompanying an early visual activity was observed. The results suggest that psychedelic effects may result from a combination of increased early sensory with lessened associative processing. At this point in time, psychedelics and schizophrenia are not known well enough to start safe trials with a combination. However, microdosing of psychedelics to curb potential hallucinatory effects has been a promising idea. This along with non-hallucinogenic 5-HT2A agonists that promote neuroplasticity should be further researched to provide more effective therapeutic options for SCZs (14).

SCZ and Psychedelic's Similar Underlying Mechanisms

Neuroplasticity Overlaps Between SCZ and Psychedelics

Neuroplasticity refers to the brain's capacity to form and reorganize synaptic connections in response to internal or external stimuli. Neuroplasticity is dependent on micro- and macro-connectivity and activity-dependent changes in neuronal synaptic strength. Long-term potentiation (LTP) occurs when frequently activated neuronal pathways strengthen their connections. The opposite, the weakening of improperly activated pathways, is called long-term depression (LTD). These two neurotransmitter release signals are also believed to be possible ways in which learning, and memory operate. In schizophrenia's pathophysiology, altered neuroplasticity is demonstrated by many lines of evidence to be a cause of cognitive and negative symptoms. In SCZ up to 60% synapse loss has been reported. Impaired plasticity in SCZ is theorized to occur from NMDA (a glutamatergic receptor) hypofunction. A similar phenomenon occurs when psychedelics enter the system. For instance, when ketamine and phencyclidine, antagonists of NMDA receptors, are delivered, hypofunction takes place, causing hypoglutamatergic and periodic hypoglutamatergic states similar to those in SCZ. Gamma amino-butyric acid (GABA) also modulates synaptic plasticity as NMDA receptors modulate the firing rate of GABAergic neurons. If the glutamate receptors' function is impaired, altered firing rates can occur for GABA neurons.

Numerous post-mortem studies have shown that disturbed GABAergic neurotransmission happens in SCZ from decreased density of GABAergic neurons and variations in the GABA-synthesizing enzyme glutamic acid decarboxylase. Non-invasive brain stimulation (NIBS) has shown to be an efficient investigatory tool because of its ability to search multiple cortical regions for cortical excitability and plasticity. This allows for NMDA receptor-dependent cortical plasticity in SZ patients to be easily accessed and observed. In a specific NIBS technique, repetitive transcranial magnetic stimulation (rTMS), and stimulation to the left promoter cortex happened to detect intracortical connectivity in SCZ patients. Dysfunctional plasticity reduced cortical inhibition, and functional promoter-motor connectivity were previously apparent in SCZ. However, in the rTMS NIBS technique, SCZ and healthy patients were compared. Healthy patients showed LTD plasticity and then a decrease in cortical excitability after rTMS, but in SCZ, LTP plasticity was displayed, and cortical inhibition deficits were observed. A leading theory attributes plasticity deficits in SCZ to NMDA receptor dysfunction and altered GABAergic neurotransmission. These two are hypothesized to take place because of the altered dopamine transmission that modulates glutamate and GABA neurotransmitters (15).

Neuronal degeneration in the prefrontal cortex (PFC) contributes to the pathophysiology of various mental disorders, including schizophrenia. To restore deficits of neurons in mental disorders, many have resorted to ketamine. Ketamine is frequently used for its unique ability to rapidly aid structural and functional plasticity in the PFC. Likewise, to ketamine, serotonergic psychedelics, such as LSD and psilocybin, are proficient in increasing neuritogenesis both *in vivo* and *in vitro*. Explanations for serotonergic psychedelics' clinical effectiveness likely relate to the TrkB, mTOR, and 5-HT2A signaling pathways stimulation induced by psychedelics. In a test done to test the effects of psychedelics on sporogenesis and synaptogenesis, all three classes of psychedelics were used: tryptamine, ergoline, and amphetamine. The cortical cultures were medicated with DOI, DMT, and LSD for 24 hours. Each drug increased the number of dendritic spines per unit length, specifically LSD which was observed to double the number of spinners per 10 μm. Psychedelics were observed by colocalization of pre and postsynaptic markers which inundated promotion in synaptogenesis by increasing the density of synapse but not the physical size. Later, a test with specifically DMT was used to compare synaptogenesis results with ketamine. At the same dose as

previously tested in ketamine (10 mg/kg), DMT showed a significant increase in the density of dendritic spines on cortical neurons after 24 hours. Additionally, ex vivo slice recordings showed that dendritic spine density was accompanied by functional effects. The frequency and amplitude of spontaneous excitatory postsynaptic currents (EPSCs) were also increased after treatment.

These currents are required for adequate brain functioning as they are the bytes of information in the information processing operations of the logic circuits. Overall, neuroplasticity throughout serotonergic psychedelics is frequently proven to be increased (16).

CSTC Theory in Psychedelic and Schizophrenic Hallucinations

While there are many hypotheses about the causes of hallucinations, a prominent hypothesis for hallucinations related to SCZ symptoms and psychedelic use is the cortico-striato-thalamo-cortical (CSTC) theory, or thalamus filter hypothesis. The CSTC theory proposes that in normal brain activity, the filtering use of the thalamus is supervised by the prefrontal cortex which behaves as a selective gating mechanism for the thalamus. The thalamocortical system is necessary for conscious activity and is likely to be heavily involved in sensory and sensorimotor gating of information to the cortex. Psychedelics are then believed to limit the influence of the prefrontal cortex, causing the thalamic reticular nucleus to be unmanaged, further leading to a sensory overload to other brain regions, and possibly causing hallucinations and altered ego function. In the context of psychedelics, the drug stimulates serotonin receptors located in key areas of the CSTC transmission loop thereby altering thalamocortical system transmission (17). Neuroimaging studies have supported this hypothesis; at peak drug effect onset major neuronal activity was seen in the hypofrontality cortices, basal ganglia, and thalamus (Nichols, 2016).[14] The onset of positive symptoms in SCZ patients is likely due to a similar type of altered transmission. An fMRI study showed that in SCZ patients the prefrontal-thalamic functional connectivity was decreased, but thalamic FC with somatosensory and motor areas were strengthened. LSD selectively increased effective connectivity from the thalamus to DMN areas, while others were attenuated. Thalamic connections with the right fusiform gyrus and anterior insula were also altered, leading to theories of correlation with hallucinations. In both cases, the experiment was associated with reduced internal integration of functional networks and enhanced correlation between internally and externally oriented networks. Ultimately despite some enhancements in activity, thalamocortical connectivity was consistently altered in psychedelic states. Both SCZ and psychedelics studies have proven the existence for adjusted thalamocortical connectivity, leading the CSTC theory to be involved in both the serotonergic hallucinogenic and the mental illness, SCZ (18).

5-HT2A Mediated Hallucinations and Psychotic Effects

The 5-*hydroxytryptamine 2a* serotonin receptor subtype is a key player in the function of psychedelic actions and schizophrenia symptoms. Serotonergic psychedelics such as LSD and psilocybin are 5-HT2A receptor agonists. 5-HT2A receptors are highly expressed on the dendrites of excitatory glutamatergic pyramidal neurons in the hippocampus, thalamus, and basal ganglia. Studies have suggested that the 5-HT2A receptor mediates psychedelic drug action in thalamocortical neurons and cortical pyramidal neurons. The 5-HT2A receptor has been shown to be necessary for the cellular and behavioral responses to psychedelics, as blockade of the receptor with antagonist ketanserin blocks hallucinogenic effects (19).

In SCZ the 5-HT2A receptor is also considered to play a role in the onset of psychotic effects.

Tests have shown that the 5-HT2A receptor modulates dopamine release in the cortex and striatum. When dopamine is released, cognitive and motor skills are diminished; these symptoms are the same that are continuously seen in SCZ patients. Post-mortem studies of the receptor's pharmacology serve as evidence for 5-HT2A's role in SCZ. In these post-mortem studies, differential 5-Ht expression is seen in SCZ brains compared to non-SCZ brains. To help ameliorate the disruptive positive symptoms that characterize SCZ, 5-HT antagonist antipsychotics are often used. Unfortunately, these antipsychotics are not always effective and often come with a wide range of side effects including drowsiness, fatigue, and weight gain.

The shared characteristic of the 5-HT2A receptor highlights a potential avenue for the future of new medications for SCZ treatment. For instance, impairment of working memory is often a symptom of SCZ. and specific genetic variants of the 5-HT receptor are associated with disruption in working memory. Additionally, neuroplasticity can be abnormally disrupted in SCZ patients, and serotonergic psychedelics – which are 5-HT2A agonists – have been shown to restore loss of synaptic plasticity.

Through the 5-HT2A receptor, psychedelics enhance synapse formation in a rapid and long-lasting manner,

though the exact mechanism has not yet been elucidated. Overall, 5-HT2A receptors contribute largely to the function of psychedelics and schizophrenia, and points to possible overlaps in future directions (20).

Triple Network Disconnectivity in Psychopathology and Schizophrenia Pathology

Schizophrenia and psychedelics exhibit striking similarities and notable differences in their effects on brain function. FMRI capture studies have detected ON and OFF periods and analysis of functional connectivity to visualize phasic neuronal changes to examine the similarities and differences between SCZ and the psychedelic pharmacology. These studies focus largely on 'resting states' – the state in which the brain is not actively involved in tasks involving attention. The term 'default mode network' or DMN has been created to reference this brain state. The brain regions incorporated in the DMN have been previously noted to function abnormally in SCZ patients. The pathogenesis of SCZ is therefore hypothesized to relate to the DMN because of the mental processes included that heavily relate to the operations in SCZ brains. Studies have hypothesized that disrupted DMN connectivity and activity relate to cognitive defects and psychopathology in SCZ.

There are four components of the DMN to understand: the activity and deactivation, the connectivity, the genetic underpinnings, and the anti-correlation with the TPN or task-positive network. DMN is often measured through regional oxygen consumption and blood flow, also, any changes in brain activity are mapped based on these characteristics. Though blood oxygen level-dependent (BOLD) signals are still not proven to correlate with brain activity, these studies use BOLD signals and fMRI to detect brain activity because their oxygen binding to hemoglobin alters its paramagnetic properties. For activity and deactivation, the DMN hypothesis is built on how relative activity decreases in separated brain regions during task performance states than in activity resting states. Next, the connectivity hypothesized to occur within the DMN was studied through temporal coherence of BOLD signals from spatially clear regions by functional connectivity- fMRI (cf-fMRI). It was discovered that in resting-state fc-fMRI studies, functional connectivity with the inferior parietal cortex, mPFC, inferior temporal cortex, and parahippocampal gyrus, stays active through active and rest states. This leads to a hypothesis to be made that there is an upholding of DMN functional connectivity through both conditions. The DMN also has a heritability factor of roughly .424. This heritability alludes to the idea that DMN characteristics that are seen in specific phenotypes or endophenotypes of different neuropsychiatric disorders are shared with high-risk, relatives, and SCZ patients. DMN can be potentially used as a biomarker in conceptualizing the treatment and pathophysiology of SCZ – which already is predicted to be 80% responsible for heritability. This hypothesis is supported by the findings of studies. These studies found that neuronal excitability genes link with schizophrenia, brain activity, and working memory in major parts where the DMN is located. Also, genes were detected to mediate the innate function of this network. Finally, anti-correlation with the task-positive network relates to the DMN. DMN is a task-negative network that is associated with introspectively oriented cognitive processes, while the TPN (a task-induced increase in alertness) is associated with externally oriented attention. These two networks have a very strong inverse correlation, meaning that an abnormal pattern of the two can cause imbalance and could potentially play a role in the pathological aspects of neuropsychiatric disorders.

Now that an understanding of the DMN has been established, the results of studies in schizophrenia patients are the following. Patients with schizophrenia have shown altered activity and deactivation in the DMN regions for a variety of tasks. Positive symptoms severity in SCZ were shown to hypothetically correlate with activity in the pCC/PCUN, mPFC, and the left inferior and middle temporal cortex. Also, task performance and emotional awareness of others was found to correlate with PFC deactivation. In the end, studies hypothesized that abnormal function of the DMN can be possible insights into the pathophysiology of the neuropsychiatric illness schizophrenia (21).

This network is also commonly observed with pharmacologically induced hallucinations. The functional connectivity in the DMN is thought to be related to a wide range of biological components that create downstream therapeutic effects. Reduced FC in the four functional regions (the mPFC, PCC, precuneus, and angular gyrus) of the DMN are hypothesized to cause positive states of ego dissolution (a 'mystical state'), which may impact the cognitive effects during the psychedelic experience. Psychedelics are believed to disrupt the DMN because of the intense cognitive experience and hyper-awareness of one's internal dispositions and attributions. Additionally, while the pharmacologic impact of psychedelics at the cellular level has been explored, less has been examined at the network level. Some studies suggest there may be a potential for DMN modulation-focused hallucinogens

as therapeutics. As noted, the DMN can be used as a biomarker and cognitive marker of neuropsychiatric conditions. The DMN may help overcome numerous limitations that are faced in the diagnosis of a variation of pathologies by symptomatology. While lacking clinical data in well-controlled studies, it has been hypothesized that neuropsychiatric disorders have specific DMN function abnormalities that psychedelics could potentially normalize. This hypothesis can be proved through the use of an examination of how nodes of the DMN control thalamic activity through connectivity, to gain a deep understanding of how information is transferred. Also, microdosing can lead to reduced DMN activity or decreased mind-wandering from the lessened abnormal activity. In the end, going in the direction of discovering more about DMN modulation would be beneficial to detect the interaction between acute and enduring effects of psychedelic substances on this network (22).

Synaptic Connections Role in Neuropharmacology of Hallucinations Seen by Computational Modeling

Characteristics of psychedelic action and the pharmacology of schizophrenia have been discussed through network and cellular levels; however, many questions and explanations have been unanswered.

This is where computational modeling plays a role in discussing how information processing might be a strong hypothesis for the functioning of hallucinations. Computational modeling conceptualizes the brain as an information processing system, providing standardized reports of these processes and mapping them onto existing neural structures.

Bayesian models are a specific type of computational model that focuses on how the brain learns internal and hierarchical models to represent the instrumental structure of the world. Every new input that enters this system is merged with preexisting information so predictions can be formed about probable causes of sensory input. These new inputs can be expectations, memories, and more. The Bayesian models in these particular tests were used to detect synaptic disconnections that could provide reasoning to the neuropharmacology of hallucinations. The model's premise rests on the fact that abnormal synaptic connectivity can possibly cause a false inference from incorrect weighting of sensory evidence and previous beliefs. Hallucinations can therefore result from this inappropriate weighting from neuromodulation and could highlight how hallucinations occur in psychedelic and schizophrenic states. Ultimately, the Bayesian models take a variety of hypotheses about the world, body, or brain and it picks the most probable answer. This is the same as an inference (i.e., reaching a conclusion based on evidence and reasoning).

Bayesian inferences can be applied in numerous ways. Stated by predictive coding, inhibitory feedback signals are the brain's explanations for new sensory inputs. These new inputs are sent from high level areas to lower-level areas to control the sensory input based on the behavioral conditions or simply known as a prediction. However, sometimes the preexisting knowledge cannot completely explain the input so a residual error signal (or prediction error/PE) is sent up the ladder to challenge the original belief to minimize surprise. The surprisement can also be lessened through appropriate action. Additionally, predictions and inputs are weighted according to their reliability or '*k*' (Kalman gain), which leads to precision-weighted prediction error. Psychedelics are hypothesized to work by increasing the prior weight or decreasing k. This leads to inferences being solved by expectations. The study named this tentative neural mechanism for prior overweight as "excessive AMPA-receptor signaling in the absence of NMDA-receptor impairment". This same mechanism is thought to occur in SCZ hallucinations. The theory for SCZ is supported by over-weighted priors in a group of patients with auditory hallucinations. Through the use of computers, our knowledge behind the mechanisms of hallucinations in both SCZ and psychedelic states are continuously hypothesized to occur from related origins (23).

Nicotine's impact on SCZ patients

Although this paper examines the relationship between psychedelics and schizophrenia, it's important to note that psychedelics like LSD and psilocybin require further research to establish their safety for therapeutic use. However, another drug such as nicotine is legal and often used by patients with schizophrenia. Studies report that patients with SCZ smoke three times more than the average person.

However, clinical studies show that there is a very complex relationship between severe SCZ symptom patients and tobacco/nicotine. Some studies hypothesized that smoking serves as a self-medication for the enhancement of cognitive functioning, motor abilities, attention, and immediate memory. Additionally, smoking may be a protective factor for the development of SCZ.

Nicotine, which is the addictive component of tobacco products, has been proven to mediate the altered glutamatergic, GABAergic, and dopaminergic pathways, all of which led to an improvement in symptoms. On the

other hand, smoking has been related to an increase in serious negative symptoms.

Also, smoking has been shown to cause an increase in the risk of developing SCZ. A study reported that within 14,284 healthy patients without any psychiatric disorder, those who smoked less than 9 cigarettes were 1.38 times more likely to develop SCZ, and if more than 10 cigarettes a day were smoked, then they were 2.28 times more likely to develop SCZ. Another study gathered men drug-naïve first episode (DNFE) patients to study the correlation between smoking and SCZ. All men in the study received antipsychotics as monotherapy. The study hypothesized that with the use of smoking, negative symptoms might be eased after combined treatment with antipsychotic monotherapy in patients with DNFE SCZ after twelve weeks of treatment. After 12 weeks the Positive and Negative Syndrome Scale (PANSS) displayed that each score in every subscale was notably decreased. For each subscale score, there was a 12.0 for positive symptoms, 4.9 for negative symptoms, and 12.7 for general psychopathology. However, after Bonferroni's corrections, there was only a great difference in the improvement of negative symptoms between nonsmokers and smokers with SCZ. In the end, there is no major evidence that smoking has more beneficial effects than negative effects in SCZ (24).

CONCLUSION

Within this manuscript, the parallels between SCZ and hallucinogens were analyzed, elucidating how superficial similarities between this disorder and drug class lead to deep neurobiological overlaps. We examined various current and historical hypotheses regarding the mechanisms underlying hallucinations and how they can be used for therapeutic application to SCZ – paying particular attention towards neuroplasticity, serotonin signaling, and network disconnectivity. However, these hypotheses remain contented and current data remains largely speculative, lacking sufficient clinical validification. Because of a lack of longitudinal studies, inadequate sample sizes, and challenges in translating molecular data into clinical procedures remain as the main limitations within research. Reliable studies are rare due to little consensus regarding standardized metrics to analyze neural and behavioral results across studies. Attempts to develop universal treatments are inherently difficult because of the differences often overlooked between hallucinogenic experiences and symptoms of SCZ. For instance, hallucinations associated with hallucinogens typically demonstrate euphoria and are situationally dependent, whereas SCZ symptoms prominently involve chronic hallucinations that may potentially contribute to distress.

Also, it remains unclear whether similarities in SCZ symptoms and in hallucinogenic experiences are overlapping due to common mechanisms or if they coincidentally result from shared disruptions.

Nevertheless, until an understanding of these discrepancies exist, the use of hallucinogens as a tool for SCZ therapy remains hypothetical. However, once surpassed, in addition to reshaping our diagnostic framework with regard to our interpretation of hallucinations, a deeper comprehension of these overlaps could allow SCZ patients to receive new and possibly more effective therapy, specifically for patients who are unresponsive to conventional antipsychotics. Moreover, hallucinogens may offer a future of discoveries about fundamental neuronal mechanisms, creating new valuable opportunities for innovative research and clinical endeavors.

REFERENCES

1. Salas-Wright CP, Hodges JC, Hai AH, Alsolami A & Vaughn MG. Toward a typology of hallucinogen users in the United States. *Drug and Alcohol Dependence*. 2021; 229 (B). https://doi.org/10.1016/J.drugalcdep.2021.109139
2. Gregory SY. (2025, January 13). Understanding the 3 symptom domains of schizophrenia - positive, negative and cognitive symptoms. *Mayo Clinic*. Retrieved May 14, 2025, from https://mcpress.mayoclinic.org/mental-health/understanding-the-3-symptom-domains-of-schizophrenia-positive-negative-and-cognitive-symptoms/
3. Schizophrenia. Available from: https://my.clevelandclinic.org/health/diseases/4568-schizophrenia (accessed on 2025-5-14)
4. Brisch R, Saniotis A, Wolf R, Bielau H & Bernstein H-G. The Role of Dopamine in Schizophrenia from a Neurobiological and Evolutionary Perspective: Old Fashioned, but Still in Vogue. *Front Psychiatry.* 2014; 5. https://doi.org/10.3389/fpsyt.2014.00047
5. Shah Urjita H, Javier González-Maeso. Serotonin and glutamate interactions in preclinical schizophrenia models. *ACS chemical neuroscience*. 2019; 10 (7): 3068-3077. https://doi.org/10.1021/acschemneuro.9b00044
6. Serretti Alessandro, Fabio Macciardi, and Enrico Smeraldi. Dopamine receptor D2 Ser/Cys311 variant associated with disorganized symptomatology of schizophrenia. *Schizophrenia research*. 1998; 34 (3) : 207-210. https://doi.org/10.1016/S0920-9964(98)00093-0

7. Mohamed Saini Suriati, Chad A. Bousman, Serafino G. Mancuso, Vanessa Cropley, Tamsyn E. Van Rheenen, Rhoshel K. Lenroot, Jason Bruggemann, *et al*. Genetic variation in glutamatergic genes moderates the effects of childhood adversity on brain volume and IQ in treatment-resistant schizophrenia. *Schizophrenia.* 2023; 9 (1): 59. https://doi.org/10.1038/s41537-023-00381-w
8. Boczek Tomasz, Joanna Mackiewicz, Marta Sobolczyk, Julia Wawrzyniak, Malwina Lisek, Bozena Ferenc, Feng Guo, and Ludmila Zylinska. The role of G protein-coupled receptors (GPCRs) and calcium signaling in schizophrenia. Focus on GPCRs activated by neurotransmitters and chemokines. *Cells*. 2021; 10 (5): 1228. https://doi.org/10.3390/cells10051228
9. Saha Somdatta, and Javier González-Maeso. The crosstalk between 5-HT2AR and mGluR2 in schizophrenia. *Neuropharmacology*. 2023; 230: 109489.https://doi.org/10.1016/j.neuropharm.2023.109489
10. Hallucinogens. (2023, April 18). Cleveland Clinic. Retrieved May 14, 2025, from https://my.clevelandclinic.org/health/articles/6734-hallucinogens-lsd-peyote-psilocybin-and-pcp
11. López-Giménez JF & González-Maeso J. Hallucinogens and Serotonin 5-HT2A Receptor-Mediated Signaling Pathways. In A. L. Halberstadt, F. X. Vollenweider, & D. E. Nichols (Eds.), *Behavioral neurobiology of psychedelic drugs*. 2018: 45-73. Springer Berlin, Heidelberg. https://doi.org/10.1007/7854_2017_478
12. Davoudian Pasha A, Ling-Xiao Shao, and Alex C. Kwan. Shared and distinct brain regions targeted for immediate early gene expression by ketamine and psilocybin. *ACS Chemical Neuroscience*. 2023; 14 (3) : 468-480. https://doi.org/10.1021/acschemneuro.2c00637
13. Hoch Paul H, James P. Cattell, and Harry H. Pennes. Effects of mescaline and lysergic acid (d-LSD-25). *American Journal of Psychiatry.* 1952; 108 (8): 579-584.https://doi.org/10.1176/ajp.108.8.579
14. Calder Abigail E, and Gregor Hasler. Towards an understanding of psychedelic-induced neuroplasticity. *Neuropsychopharmacology.* 2023; 48 (1): 104-112. https://doi.org/10.1038/s41386-022-01389-z
15. Bhandari Apoorva, Daphne Voineskos, Zafiris J. Daskalakis, Tarek K. Rajji, and Daniel M. Blumberger. A review of impaired neuroplasticity in schizophrenia investigated with non-invasive brain stimulation. *Frontiers in psychiatry.* 2016; 7: 45. https://doi.org/10.3389/fpsyt.2016.00045
16. Ly Calvin, Alexandra C. Greb, Lindsay P. Cameron, Jonathan M. Wong, Eden V. Barragan, Paige C. Wilson, Kyle F. Burbach, *et al*. Psychedelics promote structural and functional neural plasticity. *Cell reports*. 2018; 23 (11): 3170-3182. https://doi.org/10.1016/j.celrep.2018.05.022
17. Vollenweider Franz X. Brain mechanisms of hallucinogens and entactogens. *Dialogues in clinical neuroscience.* 2001; 3 (4): 265-279. https://doi.org/10.31887/DCNS.2001.3.4/fxvollenweider
18. Nichols David E. Psychedelics. *Pharmacological reviews.* 2016; 68 (2): 264-355. https://doi.org/10.1124/pr.115.011478
19. Gonzalez-Maeso, Javier, and Stuart C. Sealfon. Psychedelics and schizophrenia. *Trends in neurosciences*. 2009; 32 (4): 225-232. https://doi.org/10.1016/j.tins.2008.12.005
20. Maćkowiak Marzena. Psychedelics action and schizophrenia. *Pharmacological Reports.* 2023; 75 (6) : 1350-1361. https://doi.org/10.1007/s43440-023-00546-5
21. Hu Mao-Lin, Xiao-Fen Zong, J. John Mann, Jun-Jie Zheng, Yan-Hui Liao, Zong-Chang Li, Ying He, Xiao-Gang Chen, and Jin-Song Tang. A review of the functional and anatomical default mode network in schizophrenia. Neuroscience bulletin. 2017; 33: 73-84.https://doi.org/10.1007/s12264-016-0090-1
22. Gattuso James J, Daniel Perkins, Simon Ruffell, Andrew J. Lawrence, Daniel Hoyer, Laura H. Jacobson, Christopher Timmermann *et al*. Default mode network modulation by psychedelics: a systematic review. *International Journal of Neuropsychopharmacology.* 2023; 26 (3): 155-188. https://doi.org/10.1093/ijnp/pyac074
23. Leptourgos Pantelis, Martin Fortier-Davy, Robin Carhart-Harris, Philip R. Corlett, David Dupuis, Adam L. Halberstadt, Michael Kometer *et al*. Hallucinations under psychedelics and in the schizophrenia spectrum: an interdisciplinary and multiscale comparison. *Schizophrenia Bulletin*. 2020; 46 (6): 1396-1408. https://doi.org/10.1093/schbul/sbaa117
24. Mu Xishu, Wenjing Wu, Sisi Wang, Xiuru Su, Hengyong Guan, Xiaoni Guan, Xiaobing Lu, and Zezhi Li. Smoking affects symptom improvement in schizophrenia: a prospective longitudinal study of male patients with first-episode schizophrenia. *Schizophrenia*. 2024; 10 (1): 34. https://doi.org/10.1038/s41537-024-00449-1
25. Doctrow B. (2024, August 13). How psychedelic drugs alter the brain. National Institutes of Health.Retrieved May 14, 2025, from https://www.nih.gov/news-events/nih-research-matters/how-psychedelic-drugs-alter-brain