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Research Paper

Genes-Protein-Metabolite Networks in Schizophrenia: A Systems Biology Perspective

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ABSTRACT

Schizophrenia is a complex mental disorder characterized by disturbances in thinking, perception, emotions, and behaviour. This study aims to delve into the fundamental abnormalities found in the genetic, proteomic, and metabolic processes, specifically within the dorsolateral region of the prefrontal cortex (DLPFC). Our focus is on understanding how these abnormalities contribute to the manifestation of dysfunction in schizophrenia and providing potential insights into therapeutic targets. The DLPFC plays a crucial role in essential cognitive functions such as task switching, interference prevention, inhibition, planning, and working memory. By examining proteins, metabolites, and genetic components, our objective is to unravel the metabolic pathways and establish connections between these different elements. We aim to identify patterns that contribute to both functional (executive functioning) and behavioural (delusions and hallucinations) dysregulations unique to schizophrenia. Our investigations have revealed dysregulations in gene expression, chromatin remodelling, particularly in the DLPFC. This suggests disruptions in normal gene regulation mechanisms, abnormal protein expression and signalling pathways, shedding light on the molecular mechanisms involved and identifying potential biomarker proteins associated with schizophrenia. This emphasises the significance of interventions related to cytoskeleton, oligodendrocytes, and energy metabolism for diagnosis and targeted treatments. Through transcriptome analyses, we have discovered unique gene expression patterns in schizophrenia, revealing molecular subtypes, metabolic dysregulation, changes in metabolic gene expression, energy metabolism, and imbalances in neurotransmitters, which shed light on the influence of genetic variations on cognition and provide insights into the disorder's molecular mechanisms. With our study, we also propose further investigation into the dysregulations involved in schizophrenia's complex pathophysiology, which is necessary to uncover new markers or therapeutic targets, leading to advancements in research and treatment of the disorder.

Keywords: *Schizophrenia, DLPFC, Pathophysiology*

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Schizophrenia is a persistent mental disorder marked by a range of symptoms, including positive aspects like delusions, hallucinations, disorganized speech, and behavior, as well as negative features such as reduced emotional expression, avolition, alogia, and anhedonia. Cognitively, the condition involves cognitive deficits and plays a vital role in consolidating information and exercising higher-level regulation, as indicated by the symptoms and acknowledged in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). The dorsolateral prefrontal cortex (DLPFC), a key node within the working memory network, holds a crucial role in integrating information and exerting top-down control. (5th ed.; DSM-5; American Psychiatric Association, 2013).

The DLPFC boasts complex layers that aid in upholding, encoding, and retrieving information, thus standing as a pivotal hub for various working memory processes. A noteworthy study accentuates the role of layer 3 in the DLPFC, underlining its importance in working memory function and its connection with local circuitry during delay periods. In individuals grappling with schizophrenia, there are noticeable reductions in Somal volume, dendritic arbors, and spine volume within the DLPFC, hampering effective working memory. (Guo, J. Y., et al. ,2019).

The phenomena of hallucinations and delusions are emblematic symptoms of schizophrenia. These symptoms are intrinsically tied to the DLPFC's capacity to differentiate actual experiences from internal ones and to orchestrate purposeful actions. However, these compensatory mechanisms often falter in sensory systems. Cortical thinning in the DLPFC, particularly among those experiencing auditory verbal hallucinations (AVH), highlights its role in influencing perception and attention (Lawrie et al, 2002). The initial instances of AVH are associated with diminished DLPFC volume, which affects day-to-day functionality.

The intricate nature of schizophrenia emerges from its diverse symptomatic and functional expressions (Lee et al, 2006). Genetic factors significantly shape the prevalence, likelihood of inheritance, and symptom manifestation. Deviations in genetic expression, stemming from mutations, reduced expression, or irregularities in transcription and translation, contribute to the disorder's development. Interventions encompass both pharmaceutical and behavioral methods, alongside novel approaches, aiming to optimize treatment outcomes and thwart hereditary transmission. (Salleh, M. R., 2004).

At a molecular level, proteins and metabolites play pivotal roles in cellular and tissue functions in schizophrenia (Martins-de-Souza et al, 2009). Disruptions in these processes lead to metabolic imbalances and functional disturbances, often serving as biomarkers for disease detection and progression tracking. Insight into the disease's underlying mechanisms assists in personalized medical strategies tailored to individual profiles. Grasping the molecular mechanisms involving proteins and metabolites is fundamental for comprehending the intricate networks and signaling pathways that underlie schizophrenia (Sullivan, C., et al 2018).

Within the context of schizophrenia, the disruption in glutamate balance sets off a chain reaction of intricate neural effects and observable symptoms (Konradi & Heckers, 2003). Glutamate, a key neurotransmitter responsible for exciting neural activity, plays a central role in a variety of critical neurophysiological processes, including the transmission of signals between neurons and the plasticity of their connections (Stone et al., 2007). In the

realm of schizophrenia, disturbances in the equilibrium of glutamate give rise to a series of crucial impacts:

1. **Disruption of Neural Communication:** Glutamate, acting as a principal mediator in communication between neurons, maintains the intricate equilibrium of neural transmission. When glutamate regulation falters, it leads to irregular signal propagation among neurons. This significantly contributes to the cognitive, emotional, and perceptual anomalies that are characteristic of schizophrenia (Plitman et al., 2016) (Benesh et al., 2022).
2. **Cognitive Impairment:** The complex role of glutamate in shaping synaptic plasticity—facilitating the brain's adaptation and learning—comes to the forefront. The dysregulation of glutamate transmission impairs the brain's adaptive response, affecting cognitive domains such as working memory, attention, and cognitive flexibility—key components of the cognitive deficits seen in schizophrenia. (Vallée, 2022)
3. **Unveiling Positive Symptoms:** An excess of glutamate signalling, particularly concerning the N-methyl-D-aspartate (NMDA) receptor complex, emerges as a notable trigger for positive symptoms like hallucinations and delusions. This heightened glutamate activity distorts perceptions and fosters unconventional cognitive constructs, thus substantiating the genesis of these symptomatic manifestations. (Stone et al., 2007) (Plitman et al., 2016)
4. **Initiating Negative Symptoms:** Conversely, a reduction in glutamate function, especially within specific receptor domains, plays a significant role in the emergence of negative symptoms, including emotional blunting, avolition, and anhedonia. Such disturbances amplify reduced neural responsiveness and compromise emotional processing. (Monaco et al., 2016)
5. **Pathways Toward Neurodegeneration:** Prolonged disruption in glutamate equilibrium triggers the phenomenon known as excitotoxicity—a process marked by glutamate-induced neuronal degeneration. This cascade of neurodegeneration underscores the potential exacerbation of schizophrenia's trajectory, ultimately culminating in intensified cognitive and functional decline. (Potkin et al., 2020)
6. **Examining DLPFC Impairment:** Extensive documentation highlights the involvement of the dorsolateral prefrontal cortex (DLPFC) in schizophrenia, intricately intertwined with glutamate regulation. Alterations in glutamate dynamics critically affect the DLPFC's ability to integrate information, oversee cognitive processes, and sustain working memory capacities. (Benesh et al., 2022; Konradi & Heckers, 2003; Stone et al., 2007)
7. **Implications for Therapeutic Strategies:** The deeper understanding of how glutamate dysregulation affects schizophrenia provides avenues for targeted interventions. Researchers are actively exploring pharmacotherapeutic agents that modulate glutamatergic receptors, particularly those related to NMDA receptors, as potential approaches to mitigate cognitive deficits and a broader range of symptomatic expressions. (Benesh et al., 2022; Lin & Lane, 2019; Stone et al., 2007).

The complexities arising from glutamate dysregulation in the context of schizophrenia lead to a diverse range of intricate neural effects and cognitive deviations. These effects reverberate through neural transmission, cognitive processes, symptomatic manifestations, and the critical neural circuits like the DLPFC. This collective body of evidence underscores the central role of glutamate dysregulation within the intricate fabric of schizophrenia's pathophysiology (Uno, Y., Coyle, J. T., 2019).

The glutamate hypothesis spotlights the significance of glutamate, a principal excitatory neurotransmitter with ionotropic and metabotropic receptors, including NMDA and AMPA receptors. The TCA cycle's role in energy generation and glutamate regulation is crucial. Interactions between the TCA cycle and ornithine cycle contribute to glutamate release. Imbalances in synaptic glutamate concentration, due to dysregulated transporters and receptors in the DLPFC, are linked to schizophrenia. (Vicente-Sánchez et al, 2013).

The ionotropic receptors consist of NMDA, AMPA and kainite receptors. The NMDAR comprises 2 subunits, GLUN1, and GLUN2 and GLUN3 integrated together. The expression of GLUN1 is via the GRIN1 gene whereas the GLUN2A-D and GLUN3A-B by the GRIN3A-B gene. (Peng, L et al, 1993).

Out of these GLUN2 subunits bind to glutamate for adjusting ion channel activation.
The role of the TCA cycle is essential in this aspect due to its extensive role in energy production, glucose metabolism and most importantly glutamate regulation. TCA cycle AKA Kreb cycle or citric acid cycle is a 3-step process in which cells break down metabolites such as glucose to produce energy. In this cycle the step that involves the conversion of alpha ketoglutarate to succinyl coA consists of a sub step which results in the production of glutamate this is caused due to another cycle called ornithine cycle which is arginine urea cycle where the production fumarate as a by-product of arginino succinate acts as a crucial metabolite for the TCA cycle henceforth from fumarate until the production of alpha ketoglutarate the excess of transamination occurs which results in the deliberate release of glutamate. This process is backed by multiple proteins and its underlying genetic factors as well. Peng, L et al 1993).

With these theoretical underpinnings we raise the question regarding the target specific approach and understanding from an in-depth genetic and proteomic background. The literature review suggests an intermediate understanding of the above and thus; our study embarks on a comprehensive exploration of proteomic and genetic factors influencing glutamate dysregulation in DLPFC nerve cells. We delve into the complex molecular and genetic foundations, harnessing the pivotal role of the TCA cycle in glutamate metabolism. This exploration aims to illuminate the genetic and protein elements that play a part in the dysregulation of glutamate associated with schizophrenia (Martins-de-Souza, et al 2009).

METHOD

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

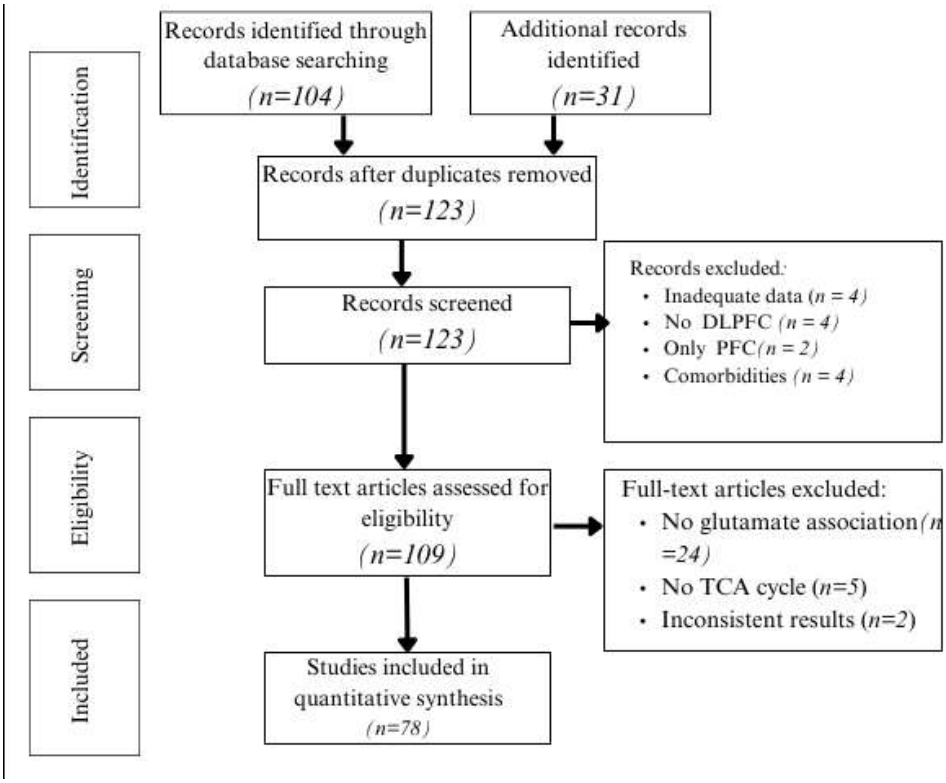
Articles were primarily eligible if they were published in English and have been published since 2010. However, through the course of the literature search we perceived the gap in literature or the lack thereof of specific parametrically relevant data. Hence, to broaden the search, we agreed to the inclusion of articles published since 2001 as well.

Through the course of data extraction, we have focused on schizophrenia pathological studies with a particular focus on the dorsolateral prefrontal cortex (DLPFC).
In terms of pathology, we aimed at genetic, proteomic and metabolic underpinnings for the substantiation of schizophrenia.

We have considered quantitative analysis data sets and excluded literature reviews with the intention of securing data resulting from scientifically backed tools such as q-PCR, microarray studies, that allow for real-time data analysis.

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=104) and through secondary searches of reference lists (n=31), we removed duplicates, leaving 123 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 DLPFC as the region of interest (n=4) or encompassed broadly the prefrontal cortex (n=2) or involved schizophrenia comorbid with other neuropsychological disorders (n=4). After initial screening, 109 articles were selected for full text analysis. However, to target our specific parameters we further narrowed them under criteria of absence of glutamate association (n=24), absence of connection with the TCA cycle (n=5) or produced inconclusive evidence that were not substantiated with other established records (n=2). With these analyses we summed up to 78 articles which met the earlier described criteria utilised in this study.

Data Extraction

After compiling the final list of articles for the study, we analysed the data for the criteria used. We organised the data in accordance to categories of genes, proteins and metabolites. Further, these categories were analysed according to study design, measurement of expression, findings, strengths and implications to the TCA cycle and glutamate dysregulation. The main variables for our data extraction included schizophrenia, DLPFC, glutamate hypothesis and dysregulation, bioenergetic models. After a comprehensive study involving critical and comparative studies for all our data sets, we compiled the information into a simple format as illustrated in the diagram/image 1.

Risk of Bias

To critically appraise the articles, we used Joanna Briggs Institute critical appraisal tools, which include specific criteria that increase the reliability and validity of a research study. Among the criteria that we selected included the DLPFC particularly focusing on the glutamate production and dysregulation in the TCA cycle. There was a valid and reliable measurement of exposure variable (schizophrenia) and appropriate control of the outcome variable, valid and reliable measurement of the exposure variable (genes and proteins), and the usage of the proper statistics. Out of all the studies we have marked, the criteria are met or not met, applicable or not applicable. The study considered relevant genes that fulfilled the established criteria. One of the genes, namely SERPINI1, didn't satisfy the criteria due to an insufficient proportion of glutamic content. Additionally, the research lacked supporting evidence regarding the interaction between this gene and glutamate. Future investigations could involve integrating this gene into the criteria used. The extent to which each criterion was fulfilled or unfulfilled contributes to the overall significance of the findings.

RESULTS

Glutamate is an excitatory neurotransmitter which plays a role in learning and memory. Following are certain specific proteins and genes that may be responsible for causing the excitotoxicity of glutamate in schizophrenia. Alpha ketoglutarate is a ketone derivative of glutaric acid, which stimulates protein synthesis. (Uno, Y., & Coyle, J. T. (2019).

EAAT (excitatory amino acid transmitters), are a major class of glutamate transporters and are responsible for reuptake of glutamate. EAATs have 5 membrane bound transporters, out of which EAAT1 and EAAT2 are predominantly expressed in Glial cells, and EAAT3 and EAAT5 are expressed in neurons. EAAT1 is a major transporter whereas, EAAT2 is accountable for transporting over 90% of glutamate into basic synaptic components known as synaptosomes (Kristiansen, L. V. et al 2006, Intson, K. et al 2022).

SLC1A2 is the gene that expresses EAAT2 which has an association to L and D aspartate and L glutamate which are responsible for the clearance of glutamate in the extracellular space. However, as established by Cherlyn et al, EAAT2 is overly expressed in a schizophrenic DLPFC. This results in its failure to mediate the overaccumulation of the negative charges by L aspartate (Cherlyn, et al., 2010).

This data suggests 2 possibilities for glutamate dysregulation:

1) due to dysregulated negative charge by aspartate accumulation, its further progression into the TCA cycle is disrupted which may result in misdirected exchange between glutamate and Alpha-ketoglutarate.
2) or due to overexpression of EAAT2, the transportation of Glutamate is hindered. This occurs due to the glutamic dehydrogenase being high in DLPFC, GDH

(glutamate dehydrogenase) increased, and GS (glutamate synthetase) reduced. In glial cells the glutamate is either converted to alpha ketoglutarate and enters the Krebs cycle or it is converted to glutamine-by-glutamine synthetase. When there is dysregulation in the conversion this results in the excitotoxicity and neuronal death as there will be no cleanse of glutamine.

G-protein signalling subtype 4 or RGS4 is a gene with diminished expression in the DLPFC of schizophrenia patients relative to controls, prompting an investigation into the possible connection between this reduced expression to glutamate dysregulation. RGS4 the gene expression Profiling reveals alteration of specific metabolic genes it is a GTPase activating protein it is present abundantly in DLPFC where it regulates GPCR (gene protein coupled receptors); it has been established that, if it is low in the layer 3 or 5 of DLPFC, will lead to hypo functionality of NMDA there will be glutamic abnormalities in schizophrenia (Prasad, K. M. R., et al 2005, Glausier, J. R., & Lewis, D. A., 2018).

Reductions in hexokinase (HXK) and phosphofructokinase (PFK) activity, along with diminished PFK1 mRNA expression, were observed in DLPFC. Moreover, the study identified neuron-specific abnormalities in glucose utilisation, evidenced by altered expressions of HXK1, PFK1, glucose transporter 1 (GLUT1), GLUT3, and an increase in monocarboxylate transporter 1 mRNA in pyramidal neurons. HXK1 codes protein complex with EAAT's, the function is to remove the glutamate from the presynaptic space and maintain the low levels in synaptic cleft. This ATP and NADH can influence the TCA cycle by providing necessary energy and reducing equivalents. When there is deficiency in GLUT1 it impairs the glucose entry and increases the glutamine, aspartate, alanine, glutamate and GABA neurotransmitters and receptors. Diminished PFK1 mRNA expression can lead to decreased activity of phosphofructokinase-1 enzyme, which is a key regulatory step in glycolysis. This could further impact the availability of pyruvate for entry into the TCA cycle. (Shan, D., et al., 2014).

HINT1, a GTPase activating protein, is reduced in the DLPFC of male individuals with schizophrenia. The reduction is localised to specific layers, with a decrease observed in layer VI. The process of GPCR and NMDA association requires HINT1 and CNR1 (cannabinoid gene), without this association, glutamate exchange with the alpha-ketoglutarate is downregulated causing hypo functionality of NMDAR. (Vicente-Sánchez, A., et al 2013)

MDH1 or malate dehydrogenase is a protein whose role is particularly crucial in the conversion of malate to oxaloacetate. This step is important for replenishing the cycle with oxaloacetate, which is needed to combine with incoming acetyl-CoA and continue the cycle. Alterations in the expression of MDH1 could potentially disrupt this step, affecting the overall flow of the TCA cycle and the production of energy-rich molecules such as NADH and FADH2. The changes observed in MDH1 expression in the DLPFC of individuals with schizophrenia, suggest that disruptions in this enzyme's activity may contribute to metabolic alterations within brain cells. Disruptions in MDH1 expression could affect the replenishment of oxaloacetate, disrupting the TCA cycle's flow and the production of energy-rich molecules like NADH (Vawter, M. P., et al 2004).

The relationship between NMDA receptors, including the subunits GRIN1 and GRIN2A, and an increased risk of developing schizophrenia. The microRNA, miR-296 is a microRNA that interacts with the 3'-UTR (3′ untranslated regions, messenger for RNA) sequences of both Grin2A and Grin2B subunits of NMDARs. This interaction may contribute to the

downregulation of the GluN2B subunit, which has implications for the abnormal NMDAR function observed in schizophrenia. (Liang, W., et al 2022, Panja, D., et al 2021)

miR-936 is a microRNA that interacts with TMOD2 which are the subunits of AMPA, miR-936 inhibits the AMPA synaptic activity, and increases the excitability of glutamate in layer 2-6 in DLPFC which results in excessive concentration of glutamate in schizophrenia
SERPINI1, microarray results have reported both increased and decreased mRNA expression in the DLPFC. As there was a gap in literature, we were not able to link this gene anywhere near TCA cycle or to glutamate, but this gene plays a vital role in the DLPFC of schizophrenia (Hu, Z., et al 2019, Gunasekaran, S., et al 2022)

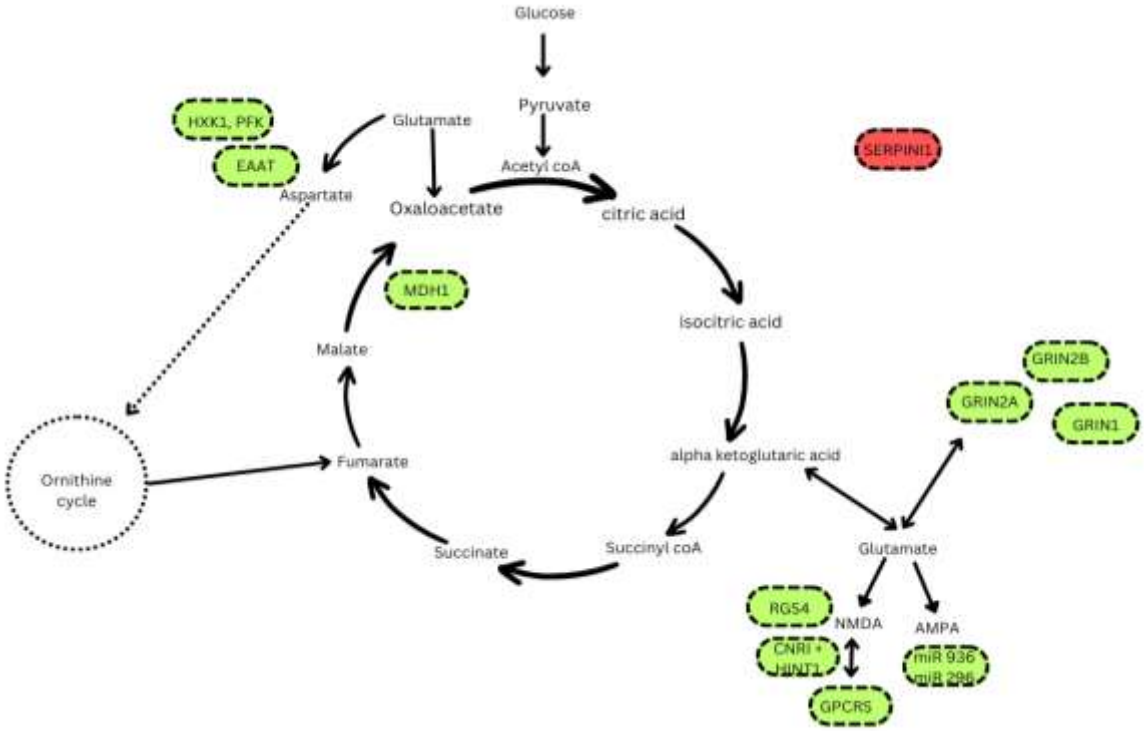


Image 1: Shows the interaction of the specific genes and proteins responsible for the glutamate dysregulation mapped into the Tricarboxylic acid cycle (TCA). The image shows the interaction of HXK1, PFK1 and EAAT2 at the glutamate production and clearing site that acts as a precursor for fumarate formation. Schizophrenia studies show under expression HXK1 and PFK1, while EAAT2 shows overexpression. Next, MDH1 acts to oxidise malate and produce oxaloacetate in the TCA cycle, schizophrenia studies show under expression of this gene. Further, at the alpha ketoglutarate exchange point, NMDA receptors are regulated by the gene RGS4 and protein HINT1 interacting with GPCRs. In schizophrenia, both of these shows diminished expression. miRNA 936 and miRNA 296 work in accordance with the GRIN1, GRIN2A and GRIN2B genes to support glutamate transport. Schizophrenia pathological studies show under expression of these genes.

The Tricarboxylic Acid (TCA) cycle, also referred to as the citric acid cycle or Krebs cycle, is a fundamental biological process involved in the oxidation of glucose. It commences after glucose is converted into pyruvate, which subsequently undergoes conversion into acetyl CoA. This acetyl CoA enters the Krebs cycle, initiating with it the synthesis of citric acid in the first step. The citric acid then undergoes isomerization to form isocitrate via isocitric acid.

During this process, a carbon dioxide molecule is liberated. Isocitrate, through a sequence of oxidation reactions, transforms into alpha-ketoglutarate. The interaction between alpha-ketoglutarate and glutamate, although potentially problematic due to receptor interactions such as AMPA or NMDA receptors, leads to the perturbation of the cycle caused by excessive glutamate accumulation. (Bubber, P., et al., 2011).

The generation of aspartate occurs through the interaction of oxaloacetate and glutamate. This event not only contributes to the ornithine cycle, a component of the urea cycle responsible for detoxifying ammonia, but also participates in the production of fumarate. In instances where the elimination of excess glutamate from the extracellular space is impaired, disruptions in the normal functioning of these processes can occur. (Psomiades, M., et al., 2018).

After the release of a carbon dioxide molecule, alpha ketoglutarate undergoes further oxidation, resulting in the formation of succinyl CoA. Enzymatic conversion of succinyl CoA yields succinate, which in turn undergoes oxidation to generate fumarate. Hydration of fumarate produces malate, culminating in the oxidation of malate to regenerate oxaloacetate, thus completing the cycle. The under expression of the MDH gene causing reduction in this process can lead to perturbations in the cycle's functionality. (Vawter, M. P., et al 2004).

With each full revolution of the cycle, oxaloacetate is regenerated, and two molecules of carbon dioxide are produced. The ornithine cycle, or urea cycle, operates in conjunction with the TCA cycle to detoxify ammonia. This process entails the conversion of ammonia and carbon dioxide into carbamoyl phosphate. The subsequent reaction with ornithine forms citrulline, which, upon interaction with aspartate, generates arginosuccinate and releases fumarate as a byproduct. Fumarate then enters the citric acid cycle, a pivotal metabolic pathway that harnesses energy through oxidative metabolism. (Peng, L., et al 1993, Mason, G. F., et al 1995)

DISCUSSION

Schizophrenia is a multifaceted disorder, whose symptomatology varies widely. For such a broadly and intensively manifested system of symptoms, a multifaceted approach is necessary. In our study, we have taken a pathological (genetic, proteomic, metabolic) approach that would provide a better understanding on the scientific causal front as well as a better target-oriented intervention. For such a goal, we have considered the glutamate hypothesis with the tricarboxylic acid cycle or the Krebs cycle as the basis. This vast bioenergetic cycle is necessary as it performs the following roles:

1. Cellular Upkeep and Biomolecule Formation as cells require constant maintenance and produce a range of essential biomolecules. These substances, including lipids, carbohydrates, proteins, and nucleic acids, play critical roles in various cellular functions, structure, and growth.
2. Primary ATP Generation Pathway as it is the major process for generating energy within cells is cellular respiration, which unfolds in several stages within mitochondria. These stages comprise glycolysis, the citric acid cycle, and the electron transport chain. These steps work together to create ATP, the cell's primary energy currency.
3. Amino Acids in Protein Construction which are fundamental building blocks for proteins. Cells perform protein synthesis, a process that combines amino acids according to the genetic instructions provided by mRNA. This results in the formation of proteins that serve essential roles in cell function and structure.

4. Nucleic Acids (NA) and Genetic Information such as DNA and RNA, are crucial for storing and transmitting genetic data. DNA replication guarantees accurate inheritance, while transcription converts DNA instructions into RNA messages for further cellular processes.
5. Purine (adenine and guanine) and Pyrimidine (cytosine, thymine, and uracil) Synthesis which are essential components of nucleic acids. These nitrogenous bases are produced through specific enzymatic reactions using amino acid precursors, contributing to genetic material formation.

Further, with this theoretical basis, the following implications were observed from our research data that allow us to visualise the significance of the previously described genes and proteins for the glutamate dysregulation in schizophrenia.

EAAT2, along with HXK1 and PFK1, plays a vital role in preserving synaptic specificity. Additionally, EAAT2 contributes to the recycling of glutamate, thus preventing its excitotoxic impact on cognitive functions. EAAT is misdirected into the exchange of glutamate to the aspartate hence there is an overexpression of glutamate in the cleft. These functions encompass not only working memory and executive functions but also extend to perceptual processes and the mediation of both positive symptoms such as negative symptoms in the dorsolateral prefrontal cortex (DLPFC). The presence of HXK1 is significant due to its capability to facilitate the conversion of glucose metabolites into phosphorylated forms, indicating its involvement in glycolysis. Due to the reduced expression of HXK1, which encodes for EAAT, the process of clearing glutamate is impaired. This further emphasises its importance in maintaining the overall health of nerve cells.

MDH is responsible for shuttling NADH energy from malate to oxaloacetate, by catalysing the breakdown of alpha keto acids using the NADH energy which facilitates the exchange of glutamate with alpha ketoglutarate. It also allows to maintain and regulate the glutamate balance. When there is an alteration in the expression of MDH, it replenishes the oxaloacetate and disturbs the TCA cycle.

Alpha ketoglutaric acid and its exchange with glutamate is facilitated in cellular level by its receptors i.e., NMDA and AMPA, in terms of NMDA receptors 2 proteins i.e. HINT1 and GPCR as well as gene RGS4 are shown to mediate glutamate uptake for these receptors. The Under expression of RGS4 gene causes the dysregulation of glutamate in the DLPFC which results in hypofrontality. The involvement of RGS4 in conjunction with NMDAR is closely linked to functions such as attention control, working memory planning, and organisation. These functions are interconnected with the occurrence of executive dysfunction, a cognitive impairment frequently observed in individuals with schizophrenia.

In terms of AMPA receptors 2 genes i.e., miR 936 and miR 296. The miR 936 gene strengthens the excitatory glutamatergic synapses by inhibiting TMOD2 gene expression however due to its excessive concentration in DLPFC miR 936 inhibits the AMPA receptors, as seen in schizophrenia there is a reduction in glutamatergic excitatory synapses. This can be one of the reasons for hypo frontality and reduced cognitive control or impairment as manifested in the cognitive impairment symptoms of schizophrenia.

The miR 296 gene exhibits interactions with GRIN1, GRIN2A, and GRIN2B within the dorsolateral prefrontal cortex (DLPFC). Notably, increased expression of GRIN1 is

observed in layers 3 and 5 of the DLPFC among individuals with schizophrenia. This observation is substantiated by the research conducted by Hu, Z., et al (2019) and Gunasekaran, S., et al (2022) where they explain the distinct refinement of circuitry in Layer 3 over the course of an individual's lifespan that may suggest a neurodevelopmental component in the context of schizophrenia. This alteration in circuitry potentially contributes to impairments in working memory and the coordination of neural activity. The genes mentioned above most likely play a significant role in these phenomena.

This study opens the potential for creating specific pharmaceutical interventions aimed at tackling problems linked to imbalances in glutamate levels and the related metabolic pathways. These interventions could encompass targeted approaches such as correcting genes by utilising gene therapy (techniques that involve the addition or replacement of a defective gene, e.g.: CRISPR-cas9), or regulating gene activation in combination with medications designed to accurately target and repair the metabolic pathways that are influenced by disruptions in glutamate equilibrium. Additionally, distinctive methods such as implementing the ketogenic diet could also contribute to the process of reconfiguring the specific protein emphasised in our research.

Our research aims to highlight the importance of tailoring pharmacological and clinical approaches to neurodegenerative disorders like schizophrenia based on specific regions (Wang, Y., et al 2023). This objective can be achieved by conducting thorough research using well-defined parameters. Moreover, these region-specific interventions could lead to the development of more precise therapeutic and neuropsychological treatments. These treatments would not only focus on the pathways targeted by drugs but also integrate a multi-faceted approach, incorporating various psycho-cognitive therapies.

In conclusion, we propose this parametrically developed study focusing on the glutamate hypothesis of schizophrenia specifically in the DLPFC region. Through this study we intend to illuminate on the potential impacts of genetic and proteomic foundations on this specific parameter and its implications on accurate drug targets as well as a potential direction in mitigating and managing schizophrenia functionality and symptomatology.

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Conflict of Interest

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

Authors contribution

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

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