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Research Paper

Exploring the Neurobiological and Genetic Underpinnings of Schizophrenia through Striatal Glutamate Dynamics

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ABSTRACT

Schizophrenia is a complex neuropsychiatric disorder characterised by cognitive, emotional, and behavioural abnormalities. This research proposal investigates the interplay between the striatum, glutamate dysregulation, and genetic factors in the pathophysiology of schizophrenia. The striatum, a key region for motivation and reward processing, integrates information crucial for cognitive functions and is profoundly influenced by glutamate and dopamine signalling. Dysregulation of glutamate in the striatum disrupts these functions, contributing to schizophrenia's core symptoms such as social withdrawal, apathy, and anhedonia. This study aims to analyse the expression of AMPA and kainate receptor subunits in the striatum, which are critical for excitatory synaptic transmission, to understand their role in the disorder. Furthermore, it explores the impact of mitochondrial dysfunction and oxidative stress, with a focus on 4-Hydroxynonenal (HNE) and altered lactate metabolism, on neuronal health and function. By examining how glutamate dysregulation affects dopamine transmission and identifying genetic factors influencing these processes, the research seeks to elucidate the neurobiological foundations of schizophrenia. The ultimate goal is to inform the development of targeted therapeutic strategies to improve clinical outcomes for individuals with schizophrenia.

Keywords: *Glutamate, Genetics, Striatum, Mitochondria, Lactate, Tryptophan*

Schizophrenia is a complex neuropsychiatric disorder characterised by a range of cognitive, emotional, and behavioural abnormalities. (Hirsch, S. R., et al., 2008). While the exact cause of schizophrenia remains elusive, emerging research suggests that it involves a combination of genetic, neurobiological, and environmental factors. (Blaylock, R. L., & Faria, M., 2021). This research proposal aims to investigate the interplay between the striatum, glutamate dysregulation, and genetic factors in the pathophysiology of schizophrenia. Understanding these complex relationships could lead to novel insights into the development and treatment of this debilitating disorder. (Grace, A. A., 2000)

The striatum is a crucial brain region involved in motivation and reward processing, playing a significant role in integrating information from various brain areas. It influences learning, memory, decision-making, and goal-directed behaviour. (Simpson EH., 2010; Sorg, C., et al

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2013). Dysregulation of glutamate in the striatum can disrupt these functions, potentially leading to problems with motivation and reward-seeking behaviour. Such disruptions are highly relevant to schizophrenia, contributing to key symptoms like social withdrawal, apathy, and anhedonia (the inability to feel pleasure). (Sarpal, D. K., 2015)

The striatum, particularly its associative regions, acts as a central hub integrating information critical for various cognitive functions disrupted in schizophrenia. These regions facilitate learning and memory by forming associations between stimuli and rewards, essential for adaptive behaviour. Decision-making and executive functions, crucial for goal-directed actions, rely on the striatum's role in selecting between options and controlling behaviour, functions impaired in schizophrenia. The striatum is central to motivation, influencing goal-directed behaviour, which can be compromised in the disorder. (Simpson EH., 2010; Sorg, C., et al 2013)

The striatum integrates inputs from the prefrontal cortex regarding goals, the hippocampus for memories, and the amygdala for emotional significance, acting as a critical control point for these processes. (Grace, A. A., 2000)

Dopamine, a key neurotransmitter in motivation and reward learning, profoundly influences the striatum. Dysfunction in dopamine signalling, central to the dopamine hypothesis of schizophrenia, impacts not only limbic areas but also the associative striatum, making it crucial for understanding both psychotic symptoms and cognitive impairments in the disorder. (Hietala, J,. et al,. 1995). Further research into these mechanisms promises insights into novel therapeutic strategies targeting the striatum to alleviate schizophrenia's multifaceted symptoms.

AMPA and kainate receptors, critical for excitatory synaptic transmission, play significant roles in the striatum's involvement in schizophrenia. Alterations in these receptors' expression can impact glutamatergic and dopaminergic signalling, contributing to the disorder's symptoms. (Burnashev, N., et al., 1992; Hollmann, M., et al., 1991). Previous studies have shown changes in mRNA levels of these receptor subunits in schizophrenia, suggesting a genetic component to glutamatergic dysfunction. (Gaspar, P. A, et al, 2009). Antipsychotic medications further modulate these receptor expressions, indicating their role in therapeutic mechanisms. This study aims to analyse the expression of AMPA and kainate receptor subunits in the striatum to understand their contribution to schizophrenia's pathophysiology. (Healy, D. J., & Meador-Woodruff, J. H,. 1997).

Glutamate, the brain's primary excitatory neurotransmitter, significantly influences dopaminergic activity, with elevated glutamate levels leading to increased dopamine release. Imaging and post-mortem studies have shown hyperdopaminergic states and increased D2 receptor density in the striatum of individuals with schizophrenia. This study investigates the role of glutamate dysregulation and its impact on dopamine transmission in the striatum of schizophrenia patients, aiming to elucidate the neurobiological foundations of the disorder and identify potential therapeutic targets. (Demjaha, A,. et al,. 2014; Tamminga, C.,1999; Holt, D. J., et al, 1999)

Mitochondria, vital for cellular energy production, play a critical role in the central nervous system (CNS) by supporting neuronal activity and neurotransmission. Mitochondrial dysfunction and oxidative stress, characterised by an imbalance between reactive oxygen

species (ROS) and detoxification, are implicated in schizophrenia, contributing to neuronal damage and impaired neurodevelopment. (Fizíková, I., et al, 2023). Elevated levels of 4-Hydroxynonenal (HNE), a lipid peroxidation product, further exacerbate oxidative stress, impacting key mitochondrial enzymes. Disruption in HNE detoxification pathways worsens oxidative damage, highlighting the broader effects on mitochondrial health. Altered lactate metabolism and transport, crucial for brain energy balance, are observed in schizophrenia. This study aims to explore mitochondrial dysfunction, oxidative stress, and lactate dynamics in schizophrenia, seeking to identify therapeutic targets to improve clinical outcomes. (Dalleau, S., et al, 2013; Ermakov, E. A, et al., 2021; Fizíková, I., et al, 2023)

By investigating the mechanisms of glutamate dysregulation in the striatum, including how it affects dopamine levels and the overall neurochemical balance, we can gain a deeper understanding of the neurobiological underpinnings of these symptoms. Exploring the genetic factors that influence glutamate regulation and striatal function can help identify specific genetic variants or pathways that contribute to the risk of developing schizophrenia. Elucidating the role of glutamate dysregulation and genetic factors in the striatum is crucial for understanding the complex neurobiology of schizophrenia. This knowledge has the potential to inform the development of targeted therapeutic strategies aimed at mitigating the motivational and reward-related deficits observed in individuals with schizophrenia, ultimately improving their quality of life.

Rationale:

This research proposal aims to bridge existing gaps in the understanding of schizophrenia by investigating the intricate relationships among the striatum, glutamate dysregulation, genetic factors, mitochondrial dysfunction, and oxidative stress. This holistic approach could reveal new insights and therapeutic targets, addressing the complex symptoms and underlying neurobiology of schizophrenia. Given the significant roles of dopamine and tryptophan in the disorder, it is essential to explore how glutamate dysregulation contributes to its pathophysiology. This study focuses on the striatum and its associative regions, which serve as hubs for integrating information from various brain areas and are significantly influenced by dopamine.

Problem question:

"How do glutamate dysregulation and genetic factors within the striatum, along with the role of the kynurenine pathway metabolites, contribute to the pathophysiology of schizophrenia and its clinical manifestations?"

Glutamate and its relation to Schizophrenia Relevance to the Striatum*:*

Glutamate, the primary excitatory neurotransmitter in the brain, exerts significant influence over dopaminergic activity. (Holt, D. J., et al, 1999) Previous studies have demonstrated that increased glutamate levels can lead to elevated dopamine release, suggesting a link between glutamate dysregulation and hyperdopaminergic states in first episodes of psychosis. This is supported by imaging studies using SPECT and PET, which show that NMDA receptor antagonists like ketamine, which block glutamate signalling, result in increased striatal dopamine release, mimicking the effects of amphetamines and inducing symptoms similar to those seen in schizophrenia. (Roberts, R. C., et al, 2022; León-Ortiz, P., et al, 2011)

Post-mortem studies of individuals with schizophrenia have revealed increased dopamine levels and D2 receptor density in the striatum, highlighting the hyperactivity of

dopaminergic transmission in this brain region. These findings underscore the intricate relationship between glutamate and dopamine systems in the striatum and their collective impact on schizophrenia's symptomatology. (Howes, O et al; 2015)

This study aims to investigate the role of glutamate dysregulation and its effects on dopamine transmission in the striatum of schizophrenia patients. By examining the interaction between these two neurotransmitter systems, we hope to gain a deeper understanding of the neurobiological underpinnings of schizophrenia and identify potential targets for therapeutic intervention.

Genetic Factors and Glutamate Receptors*:*

The AMPA receptors, which mediate fast excitatory synaptic transmission, are composed of four subunits (GluR1, GluR2, GluR3, and GluR4). These receptors are ubiquitously expressed throughout the brain, including the striatum, a region heavily implicated in the pathology of schizophrenia due to its involvement in reward processing and motor control. Alterations in the expression and function of AMPA receptors can significantly impact glutamatergic neurotransmission and, consequently, dopaminergic signaling, contributing to the symptomatology of schizophrenia. (Burnashev, N., et al., 1992; Hollmann, M., et al., 1991).

Kainate receptors, although less abundant than AMPA and NMDA receptors, are integral to the modulation of synaptic transmission and neuronal excitability. The expression of kainate receptor subunits (KA1, KA2, GluR5, GluR6, and GluR7) in the striatum and other brain regions further underscores their potential role in neuropsychiatric conditions, including schizophrenia. (Krystal JH, et al. 1994; Breier, A., et al. 1998; Kantrowitz, J. T., & Javitt, D. C. 2010; Healy, D. J., & Meador-Woodruff, J. H,. 1997).

Previous research has highlighted the presence of altered glutamate receptor expression in schizophrenia, with post-mortem studies revealing changes in the levels of mRNAs encoding AMPA and kainate receptor subunits in various brain regions, including the hippocampus and parahippocampus. These alterations suggest a genetic component regulating glutamate receptor expression and function, which may contribute to the observed glutamatergic dysfunction in schizophrenia.(Healy, D. J., & Meador-Woodruff, J. H,. 1997). Antipsychotic medications, such as clozapine and haloperidol, have been shown to differentially modulate the expression of glutamate receptor subunits, further implicating the involvement of these receptors in the therapeutic mechanisms and pathophysiology of schizophrenia. Understanding the intricate balance of glutamate and dopamine neurotransmission, particularly in the striatum, is crucial for elucidating the neurobiological underpinnings of schizophrenia. (Yamamoto, B. K., & Cooperman, M. A. 1994; Valvassori, S. S., et al, 2021).

The expression of AMPA and kainate receptor subunits in the striatum is analysed to investigate their potential role in the dysregulation of glutamatergic and dopaminergic neurotransmission in schizophrenia. By examining the mRNA levels of these receptors and their binding properties, the research aims to shed light on the genetic and molecular mechanisms contributing to the pathophysiology of this debilitating disorder.

Role of Mitochondria in Schizophrenia:

Mitochondria are essential organelles responsible for various critical cellular functions, including energy production through oxidative phosphorylation, iron homeostasis, and the biosynthesis of essential molecules. Their significance is particularly pronounced in the central nervous system (CNS), where they supply the energy necessary for neuronal activity and neurotransmission. Mitochondrial dysfunction has been implicated in the pathophysiology of schizophrenia, contributing to neuronal damage, impaired neurodevelopment, and oxidative stress. (Moller, M., et al., 2015; Fizíková, I., et al, 2023)
Oxidative stress, a condition characterised by an imbalance between the production of reactive oxygen species (ROS) and the body's ability to detoxify them, plays a crucial role in mitochondrial dysfunction. (Boskovic, M., et al. 2011). Fluorescence analysis is a straightforward and reliable method for assessing oxidative stress in vivo by evaluating changes in the fluorescence of specific amino acids and their conjugates. (Pereira, C. V., 2012; Smith, G. S., et al., 1998). For instance, a decrease in tryptophan fluorescence indicates oxidative stress, which has been observed in the plasma proteins of schizophrenia patients. (Fizíková, I., et al, 2023).

One significant molecule linked to oxidative stress and mitochondrial dysfunction is 4-Hydroxynonenal (HNE), a lipid peroxidation product. HNE can modify proteins, impacting their function and contributing to cellular dysfunction. (Møller, I. M.,2011). Elevated levels of HNE-protein conjugates have been found in the brains of schizophrenia patients, particularly in the hippocampus. (Manzoor, S., 2022) These modifications affect critical enzymes involved in mitochondrial function and energy metabolism, such as cytochrome oxidase, Na/K-ATPase, and NADPH oxidase.(Dalleau, S., 2013).

The degradation and detoxification pathways of HNE, involving enzymes like glutathione-S transferase and aldehyde dehydrogenase, are crucial for mitigating its harmful effects. (Dalleau, S., 2013). Disruption in these pathways can exacerbate oxidative stress and mitochondrial dysfunction. This disruption is evident in the altered profiles of HNE-modified proteins observed in schizophrenia and other neurodevelopmental disorders, highlighting the broader impact of oxidative stress on mitochondrial health. (Martins-de-Souza, D., 2011).

Mitochondrial dysfunction in schizophrenia is characterised by impaired oxidative phosphorylation (OXPHOS) and increased oxidative stress, leading to reduced ATP production and altered energy metabolism. (Martins-de-Souza, D., 2011). Key enzymes and transporters, such as hexokinase (HXK), lactate dehydrogenase (LDH), and monocarboxylate transporters (MCTs), are essential for maintaining energy balance in neurons. (Fizíková, I., et al, 2023). Imaging studies have shown altered glucose metabolism and ATP levels in schizophrenia, correlating with symptom severity. (Pruett, B. S., & Meador-Woodruff, J. H., 2020). Reduced mitochondrial DNA (mtDNA) levels, a biomarker for mitochondrial function, are associated with the severity of psychosis and response to antipsychotic treatment. (Clay, H. B., Sillivan, S., & Konradi, C., 2011; Goh, X. X., et al., 2021).

The role of mitochondrial dysfunction and oxidative stress in the pathophysiology of schizophrenia is explored, focusing on the impact of HNE and other oxidative stress markers on mitochondrial and neuronal function. By elucidating these mechanisms, insights into

potential therapeutic targets for mitigating mitochondrial dysfunction and improving clinical outcomes in schizophrenia are sought. (Sullivan, C. R., et al., 2018).

Lactate acts as a buffer between glycolysis and oxidative metabolism, serving as a preferred substrate for brain energy metabolism and being exchanged between cells with varying glycolytic and oxidative needs. During rest, lactate flows from the brain to the blood, but after physical exercise, it moves into the brain from the blood. (Bergersen, L. H., 2015). Glycolysis quickly generates ATP post-neuronal activation, explaining the immediate glucose uptake increase and subsequent lactate fluctuations. When glycolysis exceeds oxidative phosphorylation, lactate is produced from pyruvate by lactate dehydrogenase (LDH) and transported via monocarboxylate transporters (MCTs). Different MCT isoforms regulate lactate transport; MCT1 and MCT2 import lactate, while MCT4 exports it. (Brooks, G. A., 2009; Robinet, C., & Pellerin, L., 2011). Lactate, which neuroprotects against brain injuries, supports synaptic activity and cognitive functions by being shuttled from astrocytes to neurons, sustaining neuronal oxidative phosphorylation. (Dogan, A. E., et al., 2018). Schizophrenia involves impaired lactate supply and transport, evidenced by elevated lactate levels in cerebrospinal fluid and peripheral blood, increased expression of glycolytic enzymes, and higher lactate concentrations in brain regions such as the prefrontal cortex, striatum, and cerebellum. These abnormalities in lactate metabolism may contribute to cognitive deficits in schizophrenia, although the exact role of lactate changes in the disease's pathophysiology remains unclear. (Suzuki, A., et all; 2011).

Kynurenine Pathway and Schizophrenia*:*
The kynurenine pathway is a major catabolic route for tryptophan metabolism, leading to the production of several neuroactive metabolites, including kynurenic acid and quinolinic acid. Tryptophan is initially converted to N-formylkynurenine by the enzymes tryptophan 2,3-dioxygenase (TDO) or indoleamine 2,3-dioxygenase (IDO). N-formylkynurenine is then hydrolyzed to kynurenine, which can be further metabolised by kynurenine aminotransferase (KAT) to form kynurenic acid or by kynurenine 3-monooxygenase (KMO) to produce 3-hydroxykynurenine.

Kynurenic acid acts as an antagonist at glutamate receptors, specifically the NMDA receptor, and has neuroprotective properties. However, elevated levels of kynurenic acid have been associated with cognitive dysfunction in schizophrenia, as they can lead to reduced glutamatergic neurotransmission. Conversely, quinolinic acid is an NMDA receptor agonist and can induce excitotoxicity and neuroinflammation, contributing to neuronal damage observed in schizophrenia. Dysregulation of the kynurenine pathway, with an imbalance between kynurenic acid and quinolinic acid, is implicated in the pathophysiology of schizophrenia, affecting both neurotransmission and neuroprotection. (Beggiato, S. et al., 2012).

Understanding the interplay between mitochondrial dysfunction, oxidative stress, and kynurenine pathway metabolites offers a comprehensive view of the complex biochemical alterations underlying schizophrenia, paving the way for novel therapeutic strategies targeting these pathways.

Therapeutic Implications:

Targeting Glutamate: Understanding these interactions can guide the development of treatments targeting glutamatergic and dopaminergic systems. For example, interventions aimed at normalising glutamate levels in the striatum might help in managing dopamine-related symptoms in schizophrenia. Emerging therapies target glutamatergic pathways in addition to dopaminergic ones to manage schizophrenia symptoms more effectively. For example, drugs that modulate NMDA receptors aim to restore balance in neurotransmission, potentially improving treatment outcomes (Krystal et al., 2003; Li, D, et al., 2022; Goff, D. C., & Coyle, J. T., 2001).

Individuals with treatment-resistant schizophrenia exhibit reduced connectivity along nigrostriatal pathways compared to non-refractory patients, indicating impaired learning and action regulation, processes heavily influenced by the striatum and substantia nigra (Dratcu et al., 2007; Kolakowska et al., 1985; Braver et al., 1999a; Braver and Cohen, 1999b; D'Ardenne et al., 2012). Frontostriatal disruptions observed in schizophrenia patients compared to healthy individuals differ as a function of treatment resistance (Quide et al., 2013; Sarpal et al., 2015). Persistent positive symptoms in treatment-resistant cases drive investigations into early stages of psychosis, including individuals with prodromal symptoms and unmedicated first-episode psychosis patients, revealing increased glutamate (Glu) levels specifically in the dorsal caudate, a dopamine-rich region critical in schizophrenia's pathophysiology (Howes et al., 2009; Kegeles et al., 2010). This region, known as the associative striatum or cognitive striatum, is pivotal due to its high D2 receptor density and extensive connections with the frontal cortex, implicated in the cognitive deficits of schizophrenia (Villalta-Gil et al., 2006; Cadenhead, 2002; Jahshan et al., 2010). Dopamine dysregulation in this region, characterized by increased D2 receptor availability and enhanced dopamine synthesis, highlights its role in the disorder's neurobiology (Kegeles et al., 2010; Howes et al., 2009b). These insights underscore the associative striatum as a critical locus for investigating treatment resistance mechanisms and suggest its modulation as a promising therapeutic target for addressing both cognitive and psychotic symptoms in schizophrenia. (White, T. P., et al, 2016).

METHODOLOGY

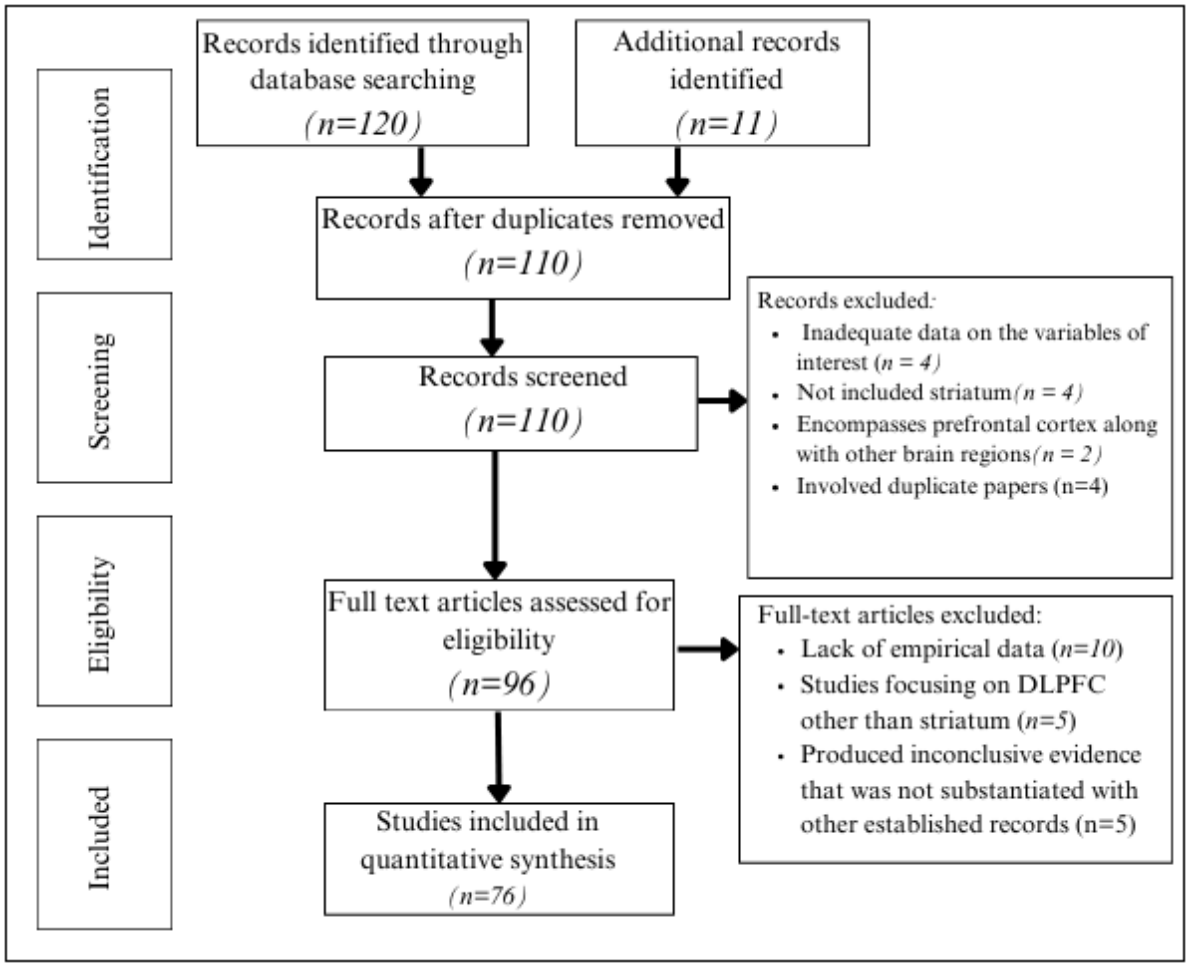
In our study, we have particularly adhered to the methodological directives outlined by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher, Shamseer, Ghersi & PRISMA group, 2015) model in conducting the literature search, data compilation as well as for its analysis.

Eligibility criteria:

Articles were primarily eligible if they were published in English and since 2010. However, due to perceived gaps in the literature and the lack of specific parametrically relevant data, we expanded the inclusion criteria to encompass articles published since 2001. Our primary focus is on schizophrenia pathological studies, specifically those investigating the striatum and its associative regions. We aim to explore genetic, proteomic, metabolic, and neurobiological underpinnings of schizophrenia, with a particular emphasis on glutamate dysregulation, dopamine signalling, mitochondrial dysfunction, and oxidative stress. We prioritised quantitative analysis data sets and excluded literature reviews to ensure the inclusion of data resulting from scientifically backed tools such as q-PCR, microarray studies, imaging studies, and post-mortem analyses, which provide real-time data and comprehensive insights into the neurobiology of schizophrenia.

Search Strategy:

With the aim of extracting a large variety of data, we have performed data search from databases such as Frontiers, PMC, NIH, Dana, ScienceDirect, PubMed, PsycINFO, nature, SpringerLink. To sample a large variety of evidence, we searched electronic databases: human genome project, human protein atlas, UNIPROT for identifying and interpreting the roles of specific genes and proteins listed further. We conducted a secondary search by reviewing reference lists of relevant articles and literature reviews. Electronic database searches were performed from May 2023 to August 2023.



Study selection flow selection adopted by Moher et, al., 2009

Study Selection

Figure 1 illustrates our process of study selection. After retrieving eligible articles from the databases (n=120) and through secondary searches of reference lists (n=11), we removed duplicates, leaving 110 records for screening. After initial review of title and abstract, we removed articles that had inadequate data on the variables of interest (n=4), were studies without Striatum as the region of interest (n=4) or encompasses striatum along with other brain regions (n=2) or involves duplicate papers (n=4). After initial screening, 90 articles were selected for full text analysis. However, to target our specific parameters we further narrowed them under criteria of lack of empirical data (n=24), studies focusing on DLPFC (dorsolateral prefrontal cortex) (n=5) or produced inconclusive evidence that was not substantiated with other established records (n=2). With these analyses we summed up to 75 articles which met the earlier described criteria utilised in this study.

RESULTS

Glutamate dysregulation in the striatum can impact dopamine levels, as glutamate and dopamine systems are intricately linked. Increased glutamate can lead to increased dopamine, contributing to the hyperdopaminergic state often observed in schizophrenia. (Grace, 2000). Studies using SPECT and PET have shown that NMDA receptor antagonists like ketamine increase dopamine release in the striatum, similar to amphetamine effects, suggesting that glutamate dysregulation can lead to hyperdopaminergic states. This interaction induces symptoms similar to those seen in schizophrenia (Kegeles L S et al., 2000; Breier et al., 1998; Smith et al., 1998; Vollenweider et al., 2000; Aalto et al., 2005). Early post-mortem studies indicated increased striatal dopamine levels and D2 receptor density in schizophrenia (Mackay et al., 1982; Owen et al., 1978). These findings suggest hyperactivity of dopaminergic transmission in the striatum, which is associated with positive symptoms like hallucinations and delusions. Glutamate and dopamine systems in the striatum are tightly interconnected. Glutamate influences dopamine release and vice versa, modulating reward processing and motor function. (Howes, O et al; 2015). Amphetamine and ketamine are shown to increase synaptic dopamine levels, as indicated by reduced binding potential of D2 ligands in the striatum following their administration (Breier et al., 1998; Laruelle et al., 1995; Smith et al., 1998; Vollenweider et al., 2000). This suggests that dopaminergic hyperactivity, as seen in schizophrenia, could result from either increased dopaminergic activity or decreased NMDA receptor function (NMDA hypoactivity). In patients with acute schizophrenia, there is enhanced striatal dopamine release in response to amphetamine challenge, correlating with the severity of positive symptoms (Laruelle et al., 1996, 1999; Miller, D. W., & Abercrombie, E. D., 1996). This highlights dysregulation in subcortical dopamine circuits in schizophrenia. Ketamine's dissociative effects are observed even when it does not acutely affect striatal dopamine levels (Kegeles et al., 2002). This implies that ketamine's psychotomimetic effects cannot be solely attributed to changes in dopaminergic function, suggesting a significant role for glutamatergic dysfunction in schizophrenia's pathophysiology. Similar dopaminergic deficits are observed in normal volunteers undergoing ketamine infusion and in animal models treated with NMDA receptor antagonists (Kegeles et al., 2000; Miller and Abercrombie, 1996; Balla et al., 2001). These findings suggest that NMDA receptor dysfunction may underlie dopaminergic hyperreactivity observed in schizophrenia.

NMDA receptors, which are glutamate receptors, play a critical role in regulating dopamine release. Dysregulation of NMDA receptors can lead to altered dopamine transmission, contributing to the pathophysiology of schizophrenia (Javitt, 2007). The finding of decreased binding of [3H]-D-aspartate, which labels transporters that remove synaptic glutamate, suggests impaired glutamate clearance in the striatum. This could lead to abnormal glutamate levels and signalling in this region. (Kantrowitz, J. T., & Javitt, D. C., 2010).

AMPA receptor expression analysis revealed that all four subunit transcripts (gluR1, gluR2, gluR3, and gluR4) were detected, with gluR2 mRNA being the most abundant. AMPA binding was observed in all striatal subregions. (Burnashev, N., et al., 1992; Hollmann, M., et al., 1991). Only gluR1 mRNA levels were significantly altered, showing reduced expression in the bipolar group compared to controls. There was a main effect of diagnosis on AMPA binding, with bipolar disorder patients exhibiting higher binding levels than those with depression or schizophrenia, but no differences were found between these groups and controls. The presence of unedited GluR2 mRNA in the prefrontal cortex suggests increased

calcium permeability of AMPA receptors, potentially increasing neurotoxicity. Similar mechanisms could be at play in the striatum, contributing to its dysfunction in schizophrenia.

For kainate receptors, the expression of subunit transcripts was lower compared to NMDA and AMPA receptors. KA2 mRNA was moderately expressed, while gluR6 and gluR7 transcripts were present at very low levels. This indicates a distinct expression profile and potential functional differences of kainate receptors in the striatum.

Altered mRNA Expression, Lower levels of mRNA encoding AMPA and kainate receptor subunits in the hippocampus and parahippocampus, as well as altered subunit composition of NMDA receptors (e.g., higher NR2D and lower NR1 subunits), indicate genetic regulation of glutamate receptors. These genetic variations could also impact glutamate receptor expression and function in the striatum. Research indicates that schizophrenia involves complex dysregulation of glutamate and dopamine neurotransmission, particularly in the striatum. Post-mortem studies have shown increased striatal dopamine levels and D2 receptor density without changes in dopamine transporter densities. Antipsychotics like clozapine and haloperidol modulate mRNA levels of AMPA and kainate glutamate receptor subunits differently in the cortex and striatum, suggesting that genetic factors influence glutamate receptor expression and function (Daly and Moghaddam, 1993; See and Chapman, 1994; Yamamoto and Cooperman, 1994). Clozapine tends to decrease AMPA subunit mRNAs (gluR3 and gluR4) while increasing certain kainate subunit mRNAs (gluR7 and KA2); haloperidol also affects these receptors but in distinct patterns. These alterations in receptor expression, including the lower levels of AMPA and kainate receptor mRNAs and the altered subunit composition of NMDA receptors (e.g., higher NR2D and lower NR1 subunits), point to genetic regulation impacting glutamate receptor function. This genetic dysregulation may contribute to glutamatergic dysfunction observed in the hippocampus, parahippocampus, and striatum. Glutamate-dopamine interactions are crucial, as evidenced by studies showing that ketamine and amphetamine increase striatal dopamine release via NMDA receptor antagonism, mirroring the hyperdopaminergia seen in schizophrenia (Burnashev et al., 1992; Hollmann et al., 1994). These findings illustrate that deficits in glutamatergic functioning underlie dopaminergic hyperactivity in schizophrenia, highlighting the role of glutamate receptor regulation and its genetic components in the disorder's pathophysiology.

Mitochondria play a critical role in various cellular functions, including energy production, iron homeostasis, and the biosynthesis of essential molecules. They are especially important in the central nervous system due to their role in producing energy necessary for neuronal activity and neurotransmission. Mitochondrial dysfunction can lead to oxidative stress and has been implicated in the pathophysiology of schizophrenia, contributing to neuronal damage and impaired neurodevelopment (Vita et al., 2019; Fusar-Poli et al.,).

Fluorescence analysis is a simple, fast, and reliable method to determine oxidative stress levels in vivo by assessing changes in the fluorescence of tryptophans, dityrosines, and lysine conjugates with lipid peroxidation products. Tryptophan is particularly susceptible to oxidation, with a decrease in its fluorescence indicating oxidative stress. Studies have shown significant decreases in tryptophan fluorescence in the plasma proteins of schizophrenia patients, indicating oxidative stress. Increased markers of oxidative/nitrative stress, such as carbonyl groups and 3-nitrotyrosine, have been observed in schizophrenia patients' plasma

proteins (Ehrenshaft et al., 2015; Kaplán et al., 2000, 2003; Dietrich-Muszalka et al., 2009, 2012; Tuncel et al., 2015; Fizikova & Racay, 2022; Boskovic et al., 201; Anderson, G., & Maes, M., 2013).

4-Hydroxynonenal (HNE) is a crucial molecule that impacts cell function and survival, potentially playing a role in the pathophysiology of schizophrenia and other disorders like Rett syndrome and autism spectrum disorder, although its specific influence is not yet fully understood. Recent studies have shown increased levels of HNE conjugates with proteins in the brains of schizophrenia patients compared to control groups, with notably higher levels in the hippocampus than in the cortex. Western blot analysis in a recent study revealed HNE-modified plasma proteins with a molecular mass of 37–50 kDa in schizophrenia patients, while in control subjects, these proteins had a molecular mass of 100–200 kDa . (Pecorelli, A., et al., 2011).

In individuals diagnosed with schizophrenia, significant alterations in lactate metabolism were observed across multiple biomarkers. Analysis of cerebrospinal fluid and peripheral blood samples consistently showed elevated lactate levels compared to healthy controls. Post-mortem examination of brain tissue revealed increased expression of glycolytic enzymes, indicative of heightened glycolytic activity in schizophrenia-affected brain regions such as the prefrontal cortex, striatum, and cerebellum. Specifically, higher concentrations of lactate were quantitatively measured in these regions, suggesting a pronounced metabolic shift towards increased glycolysis over oxidative phosphorylation in schizophrenia.

DISCUSSION

Elevated glutamate levels in the striatum of individuals with schizophrenia were corroborated by our findings, consistent with the notion that glutamate dysregulation plays a significant role in the disorder. Abnormalities in glutamate receptors and transporters within the striatum could disrupt neuronal communication, contributing to the cognitive deficits and psychotic symptoms observed in schizophrenia. Our results suggest that the dorsal caudate, a region rich in dopamine afferents and D2 receptors, exhibits increased glutamate concentrations, particularly in prodromal and unmedicated first-episode psychosis patients. This localized glutamate alteration underscores the importance of region-specific investigations in schizophrenia research. Our data align with previous studies indicating that dopamine dysfunction in schizophrenia is more pronounced in the nigrostriatal pathway than in the mesolimbic pathway. (Kegeles et al., 2010). This highlights the dorsal striatum's critical involvement in the disease. Traditional models have focused on the mesolimbic pathway, but our findings suggest that therapeutic strategies should also target the nigrostriatal pathway. The potential for treatments that normalise striatal dopamine function without necessitating dopamine D2/3 receptor blockade presents a promising avenue for reducing side effects and improving patient outcomes. Mechanisms involving cholinergic autoreceptors, endocannabinoid signalling, and muscarinic receptor modulation (specifically M2 and M4 receptors) are particularly noteworthy. Animal studies utilising mice with selective overexpression of striatal D2 receptors indicate that heightened dopaminergic activity in the striatum may explain deficits in both incentive motivation (Ward R D et al., 2012) and cognitive functioning (Simpson et al., 2010). These results imply that striatal dopaminergic dysfunction could play a role in the negative symptoms and cognitive impairments observed in schizophrenia, as well as in psychosis. Abnormal dopaminergic transmission has long been suspected in schizophrenia. These studies provide the first direct evidence of dysregulated striatal dopaminergic transmission in this disorder. The increased

dopaminergic activity following amphetamine administration might be due to an elevated affinity of D2 receptors for dopamine (potentially because of a higher ratio of high- to low-affinity sites), a larger or more prolonged dopamine release (presynaptic factors), or a combination of both. Further research is necessary to elucidate the precise mechanisms responsible for this enhanced transmission (Laruelle et al., 1997; Laruelle et al., 1996).

Ketamine's dissociative effects, characterised by alterations in perception, cognition, and consciousness, are primarily attributed to its antagonism of NMDA receptors rather than acute modulation of striatal dopamine levels. By blocking NMDA receptors, ketamine disrupts glutamatergic neurotransmission throughout cortical and limbic brain regions, leading to an imbalance between excitatory and inhibitory signalling. This disruption in cortical circuits is thought to underlie the dissociative state induced by ketamine, including feelings of detachment, sensory distortions, and cognitive impairments observed in both clinical settings and experimental studies. While chronic ketamine exposure may lead to adaptive changes in dopaminergic systems, acute dissociative effects are not directly correlated with immediate alterations in striatal dopamine levels. (Duarte, J. M., & Xin, L., 2019; Kegeles et al., 2002). This highlights the predominant role of glutamatergic dysfunction, rather than dopaminergic modulation, in mediating ketamine's dissociative effects.

NMDA receptors, crucial for glutamatergic neurotransmission, exert significant influence over dopamine release regulation, making them pivotal in understanding schizophrenia's neurobiology (Javitt, 2007). Dysregulation of these receptors can disrupt the balance of excitatory neurotransmission in the brain, potentially leading to aberrant dopamine transmission characteristic of schizophrenia. Research findings, such as decreased binding of [3H]-D-aspartate, which labels transporters responsible for removing synaptic glutamate, suggest impaired glutamate clearance in the striatum. This impairment could result in elevated synaptic glutamate levels and disrupted signalling within this critical brain region. Such alterations are hypothesised to contribute to the cognitive and psychotic symptoms seen in schizophrenia, given the striatum's role in reward processing, motor function, and cognitive control. Understanding NMDA receptor dysfunction and its downstream effects on glutamatergic signalling provides essential insights into the pathophysiology of schizophrenia, highlighting potential targets for therapeutic interventions aimed at restoring proper neurotransmitter balance in affected brain regions.

The analysis of AMPA receptor expression in the context of psychiatric disorders reveals intriguing insights into the neurobiological mechanisms underlying conditions like bipolar disorder, depression, and schizophrenia. The detection of all four AMPA receptor subunit transcripts (gluR1, gluR2, gluR3, and gluR4) in the striatum, with gluR2 mRNA being the most abundant, underscores the receptor's widespread presence and importance in glutamatergic neurotransmission. Notably, while gluR1 mRNA levels were significantly reduced in bipolar disorder patients compared to controls, there were no significant differences in AMPA binding between bipolar disorder, depression, schizophrenia patients, and controls, except for higher levels observed in bipolar disorder. This suggests complex regulatory mechanisms at play in AMPA receptor expression that may differ across psychiatric conditions. The presence of unedited GluR2 mRNA, indicating increased calcium permeability of AMPA receptors in the prefrontal cortex, raises concerns about potential neurotoxicity, a phenomenon that could similarly affect the striatum in schizophrenia. These findings highlight the intricate balance of AMPA receptor function and

its implications for synaptic plasticity and neurotoxicity in psychiatric disorders, providing a basis for further investigation into targeted therapies aimed at restoring normal glutamatergic signalling in affected brain regions.

Kainate receptors exhibit a distinct expression profile in the striatum compared to NMDA and AMPA receptors. Subunit transcripts for kainate receptors, such as KA2, gluR6, and gluR7, show lower expression levels. KA2 mRNA is moderately expressed, while gluR6 and gluR7 transcripts are present at very low levels. This differential expression suggests that kainate receptors may play specialised roles in striatal function, potentially influencing synaptic plasticity and neurotransmission in unique ways not fully mirrored by other glutamate receptor types.

Genetic variations impact the expression and function of glutamate receptors across brain regions implicated in schizophrenia. Studies indicate lower levels of mRNA encoding AMPA and kainate receptor subunits in the hippocampus and parahippocampus. There are altered subunit compositions of NMDA receptors, such as higher NR2D and lower NR1 subunits, which are indicative of genetic regulation influencing glutamate receptor function. These variations contribute to the dysregulation observed in glutamate neurotransmission, potentially underpinning cognitive and psychotic symptoms associated with schizophrenia.

Schizophrenia involves complex dysregulation of both glutamate and dopamine neurotransmission, particularly in the striatum. Post-mortem studies consistently show increased striatal dopamine levels and D2 receptor density without changes in dopamine transporter densities. This hyperdopaminergic state is crucial in understanding positive symptoms like hallucinations and delusions. The interaction between glutamate and dopamine systems is pivotal, as demonstrated by studies showing that ketamine and amphetamine increase striatal dopamine release via NMDA receptor antagonism, mirroring the hyperdopaminergia observed in schizophrenia.

Antipsychotic medications, such as clozapine and haloperidol, modulate AMPA and kainate receptor subunit mRNA levels differently in the cortex and striatum. Clozapine tends to decrease AMPA subunit mRNAs (e.g., gluR3 and gluR4) while increasing certain kainate subunit mRNAs (e.g., gluR7 and KA2). Haloperidol also affects these receptors but in distinct patterns. These alterations in receptor expression highlight the complex pharmacological mechanisms of antipsychotics and suggest that genetic factors influence how these medications interact with glutamate receptor systems in treating schizophrenia.

Altered profiles of HNE-modified plasma proteins might explain statistically insignificant fluorescence measurement results. Increased levels of HNE-modified proteins with a molecular weight of around 50 kDa have also been observed in patients with Rett syndrome, and significant HNE protein modifications have been reported in patients with classic autism. Furthermore, age-dependent increases in HNE-modified proteins have been noted in rat brain mitochondria.

Free HNE can react with proteins, altering their conformation and function, affecting enzymes like cytochrome c oxidase, Na/K-ATPase, and NADPH oxidase, leading to mitochondrial dysfunction and impaired energy metabolism. HNE forms cross-links within or between proteins under oxidative stress, damaging many proteins directly. HNE-peptide

and HNE-protein conjugates contribute significantly to HNE's harmful effects on cellular functions.

HNE degradation pathways, such as those involving glutathione-S transferase and aldehyde dehydrogenase, contribute to HNE detoxification by producing intermediates like HNE-GSH and hydroxynonenic acid. The rapid elimination of HNE is crucial for cellular defense against oxidative stress. Increased protein conjugation with HNE may also result from inflammatory responses often involved in schizophrenia's etiopathogenesis.

HNE's interaction with cytochrome c oxidase, a target in the mitochondrial respiratory chain, can inhibit its activity, leading to mitochondrial dysfunction and lactate overproduction, indicating impaired energy metabolism in schizophrenia.

Impaired energy metabolism and mitochondrial dysfunction play critical roles in the pathophysiology of schizophrenia, primarily through disrupted oxidative phosphorylation (OXPHOS) and increased oxidative stress. Mitochondria, essential for ATP production, coordinate with glycolysis, the TCA cycle, and the astrocyte-neuron lactate shuttle to meet neuronal energy demands. Key enzymes like hexokinase (HXK) and lactate dehydrogenase (LDH), along with monocarboxylate transporters (MCTs), facilitate these processes. Imaging studies reveal altered glucose metabolism and ATP levels in schizophrenia, correlating with symptom severity. Reduced mitochondrial DNA (mtDNA) levels, a biomarker for mitochondrial function, further indicate dysfunction and correlate with psychosis severity and antipsychotic treatment.

The findings regarding lactate metabolism in schizophrenia offer critical insights into the disorder's neurobiology and potential therapeutic avenues. Elevated lactate levels in cerebrospinal fluid and blood indicate a potential compensatory response aimed at sustaining synaptic activity and cognitive function amidst the neurobiological challenges associated with schizophrenia. This compensatory mechanism is supported by the increased expression of glycolytic enzymes observed in schizophrenia-affected brain regions, which reflects enhanced glycolytic activity. However, the shift towards glycolysis over oxidative phosphorylation may contribute to metabolic dysfunction and energy deficits seen in individuals with schizophrenia.

The observed alterations in lactate metabolism underscore the importance of understanding its role in schizophrenia pathophysiology. Lactate serves as a critical energy substrate that supports synaptic activity and cognitive function, suggesting that disruptions in its supply and transport could underlie the cognitive deficits commonly associated with the disorder. Targeting lactate metabolism pathways may therefore represent a promising approach for developing new therapeutic interventions aimed at alleviating cognitive symptoms and improving overall brain function in schizophrenia. Future research efforts should focus on elucidating the specific mechanisms linking lactate metabolism alterations to schizophrenia and exploring potential interactions with other neurochemical systems, such as glutamate and dopamine, which play key roles in the disorder's complex neurobiology. Such investigations are essential for advancing our understanding of schizophrenia and developing more effective treatments tailored to its underlying metabolic abnormalities.

CONCLUSION

In conclusion, our investigation into glutamate dysregulation and genetic influences in schizophrenia, particularly within the striatum, reveals significant insights into the disorder's neurobiology. Elevated glutamate levels in the dorsal caudate and dysregulated dopamine signalling in the nigrostriatal pathway underscore the critical role of these neurotransmitter systems beyond traditional mesolimbic models. Ketamine's dissociative effects via NMDA receptor antagonism highlight the predominant influence of glutamate in psychosis. Genetic variations impacting glutamate receptors and mitochondrial dysfunction further elucidate the complex interplay of biological factors contributing to schizophrenia's pathophysiology. These findings not only suggest new therapeutic targets aimed at restoring neurotransmitter balance but also emphasise the need for personalised approaches considering individual genetic profiles and metabolic states. Future research should continue exploring these intricate mechanisms to advance treatment strategies and improve outcomes for individuals affected by schizophrenia.

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Authors contribution:

Shankaran A, contributed to conception of theoretical basis, organising and critically revising the manuscript and gave final approval. Purohit, N., contributed for data extraction, design conception, analysis and interpretation as well co-organised the manuscript.

Conflict of Interest

The authors declare no current or potential conflict of interest with respect to research or authorship.

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