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Research Paper

Overview of Cognition and Neurotransmitters in Schizophrenia

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ABSTRACT

Schizophrenia is a complex mental disorder characterized by a wide range of symptoms, including psychosis, hallucinations, delusions, and cognitive deficits. While much research has focused on the positive and negative symptoms of schizophrenia, such as hallucinations and lack of motivation, cognitive deficits are also prominent features of the disorder but have been understudied. In this article, we discuss cognition in schizophrenia, including the maintenance of cognitive function and the deficits that are commonly observed. We also review typical treatments for schizophrenia and how they target neurotransmitter dysfunction in the brain. Despite the availability of antipsychotic medications that primarily target positive symptoms, current treatments have limited efficacy in improving cognitive deficits in schizophrenia. We highlight the need for further research and development of novel treatments that specifically target cognitive deficits in schizophrenia to improve the overall functioning and quality of life for individuals with this debilitating disorder.

Keywords: *Schizophrenia, Nosology, Cognition, Neurosciences.*

Schizophrenia is a severe disorder, characterized by psychosis, apathy, social withdrawal, and cognitive deficits, which culminate in fractured daily living (Mueser & McGurk, 2004). Diagnosis of Schizophrenia requires a person to demonstrate psychosis for more than 6 months, which is not attributable to another factor. Schizophrenia affects 1 in 300 people worldwide, with only 1/3 of patients achieving complete remission of symptoms, which contributes to the elevated mortality risk compared to the general population [WHO Report].

Although early reports characterized schizophrenia as a prodromal indicator of dementia, cognitive symptoms have largely been ignored when considering treatment strategies (Zuckerman et al., 2018). However, cognition is beginning to be considered an important aspect of schizophrenia, particularly because cognitive impairment is one of the earliest symptoms and is highly disabling (Bora, 2019). Cognitive deficits span a range of domains including processing speed, attention, working memory, verbal and visual learning, and social cognition (Bezdicek et al., 2020). This is further exacerbated by the fact that first-line therapeutics used to treat schizophrenia leave cognitive deficits untouched.

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By the mid-1980s oral anti-psychotic medications began to be used in the clinic, and are still in use today, which have improved patients' quality of life and day-to-day activities. These antipsychotic medications are first-line therapeutics that primarily target positive symptoms such as hallucinations and delusions. Unfortunately, these medications have limited efficacy in addressing the cognitive deficits associated with schizophrenia (Xu & Wong, 2018).

The reasons for the lack of efficacy of first-line therapeutics in addressing cognitive deficits in schizophrenia are complex and not fully understood. However, it is believed that cognitive deficits in schizophrenia may be related to dysfunction in various neurotransmitter systems in the brain, including dopamine, glutamate, and other neurotransmitters that play a role in cognitive processes. Antipsychotic medications primarily target dopamine receptors, which are implicated in positive symptoms of schizophrenia, but may not effectively modulate other neurotransmitters that are involved in cognitive functioning.

Moreover, cognitive deficits in schizophrenia are thought to arise from a combination of neurobiological, genetic, and environmental factors. There is evidence to suggest that early developmental abnormalities, such as alterations in brain structure and connectivity, may contribute to the cognitive impairments observed in schizophrenia. Additionally, genetic factors may play a role in determining the severity and extent of cognitive deficits in individuals with schizophrenia.

The impact of cognitive deficits in schizophrenia cannot be overstated, as they significantly affect the ability of individuals to perform everyday tasks, maintain employment, and engage in social interactions. These deficits often result in long-term functional impairments and reduced quality of life, and addressing them is crucial for improving overall outcomes for individuals with schizophrenia.

As such, there is a growing recognition of the need for novel treatments that specifically target cognitive deficits in schizophrenia. Several experimental treatments, such as cognitive remediation therapies, which aim to improve cognitive functioning through targeted cognitive exercises and training, have shown promising results in improving cognitive deficits in schizophrenia. Additionally, other approaches, such as pharmacological interventions that target specific neurotransmitters systems involved in cognition, are being explored as potential strategies to improve cognitive function in individuals with schizophrenia.

In this review, we begin by expanding on the aforementioned cognitive deficits in schizophrenia, including their presentation. We next delve into current treatments of schizophrenia and discuss their limited ability to ameliorate cognitive deficits. We finally discuss neurotransmitter dysfunction in schizophrenia and how targeting these systems with combination therapies may provide relief for those who do not respond to common treatments.

Cognition in Schizophrenia

Although schizophrenia is primarily diagnosed via the presentation of chronic psychosis, patients also demonstrate varying degrees of ability in cognitive domains like language, perception, memory, and attention (Tripathi, Kar, & Shukla, 2018). Deficiencies in these categories often appear in those at risk of developing schizophrenia long before the onset of psychosis (Tripathi, Kar, & Shukla, 2018).

These deficits are assessed using standard neuropsychological tests and batteries, such as the MATRICS Consensus Cognitive Battery which assesses several cognitive domains, including

verbal and visual learning and memory, working memory, attention and vigilance, processing speed, reasoning and problem-solving, and social cognition.

Cognitive deficits persist to varying extents in patients, due to the fact that they are inadequately addressed during standard treatment regimens. Theories have posited that cognitive deficits may arise from several sources including being secondary to positive symptoms and depression, exacerbation by first-line therapies, and/or being a core symptom of underlying structural brain abnormalities or neurotransmitter dysfunction. (Tripathi et al., 2018)

Role of Neurotransmitters:

From a neurotransmitter perspective, cognitive deficits may arise from multiple sources. For example, primary hyperdopaminergic in the prefrontal mesocortical system may lead to memory impairments (Torrisi et al., 2020). To some extent, this may be corrected by the downstream effects of 5HT2 receptor antagonism as an atypical antipsychotic mechanism. (Andrade & Rao, 2010)

Memory and attention have also been suggested to arise from glutamatergic dysfunction, such as NMDA receptor hypofunction.(Andrade & Rao, 2010). We will review these systems and their respective contributions to cognitive deficits in the following sections.

Dopamine

The hypothesis suggests that an overactive dopaminergic system in certain areas of the brain leads to the positive symptoms of schizophrenia. This theory is supported by the fact that drugs that block dopamine receptors, such as antipsychotics, are effective in reducing the positive symptoms of schizophrenia.

Studies have also shown that individuals with schizophrenia have increased levels of dopamine in certain areas of the brain, particularly in the striatum and prefrontal cortex. These brain regions are involved in reward processing and cognitive functions, respectively, which are disrupted in schizophrenia.

Moreover, genetic studies have identified several genes that are involved in dopamine signaling, and variations in these genes have been linked to an increased risk of schizophrenia. For example, the gene that codes for the dopamine receptor D2 (DRD2) has been extensively studied, and variations in this gene have been associated with altered dopaminergic function and increased susceptibility to schizophrenia.

However, the role of dopamine in schizophrenia is complex, and it is not just about the overactive dopaminergic system. Recent research has highlighted the importance of the mesolimbic and mesocortical pathways in the development and progression of schizophrenia. These pathways are involved in regulating motivation, emotion, and cognition, and they are modulated by dopamine signaling.

Studies

Studies have shown that individuals with schizophrenia have alterations in the mesolimbic and mesocortical pathways, which may lead to abnormal dopamine release and dysregulation of dopamine signaling. For example, in the mesolimbic pathway, excessive dopamine release in response to stress or other stimuli may contribute to the development of positive symptoms of schizophrenia, such as hallucinations and delusions. In contrast, the mesocortical pathway,

which is involved in cognitive functions, may be underactive in schizophrenia, leading to negative symptoms and cognitive impairments.

The potential mechanisms underlying the development and presentation of schizophrenia were a mystery until the discovery and implementation of the anti-psychotic medications reserpine and chlorpromazine in the 1950s. These pharmaceuticals were shown to suppress the action of DA signaling. This led to the development of the DA theory of schizophrenia, which posited that excessive DA signaling was responsible for schizophrenia. [Laruelle,1999]. This has been supported by numerous other studies of DA neurotransmission (Howes et al., 2009). For example, striatal dopamine signaling is germane to the emotional reaction to and salience of events. Thus, excessive DA signaling may cause random or irrelevant stimuli to be interpreted as being salient (Howes et al., 2009). Excessive striatal dopaminergic signaling might also muddle meaningful DA signaling, such as reward-related activity, and culminate in symptoms such as anhedonia, which is prominent in schizophrenia (Howes et al., 2009).

However, negative symptoms of schizophrenia are generally unaffected by DA treatments. As with any disease, a singular cause for a complex disorder, DA hyperactivity in this case, is unlikely, which has led to revised models of the DA theory of schizophrenia that have been backed by various studies. (Howes & Kapur, 2014)

Therefore, both hypo and hyperactivity of DA signaling may contribute to the negative and positive symptoms of schizophrenia, respectively. [Laruelle,1999]

Beyond outright hypo- and hyperactivity in schizophrenia, there are other changes in DA signaling that contribute to disease progression. Two independent studies have found higher rates of polymorphism of the dopamine D3 receptor gene in patients with schizophrenia. (Anissa Abi-Dargham, 2003.)

Imbalances in DA singling may arise from different DA sources, adding another layer of complexity to the DA theory of schizophrenia. Specifically mesolimbic DA projections to subcortical and cortical regions are hyper and hypoactive, respectively. Since in the seminal studies by Pocock et al. (1980), multitudinous laboratories have defined reciprocal and contrary rules among cortical and subcortical DA structures. From that obedience, it's been proposed that, in schizophrenia, each galettes of the DA imbalance interpretation is presumably related, inasmuch as an insufficiency in meso- cortical DA point would possibly translate into disinhibition of mesolimbic DA interest (Weinberger, 1987). Despite multitudinous times of eVort to induce experimental information helping those suppositions, documentation of abnormalities of DA point in schizophrenia has been di cult. Post-mortem disquisition measuring DA and its metabolites and DA receptors in the brainpower of victims with schizophrenia yielded inconsistent or inconclusive results (for evaluation see Davisetal., 1991). Over the former numerous times, the improvement of new mind imaging ways primarily predicated fully on the precept of endogenous opposition enabled direct dimension of DA transmission at D2 receptor withinside the striatum Combined with disquisition that proved extended striatal18F) dopa accumulation in schizophrenia, software of those new strategist. (Laruella,2003) Observations of schizophrenia furnished new data into subcortical DA point dysregulation in schizophrenia Imaging disquisition has always validated that schizophrenia is associated with extended presynaptic interest of DA neurons projecting to the striatum. Thus, the primary arm of the dopaminergic imbalance thesis (hyperactivity in the subcortical home) has acquired sturdy backing from imaging disquisition. On the other

hand, the alternate bone. Anissa Abi-Dargham,2003 this thesis (DA insufficiency in cortical projections) continues to be in large part primarily predicated fully on consequences from preclinical performances or indirect medical substantiation. In evaluation to the striatum, the presynaptic DA point withinside the PFC is now no longer a gift available to non-invasive imaging strategies. (Laruelle,2003) D1 receptor vacuity is the swish parameter of prefrontal DA point that is presently quantifiable in vivo with good enough responsibility. Despite the restrained data that this parameter provides to symbolize DA point, PET imaging disquisition has defined provocative connections among changes of D1 receptor vacuity and cognitive functions in schizophrenia. (Anissa Abi,2003)

NMDAR

N-methyl-D-aspartate receptors (NMDARs) are a subtype of glutamate receptors that play a crucial role in various aspects of cognition, including learning and memory. These receptors are important for synaptic plasticity, which is the ability of neurons to change their strength of connections based on experience.

In schizophrenia, dysfunction of NMDARs has been implicated in cognitive deficits observed in patients.
Several studies have shown that NMDAR hypofunction, or reduced activity of these receptors, may contribute to the cognitive symptoms of schizophrenia.
Specifically, NMDAR hypofunction has been associated with deficits in attention, working memory, and executive function in patients with schizophrenia.

The exact mechanisms by which NMDAR hypofunction leads to cognitive deficits in schizophrenia are not fully understood.
One theory is that this dysfunction impairs the ability of neurons to form new connections and modify existing ones, which is crucial for learning and memory. Another theory suggests that NMDAR hypofunction may lead to changes in neural oscillations, which are thought to play a role in coordinating cognitive processes.

Despite the exact mechanisms being unclear, there is evidence to suggest that drugs that modulate NMDAR activity may be useful for treating cognitive deficits in schizophrenia. For example, some studies have shown that drugs that enhance NMDAR function can improve cognitive performance in patients with schizophrenia.

Recent studies also suggest that hypofunction of the N-methyl-D-aspartate (NMDA) glutamatergic receptor also contributes to schizophrenia. (Bygrave, A. M., Kilonzo, 2019)

Patients with NMDAR autoimmune encephalitis that produce antibodies against the GluN1 subunit, initially present with psychiatric symptoms similar to schizophrenia. Furthermore, evidence suggests that a certain population of patients with schizophrenia produce antibodies against the NMDAR. (Subeh, Lajber, Patel, & Mostafa, 2021)

Glutamate in schizophrenia-

It is known to play a critical role in the regulation of cognitive function, including learning, memory, attention, and executive function. The disruption of glutamate signaling has been linked to cognitive dysfunction in patients with schizophrenia.

Studies have shown that altered glutamate signaling is associated with cognitive deficits in schizophrenia. The Wisconsin Card Sorting Test (WCST) is a commonly used measure of

cognitive function in schizophrenia, and deficits on this test have been linked to abnormal activation in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DLPFC) in patients with schizophrenia. In particular, poor performance on the WCST has been found to be associated with abnormal activity in the medial prefrontal cortex (mPFC), which includes the ACC.

A study of 19 patients with chronic schizophrenia found that poor overall performance on the WCST was associated with abnormal activity in the mPFC. In contrast, a larger study of 43 patients with chronic schizophrenia found that abnormal glutamate levels in the ACC, but not the DLPFC, were associated with WCST learning ability.

These findings suggest that altered glutamate signaling, particularly in the ACC and mPFC, may play a critical role in the cognitive deficits observed in schizophrenia. Understanding the role of glutamate in schizophrenia and its impact on cognitive function may lead to the development of more effective treatments for this debilitating disorder.

GABA Levels in Schizophrenia:

GABA, the primary inhibitory neurotransmitter in the mammalian central nervous system, has been implicated in various mechanisms of schizophrenia, including cognitive deficits (Marsman et al., 2014). In patients with relapsing-remitting multiple sclerosis, lower GABA+ levels have been correlated with poorer cognitive performance in multiple domains (Cao et al., 2018).

Some evidence suggests that patients with schizophrenia may present with lower GABA levels and α5 GABA receptors, particularly in the hippocampus. Notably, a significant decrease in the GABA ratio was found in the prefrontal cortex of patients with schizophrenia compared to healthy controls, and a negative correlation between GABA/Cr ratio and glutamate levels was observed in the parieto-occipital cortex of controls (Marsman et al., 2014). However, this association did not reach significance in patients (Marsman et al., 2014).

Receptor autoradiography studies have consistently shown an increase in binding density of 3H-muscimol, an agonist at the GABA binding site on the GABAA/benzodiazepine receptor complex, in the prefrontal, cingulate, and temporal cortices, as well as the caudate nucleus, in patients with schizophrenia. In contrast, the density of binding to the BZ binding site of the GABAA/BZR complex has shown inconsistent results, with some studies reporting no changes, while others reporting increases or decreases (Egerton, Modinos, Ferrera, & McGuire, 2017). Studies investigating GABAA α subunit expression post-mortem have found reductions in α1 and increases in α2 expression in schizophrenia, but findings for the α5 subunit have been inconsistent (Egerton et al., 2017).

The basal ganglia, a group of brain structures, depend on GABAergic signaling for proper functioning. (Jin, Galvan, Wichmann, & Smith, 2011).

Neuroimaging studies of GABA function in schizophrenia are important as they allow for in vivo testing of hypotheses regarding GABA dysfunction in this disorder. Pharmacological compounds that act on GABA function, such as benzodiazepines, have been explored for their potential therapeutic effects in schizophrenia based on data from animal studies suggesting that they can prevent the development of neuroanatomical and neurophysiological abnormalities associated with the disorder (Egerton et al., 2017). However, the nature of

GABAergic abnormalities in schizophrenia in vivo remains unclear, despite several neuroimaging studies (Egerton et al., 2017).

Bradykinesia

Anatomical changes in first-episode schizophrenia broadly coincide with a basal ganglia-thalamocortical circuit. These changes include bilateral reductions in the gray matter of the caudate head, which are absent in chronic schizophrenia.

Role of Neurotransmitters in Schizophrenia and subsequent cognitive disturbances-

Cognitive deficits in schizophrenia have been linked to imbalances in glutamate, GABA, dopamine, acetylcholine, and histamine (M. Huang et al., 2014). For example, glutamate and GABA signaling dysfunction has been noted in the dorsolateral prefrontal cortex, a key area mediating recollection (Fang et al., 2018; Schoonover, Dienel, & Lewis, 2020) . Specifically, recollection depends on synchronous gamma oscillations of glutamatergic pyramidal neurons, which is largely influenced by excitatory: inhibitory tone (Chiu et al., 2018). In sufferers with schizophrenia-associated cognitive deficit, there is a lack of gamma oscillations during recollection (Cho, Konecky, & Carter, 2006).

We will expand on the influence of the major neurotransmitters in the manifestation of cognitive deficits in schizophrenia and how they may be useful for more efficacious treatments.

Alterations to Brain Regions and their Neurotransmitters:

Brain structures-

There are several brain structures that are affected in patients with schizophrenia. The prefrontal cortex is one such brain region heavily involved in cognition and other symptoms of schizophrenia.

Many studies have shown that people with schizophrenia show hypoactivity of the prefrontal cortex, which could contribute to hallucinations and delusions.
Some patients also suffer from disorganized thought patterns. Since the prefrontal cortex also helps organize thoughts, less activity in that area might be a cause of disordered thinking, as well as delusions.

Studies have also shown that patients suffering from hallucinations show abnormal brain activity in the visual and auditory cortices, which could play a major role in visual and auditory hallucinations common to the disorder.

Another brain structure that is different in patients with schizophrenia is the amygdala. The amygdala is the part of the brain that is responsible for basic feelings, like fear, lust and hunger. Patients with schizophrenia often demonstrate anhedonia and a smaller amygdala.

Anatomical changes in Schizophrenia

When there is a dysregulation of this signaling, it can contribute to the development of disorders associated with the basal ganglia.

The disorder associated with dysregulation of GABAergic signaling in the basal ganglia is Parkinson's disease. In Parkinson's disease, there is a loss of dopamine-producing cells in the substantia nigra, which leads to decreased dopamine signaling in the basal ganglia. This disruption in the delicate balance between GABA and dopamine signaling results in the

characteristic motor symptoms of Parkinson's disease, including tremors, rigidity, and Treatments for Schizophrenia.

Acetylcholine treatment in schizophrenia-Effective Treatment for Schizophrenia

There are currently no FDA-approved drugs that specifically target acetylcholine signaling for the treatment of schizophrenia.However, some antipsychotic medications indirectly affect acetylcholine signaling by blocking dopamine receptors, which can lead to an increase in acetylcholine release in certain regions of the brain.

Additionally, studies have shown that cholinergic agents, which increase the activity of acetylcholine in the brain, may be beneficial in treating certain symptoms of schizophrenia, such as cognitive impairment. For example, drugs such as donepezil, which are used to treat Alzheimer's disease by increasing acetylcholine levels, have been shown to improve cognitive function in some patients with schizophrenia.

Other studies have investigated the use of selective muscarinic receptor agonists, which specifically target acetylcholine signaling pathways, as a potential treatment for schizophrenia. While the results of these studies have been mixed, some have shown promising results in improving cognitive function and reducing negative symptoms of the disorder.

Non-common treatments for Schizophrenia

Individual therapy, social skills training, family therapy, and vocational rehabilitation are all forms of psychotherapy that can help individuals with schizophrenia manage their symptoms and improve their daily functioning. These therapies do not directly target neurotransmitter levels, but they can help to reduce stress, improve communication and social interactions, and increase self-esteem, all of which may have an indirect effect on neurotransmitter function.

Meditation practices such as Vipassana and yoga have also been studied as potential treatments for schizophrenia.

Vipassana is a self-observation-based meditation practice that aims to dissolve mental impurities, resulting in a balanced mind full of love and compassion. While there is limited research on the use of Vipassana in schizophrenia, some studies have shown that it may improve symptoms such as anxiety and depression.

Yoga, on the other hand, has been shown to improve schizophrenia symptoms and overall well-being in small studies. Mindfulness-based interventions have also been found to be useful as an adjunct in the treatment of serious mental illnesses, including schizophrenia. These practices focus on developing greater awareness and acceptance of thoughts and emotions, which may help individuals with schizophrenia to better manage their symptoms and improve their overall quality of life.

Small studies have suggested that yoga may help improve schizophrenia symptoms Both yoga and mindfulness interventions appear to be useful as an adjunct in the treatment of serious mental illness. Studies have shown improvement in the psychopathology, anxiety, cognition, and functioning of patients with schizophrenia (Sathyanarayanan, Vengadavaradan, & Bharadwaj, 2019).

Currently, there are no studies showing how these treatments affects the neurotransmitters.

CONCLUSION

In summary, although our understanding of the causes and treatments of schizophrenia remains limited, several important paradigm shifts have occurred. The diagnosis of schizophrenia is still symptom-based, but increasing amounts of data point to the large genetic and environmental triggers, which alter various pathways in the brain that can be leveraged to achieve better patient outcomes. (Anissa Abi-Dargham, 2003)

Specifically, current treatments operate using the same mechanism, blockade of dopamine D2 receptors (Anissa Abi-Dargham, 2003)

Our literature review intrigued a very key question: Why do we see Noble Prize Winners, mathematicians, painters, and writers; diagnosed with Schizophrenia: a disease which shows retardation in day-to-day activity, however, what each and every case study of these people show is that their grey matter wasn't affected: an area where: a large number of neurons present, which allows it to process information and release new information through axon signaling found in the white matter. The authors even suggest that those 20% population have high creativity than the rest of patients with Schizophrenia.

The authors propose that 20% of patients with Schizophrenia don't show any cognitive deficits and urge American Psychiatric Association's DSM-V-TR to have separate symptoms and classifications for those who don't show any cognitive deficits. The authors even suggest having different treatments for those patients. The authors have attached a few key questions for future researchers.

Key Questions for future research-

1. Why did DSM-V-TR eliminate all subsections in the criteria for Schizophrenia, which were there in DSM-IV-TR Edition?
2. In clinical practice, we generally see approximately 30% of patients with Schizophrenia, whose IQ is not affected, however, for the rest 70% it does, there should be specific criteria of diagnosis for these patients.
3. In clinical practice, when a patient shows no cognitively affected symptoms, sometimes, a patient can manipulate the rest of the symptoms, border criteria should be found.
4. Do deficits within the potential limit of strategically controlling events to effectively. Encode them in episodic memory reflect the same mental or neural mechanisms as deficits in proactive manipulation (Barch & Ceaser, 2012)?
5. There are several examples of deficits in 'predictive' behavior in schizophrenia consisting of poor performance with clean tracking. Do these types of deficits also reflect altered "proactive" manipulative deficits, or do they reflect unique cognitive and neural mechanisms? Among at least a subset of cognitive impairments in schizophrenia, the cognitive mechanisms involved in proactive manipulation or DLPFC dysfunction? (Barch & Ceaser, 2012)
6. There should be different pathologies for different types and different symptoms.
7. The authors found that there should be an interesting study conducted on whether winter births [born or diagnosed in winter] may have any relation with higher levels of IQ.
8. How treatments like Vipassana and Yoga affect the neurotransmitters?
9. How Creativity can affect patients of Schizophrenia than the rest of the population?

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