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A Graph-Theoretical and MRS-Based Mathematical Model of Glutamatergic Dysfunction in Schizophrenia

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Abstract

In this study, the effects of glutamatergic dysfunction on the dopaminergic system in schizophrenia are investigated using a graph-theoretical framework integrated with magnetic resonance spectroscopy (MRS) data. The classical dopamine hypothesis associates positive symptoms with increased mesolimbic dopamine activity and negative as well as cognitive symptoms with reduced mesocortical dopamine transmission. However, this hypothesis alone does not fully explain the upstream mechanisms responsible for dopaminergic dysregulation. Consequently, the glutamate hypothesis has emerged as a complementary framework emphasizing NMDA receptor hypofunction and impaired GABAergic inhibition. The proposed model represents cortical pyramidal neurons, GABAergic interneurons, the ventral tegmental area, the nucleus accumbens, and the prefrontal cortex as nodes of a directed weighted graph. Furthermore, glutamate, GABA, and total N-acetylaspartate (tNAA) measurements reported in ultra-high-field 7 Tesla MRS studies are incorporated into the mathematical framework. Based on these biomarkers, a schizophrenia connectivity index is introduced to quantify excitatory-inhibitory imbalance and neuronal integrity loss simultaneously. The obtained results suggest that reductions in glutamate and tNAA levels may contribute substantially to network instability and functional dysregulation in schizophrenia.

Keywords

Schizophrenia, Glutamate, NMDA Receptor, GABA, Dopamine, Magnetic Resonance Spectroscopy, Graph Theory, Mathematical Modeling

1. Introduction

Schizophrenia is a complex neuropsychiatric disorder characterized by a broad spectrum of symptoms, including hallucinations, delusions, social withdrawal, motivational deficits, and cognitive impairments. These manifestations are commonly classified into three major domains: positive, negative, and cognitive symptoms.

According to the classical dopamine hypothesis, positive symptoms are associated with increased dopaminergic activity within the mesolimbic pathway, whereas negative and cognitive symptoms are related to reduced dopaminergic transmission within the mesocortical pathway [1]. Grace *et al.* further emphasized that this imbalance between the mesolimbic and mesocortical pathways plays a central role in the development of psychotic and cognitive symptoms [2]. Although this framework has significantly improved our understanding of schizophrenia, it does not fully explain the biological mechanisms underlying dopaminergic dysregulation.

Consequently, increasing attention has been directed toward the glutamate hypothesis of schizophrenia. Coyle first proposed that glutamatergic dysfunction represents one of the major neurobiological mechanisms underlying schizophrenia [3]. Javitt further suggested that hypofunction of N-methyl-D-aspartate (NMDA) receptors contributes to impaired cortical information processing and cognitive dysfunction [4]. Moghaddam and Krystal subsequently demonstrated that NMDA receptor hypofunction may impair the activity of GABAergic interneurons, thereby weakening cortical inhibition and disrupting glutamate-dopamine interactions [5].

N-acetylaspartate (NAA) is widely recognized as a marker of neuronal integrity and viability within the central nervous system [6]. Recent advances in proton magnetic resonance spectroscopy (^{1}H-MRS) have enabled the non-invasive quantification of neurochemical metabolites such as glutamate, glutamine, gamma-aminobutyric acid (GABA), and N-acetylaspartate (NAA) in the living human brain. Using ultra-high-field 7 Tesla MRS, Reid *et al.* [7] reported significantly lower glutamate and total NAA concentrations in the anterior cingulate cortex of individuals experiencing first-episode schizophrenia compared with healthy controls. These findings indicate that glutamatergic abnormalities may vary according to disease stage, medication status, and brain region. Alterations in NAA levels have also been consistently reported in schizophrenia, highlighting its importance as a neurochemical marker in proton magnetic resonance spectroscopy studies [8].

From a mathematical perspective, interactions among neurotransmitters and neuronal populations can be represented by weighted directed graphs, where vertices correspond to neuronal structures and edges describe excitatory or inhibitory influences. Graph-theoretical methods provide a powerful framework for analyzing complex biological networks and understanding how local abnormalities propagate through large-scale systems [9]. Consequently, graph-based approaches

offer a natural mathematical setting for studying glutamatergic dysfunction in schizophrenia.

More recently, Lopes *et al.* [10] conducted a comprehensive systematic review and quantitative synthesis of proton MRS studies investigating glutamate, glutamine, and Glx concentrations in schizophrenia spectrum disorders. Their meta-analysis included 92 independent studies comprising 2822 patients and 2721 healthy controls. The authors concluded that glutamatergic alterations are highly heterogeneous and depend on factors such as illness stage, treatment resistance, antipsychotic exposure, and neuroanatomical location.

Motivated by these observations, the aim of the present study is to develop a graph-theoretical model describing glutamate-mediated network dysfunction in schizophrenia and to integrate experimentally measured MRS biomarkers into this mathematical framework. It should be emphasized that the present work is intended as a conceptual proof-of-principle mathematical model rather than a validated predictive model. The proposed graph-theoretical framework is calibrated using published summary MRS measurements reported in the literature and is designed to illustrate how experimentally observed neurochemical alterations can be incorporated into a mathematical representation of glutamatergic dysfunction in schizophrenia. Consequently, the model should be regarded as a theoretical framework for hypothesis generation rather than as a clinically validated diagnostic or predictive tool.

2. Biological Background

Glutamate is the principal excitatory neurotransmitter of the central nervous system, whereas GABA serves as its primary inhibitory counterpart. Under physiological conditions, these neurotransmitter systems maintain a dynamic equilibrium:

$$\begin{aligned}\text{Glutamatergic excitation} &\rightarrow \text{NMDA receptor activation}\\ &\rightarrow \text{GABAergic interneuron activation}\\ &\rightarrow \text{Controlled inhibition.}\end{aligned}$$

In schizophrenia, NMDA receptor hypofunction is believed to reduce the activation of GABAergic interneurons, thereby weakening inhibitory control mechanisms:

$$\begin{aligned}\text{NMDA hypofunction} &\rightarrow \text{Reduced GABA ergicinhibition}\\ &\rightarrow \text{Glutamatergic dysregulation.}\end{aligned}$$

This imbalance may subsequently influence dopaminergic signaling through two distinct pathways. Increased mesolimbic dopamine activity is associated with positive symptoms, whereas decreased mesocortical dopamine transmission is linked to negative and cognitive symptoms.

3. Nodes of the Mathematical Model

Definition 1. Let

$$V = P, I, V_T, N, C$$

denote the set of nodes representing the glutamate-GABA-dopamine network in schizophrenia, where

P Cortical pyramidal glutamatergic neuron,

I GABAergic interneuron,

V_T Ventral tegmental area (VTA),

N Nucleus accumbens,

C Prefrontal cortex.

The notation V_T refers specifically to the ventral tegmental area, whereas V denotes the complete node set. This distinction avoids notational ambiguity throughout the mathematical formulation.

4. Graph-Theoretical Model

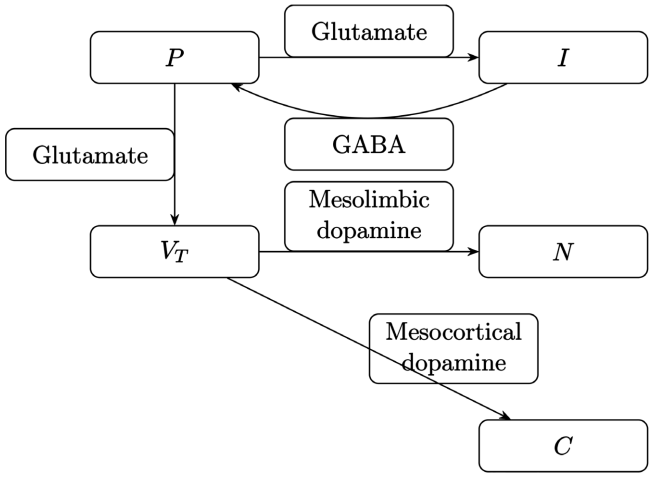

Figure 1. Graph-theoretical representation of glutamate-GABA-dopamine interactions in schizophrenia.

Figure 1 illustrates the proposed directed network structure. The edge $P \to I$ represents glutamatergic excitation of GABAergic interneurons, whereas $I \to P$ represents inhibitory feedback. The pathway $P \to V_T$ models the influence of cortical glutamatergic signaling on the ventral tegmental area. Finally, the edges $V_T \to N$ and $V_T \to C$ represent mesolimbic and mesocortical dopaminergic projections, respectively.

Definition 2. The directed weighted graph representing glutamatergic dysfunction in schizophrenia is defined by

$$\mathcal{G} = (V, E, W),$$

where V denotes the set of vertices, E denotes the set of directed edges, and $W : E \to \mathbb{R}$ is the corresponding weight function.

The directed interactions of the network are given by

$$P \to I, \quad I \to P, \quad P \to V_T, \quad V_T \to N, \quad V_T \to C.$$

These edges represent glutamatergic excitation, GABAergic inhibition, and do-

paminergic projections that collectively contribute to the pathophysiology of schizophrenia.

5. Weighted Adjacency Matrix

Assume that the vertices are ordered as $V = \{P, I, V_T, N, C\}$

The rows of the matrix represent source vertices, whereas the columns represent target vertices. Accordingly, the weighted adjacency matrix corresponding to the physiological condition is given by

$$A_N = \begin{pmatrix} 0 & g & h & 0 & 0 \\ -i & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & d_M & d_C \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

Here,

$$g > 0$$

denotes the glutamatergic excitation from the cortical pyramidal neuron to the GABAergic interneuron,

$$i > 0$$

represents the strength of GABAergic inhibition,

$$h > 0$$

denotes the influence of the cortical glutamatergic pathway on the ventral tegmental area,

$$d_M > 0$$

represents mesolimbic dopaminergic activity, and

$$d_C > 0$$

represents mesocortical dopaminergic activity. The negative sign indicates inhibitory influence, while $i > 0$ denotes its magnitude.

6. NMDA Hypofunction Parameter

The functional relationships introduced in this section are intentionally modeled as linear approximations. Such first-order parameterizations are commonly adopted in conceptual mathematical models when the precise nonlinear dependence between biological variables is unknown or cannot be estimated from available experimental data. The linear formulation provides a simple and interpretable framework for investigating how progressive reductions in NMDA receptor activity may influence inhibitory and dopaminergic pathways while preserving analytical tractability.

Definition 3. Let

$$\lambda \in [0,1]$$

denote the NMDA receptor activity parameter, where $\lambda = 1$ corresponds to nor-

mal NMDA receptor function and $\lambda = 0$ corresponds to complete loss of NMDA receptor activity.

In schizophrenia, NMDA receptor activity is assumed to be reduced. Therefore,

$$0 < \lambda < 1$$

is considered.

As NMDA receptor activity decreases, GABAergic inhibition is also weakened. Hence, the inhibitory weight is defined by

$$i(\lambda) = \lambda i_0,$$

where $i_0 > 0$ denotes the physiological inhibition level. This linear relationship reflects the assumption that reduced NMDA receptor activity proportionally weakens the activation of GABAergic interneurons, resulting in a gradual loss of inhibitory control. The influence of the cortical glutamatergic pathway on the ventral tegmental area is modeled as

$$h(\lambda) = h_0 + \gamma(1-\lambda),$$

where $h_0 > 0$ denotes the baseline glutamatergic influence and $\gamma > 0$ measures the increase induced by NMDA hypofunction. The increase in cortical influence on the ventral tegmental area is modeled linearly as a first-order approximation of the progressive network disinhibition associated with NMDA receptor hypofunction.

Similarly, mesolimbic dopaminergic activity is defined by

$$d_M(\lambda) = d_0 + \alpha(1-\lambda),$$

The linear increase in mesolimbic dopaminergic activity represents the widely accepted hypothesis that reduced NMDA receptor function contributes to dopaminergic hyperactivity associated with positive symptoms of schizophrenia. whereas mesocortical dopaminergic activity is defined by

$$d_C(\lambda) = c_0 - \beta(1-\lambda).$$

Conversely, the linear decrease in mesocortical dopaminergic activity reflects the reduced dopaminergic transmission that has been associated with negative and cognitive symptoms in schizophrenia. Assume that

$$d_0, c_0, \alpha, \beta > 0$$

and

$$c_0 > \beta.$$

Consequently, the weighted adjacency matrix associated with schizophrenia is

$$A_S(\lambda) = \begin{pmatrix} 0 & g & h_0 + \gamma(1-\lambda) & 0 & 0 \\ -\lambda i_0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & d_0 + \alpha(1-\lambda) & c_0 - \beta(1-\lambda) \\ 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 \end{pmatrix}.$$

7. Pathway Activity Functions

Definition 4. The mesolimbic pathway activity is defined by

$$M(\lambda) = d_M(\lambda) = d_0 + \alpha(1-\lambda).$$

Definition 5. The mesocortical pathway activity is defined by

$$K(\lambda) = d_C(\lambda) = c_0 - \beta(1-\lambda).$$

Definition 6. The dopaminergic imbalance index is defined as

$$S(\lambda) = \frac{M(\lambda)}{K(\lambda)}.$$

The quantity $S(\lambda)$ measures the ratio between mesolimbic and mesocortical dopaminergic activity. Larger values of $S(\lambda)$ indicate a stronger imbalance between the two dopaminergic pathways.

8. Fundamental Mathematical Results

Lemma 1. The function $M(\lambda)$ increases as λ decreases.

Proof. Since

$$M(\lambda) = d_0 + \alpha(1-\lambda),$$

we obtain

$$M'(\lambda) = -\alpha < 0.$$

Therefore, $M(\lambda)$ increases as λ decreases.

□

Lemma 2. The function $K(\lambda)$ decreases as λ decreases.

Proof. Since

$$K(\lambda) = c_0 - \beta(1-\lambda) = c_0 - \beta + \beta\lambda,$$

it follows that

$$K'(\lambda) = \beta > 0.$$

Hence, $K(\lambda)$ decreases as λ decreases.

□

Theorem 3. As NMDA receptor activity decreases, the dopaminergic imbalance index

$$S(\lambda) = \frac{M(\lambda)}{K(\lambda)}$$

increases.

Proof. Since

$$S(\lambda) = \frac{d_0 + \alpha(1-\lambda)}{c_0 - \beta(1-\lambda)},$$

we obtain

$$S'(\lambda)=\frac{M'(\lambda)K(\lambda)-M(\lambda)K'(\lambda)}{K(\lambda)^2}.$$

Using

$$M'(\lambda)=-\alpha,\quad K'(\lambda)=\beta,$$

we obtain

$$S'(\lambda)=\frac{-\alpha K(\lambda)-\beta M(\lambda)}{K(\lambda)^2}.$$

Since

$$M(\lambda)>0,\quad K(\lambda)>0,\quad \alpha>0,\quad \beta>0,$$

it follows that

$$S'(\lambda)<0.$$

Therefore, $S(\lambda)$ decreases as λ increases. Equivalently, $S(\lambda)$ increases as λ decreases.

□

9. Integration of MRS Data into the Model

In this section, the proposed graph-theoretical framework is calibrated using experimentally reported MRS measurements. Reid *et al.* performed ultra-high-field 7 Tesla proton magnetic resonance spectroscopy (^{1}H-MRS) measurements in the anterior cingulate cortex of first-episode schizophrenia patients and healthy controls. It should be noted that the MRS measurements employed in this study were obtained exclusively from the anterior cingulate cortex (ACC). In the present mathematical framework, these measurements are not intended to represent metabolite concentrations throughout the entire brain. Instead, they are used as representative calibration values for the proposed network under the assumption that glutamatergic dysfunction observed in the ACC reflects the broader excitatory-inhibitory imbalance underlying the interconnected cortical-subcortical circuitry involved in schizophrenia. Accordingly, this regional transfer should be interpreted as a modeling assumption adopted for the construction of the conceptual framework rather than as direct experimental evidence for all network nodes. Their study reported significantly reduced glutamate and total N-acetylaspartate (tNAA) concentrations in the schizophrenia group, whereas no statistically significant difference was observed for GABA levels. The metabolite concentrations summarized in Table 1 were obtained from the study of Reid *et al.*, which included $n=21$ healthy controls and $n=21$ patients with first-episode schizophrenia. The mean metabolite concentrations reported in [7] are summarized in Table 1.

Accordingly, the absolute reduction in glutamate concentration is

$$\Delta Glu = Glu_N - Glu_S = 6.93 - 6.57 = 0.36.$$

The corresponding percentage decrease is

Table 1. Metabolite concentrations reported in the 7T MRS study [7].

Metabolite	Control	Schizophrenia	Interpretation
Glutamate	6.93	6.57	Decreased
Glutamine	1.91	1.82	No substantial difference
GABA	0.93	0.91	No substantial difference
Total NAA	7.27	6.84	Decreased

$$\frac{0.36}{6.93}\times 100 \approx 5.19\%.$$

Similarly, the absolute reduction in total NAA is

$$\Delta NAA = NAA_N - NAA_S = 7.27 - 6.84 = 0.43,$$

yielding a percentage decrease of

$$\frac{0.43}{7.27}\times 100 \approx 5.91\%.$$

Therefore, the MRS measurements employed in this study should not be interpreted as universally valid biomarkers but rather as numerical calibration data corresponding to a specific brain region and disease stage. Furthermore, the comprehensive systematic review of Lopes *et al.* demonstrated that glutamatergic abnormalities are region- and stage-dependent. Therefore, the numerical calibration presented in this study should be regarded as region-specific and illustrative. Future studies may incorporate metabolite measurements from multiple brain regions to obtain region-dependent network parameters. Their analysis reported increased glutamate concentrations in certain regions, including the basal ganglia, frontal cortex, and medial prefrontal cortex during early psychosis, whereas lower glutamate concentrations were frequently observed in established schizophrenia. This observation is consistent with the reduced anterior cingulate glutamate concentration reported by Reid *et al.* Therefore, the *EI* and *SCI* indices derived in this study should be regarded as illustrative mathematical quantities calibrated from published summary data and interpreted within the statistical context of the original MRS investigation. The metabolite values presented in **Table 1** are reproduced from the summary statistics reported by Reid *et al.* Accordingly, the *EI* and *SCI* indices derived in this study should be interpreted within the statistical context of the original MRS investigation. The proposed indices provide descriptive mathematical measures based on published group-level data and are not intended to replace statistical analyses performed on individual subject measurements.

10. Excitatory-Inhibitory Balance Index

Definition 7. The excitatory-inhibitory balance index is defined by

$$EI = \frac{GABA}{Glu}.$$

For the control group,

$$EI_N = \frac{0.93}{6.93} \approx 0.1342.$$

For the schizophrenia group,

$$EI_S = \frac{0.91}{6.57} \approx 0.1385.$$

Hence,

$$EI_S > EI_N.$$

This result indicates that even though GABA levels remain approximately unchanged, the reduction in glutamate concentration modifies the excitatory-inhibitory balance of the network. It should be noted that the observed differences in the EI values are derived from published mean metabolite concentrations rather than from individual subject measurements. Consequently, these numerical differences should be interpreted as descriptive indicators within the proposed mathematical framework rather than as evidence of statistically significant physiological changes.

11. Schizophrenia Connectivity Index

N-acetylaspartate (NAA) is widely regarded as a marker of neuronal integrity and neuronal viability within the central nervous system. In addition, NAA has been associated with neuronal metabolic function and is frequently used as an indicator of neuronal health in magnetic resonance spectroscopy studies. Reid *et al.* further demonstrated the importance of total N-acetylaspartate (tNAA) measurements for evaluating neuronal integrity in patients with schizophrenia using ultra-high-field proton magnetic resonance spectroscopy.

The Schizophrenia Connectivity Index (SCI) is introduced as a simple relative measure that combines three neurochemical quantities associated with excitatory transmission, inhibitory regulation, and neuronal integrity. Glutamate reflects the principal excitatory neurotransmitter, GABA represents inhibitory control, and total N-acetylaspartate (tNAA) serves as an indicator of neuronal integrity. Consequently, the proposed index is intended to summarize the combined balance among these components within a single mathematical quantity.

Definition 8. The Schizophrenia Connectivity Index (SCI) is defined by

$$SCI = \frac{GABA}{Glu \cdot NAA}.$$

Here, Glu denotes excitatory glutamatergic activity, $GABA$ denotes inhibitory activity, and NAA represents neuronal integrity.

The proposed index combines neurotransmitter balance and neuronal integrity within a single quantity. Higher values of SCI indicate a larger deviation from the physiological state and therefore a greater degree of network dysfunction. The denominator contains glutamate and tNAA because reductions in both metabolites have been associated with impaired excitatory function and decreased neuronal

integrity, whereas GABA appears in the numerator as a measure of inhibitory activity. Accordingly, larger SCI values correspond to a relatively greater inhibitory contribution with respect to excitatory and neuronal integrity components.

Theorem 4. The Schizophrenia Connectivity Index

$$SCI = \frac{GABA}{Glu \cdot NAA}$$

is an increasing function of $GABA$ and a decreasing function of both Glu and NAA.

Proof. Treating the remaining variables as constants, we obtain

$$\frac{\partial SCI}{\partial GABA} = \frac{1}{Glu \cdot NAA} > 0.$$

Similarly,

$$\frac{\partial SCI}{\partial Glu} = -\frac{GABA}{Glu^2 NAA} < 0$$

and

$$\frac{\partial SCI}{\partial NAA} = -\frac{GABA}{Glu\, NAA^2} < 0.$$

Therefore, increasing inhibitory activity increases the index, whereas increasing glutamatergic activity or neuronal integrity decreases it.

□

A decrease in the denominator indicates a reduction in both excitatory capacity and neuronal health.

For the control group,

$$SCI_N = \frac{0.93}{6.93 \times 7.27} \approx 0.0185.$$

For the schizophrenia group,

$$SCI_S = \frac{0.91}{6.57 \times 6.84} \approx 0.0203.$$

Therefore,

$$SCI_S > SCI_N.$$

The percentage increase is

$$\frac{SCI_S - SCI_N}{SCI_N} \times 100 \approx 9.7\%.$$

It should be emphasized that the SCI is not intended to represent a direct

Table 2. Index values derived from MRS measurements.

Group	$EI = \frac{GABA}{Glu}$	$SCI = \frac{GABA}{Glu \cdot NAA}$	Interpretation
Control	0.1342	0.0185	Physiological balance
Schizophrenia	0.1385	0.0203	Increased imbalance

biological biomarker or a clinically validated diagnostic index (see Table 2). Rather, it is introduced as a relative mathematical score designed to facilitate comparison of excitatory-inhibitory balance within the proposed conceptual framework. Similarly, the *SCI* values should be interpreted as relative quantitative measures within the proposed conceptual model. Since they are calculated from published summary statistics, they do not by themselves provide evidence of statistical significance or clinical diagnostic performance.

12. Theorem Based on MRS Measurements

Theorem 5. Assume that glutamate and NAA concentrations decrease while GABA concentration remains approximately constant. Then the Schizophrenia Connectivity Index increases.

Proof. By definition,

$$SCI = \frac{GABA}{Glu \cdot NAA}.$$

For the control and schizophrenia groups we have

$$SCI_N = \frac{GABA_N}{Glu_N \cdot NAA_N}, \quad SCI_S = \frac{GABA_S}{Glu_S \cdot NAA_S}.$$

According to the MRS measurements,

$$Glu_S < Glu_N,$$

and

$$NAA_S < NAA_N.$$

Moreover,

$$GABA_S \approx GABA_N.$$

Consequently,

$$Glu_S \cdot NAA_S < Glu_N \cdot NAA_N.$$

Since the numerator remains approximately unchanged while the denominator decreases, it follows that

$$SCI_S > SCI_N.$$

Therefore, the MRS data indicate an increased connectivity index in schizophrenia.

□

The indices $S(\lambda)$ and *SCI* describe complementary aspects of schizophrenia. The quantity $S(\lambda)$ is a theoretical measure derived from the graph-theoretical model and quantifies dopaminergic pathway imbalance induced by NMDA receptor hypofunction. In contrast, *SCI* is an experimentally calibrated index obtained from MRS measurements. Thus, *SCI* may be interpreted as an empirical counterpart of the theoretical imbalance represented by $S(\lambda)$.

13. Biological Interpretation

The graph-theoretical model suggests that NMDA receptor hypofunction may

disrupt glutamate-dopamine interactions by weakening GABAergic inhibition. Within the theoretical framework, this mechanism is quantified through the dopaminergic imbalance index

$$S(\lambda)=\frac{M(\lambda)}{K(\lambda)}.$$

The MRS measurements provide an additional quantitative layer supporting this theoretical prediction. Reid *et al.* reported reduced glutamate and total NAA concentrations in the anterior cingulate cortex of schizophrenia patients. These findings suggest impairments not only in neurotransmitter regulation but also in neuronal integrity.

Accordingly, the proposed index

$$SCI=\frac{GABA}{Glu\cdot NAA}$$

combines glutamatergic dysfunction, inhibitory regulation, and neuronal integrity within a single mathematical expression.

The observed increase of *SCI* in schizophrenia indicates a deterioration of both excitatory-inhibitory balance and neuronal integrity at the network level. Thus, *SCI* may be viewed as an empirical counterpart of the theoretical imbalance represented by $S(\lambda)$.

14. Conclusions

In this study, the role of glutamatergic dysfunction in schizophrenia was investigated through a graph-theoretical framework and subsequently calibrated using experimentally reported MRS measurements. The proposed framework should be interpreted as a conceptual proof-of-principle mathematical model calibrated with published MRS summary data rather than as a validated predictive model for schizophrenia.

The proposed model incorporates NMDA receptor activity through the parameter λ and demonstrates that reduced NMDA receptor function weakens GABAergic inhibition while increasing dopaminergic pathway imbalance.

Furthermore, glutamate, GABA, and total NAA concentrations were integrated into the model and used to construct quantitative network indices. The resulting calculations yielded. Future studies may refine and validate the proposed framework using patient-specific neuroimaging datasets, longitudinal measurements, and multimodal biomarkers to assess its predictive performance in clinical applications.

$$SCI_N \approx 0.0185, \quad SCI_S \approx 0.0203,$$

indicating an increased connectivity index in schizophrenia.

These findings suggest that reductions in glutamate and NAA may generate measurable network-level abnormalities.

One limitation of the present study is that numerical calibration relies on anterior cingulate cortex measurements obtained from a single MRS study. Neverthe-

less, the large-scale review conducted by Lopes *et al.* demonstrates that glutamatergic abnormalities vary across brain regions and disease stages. Consequently, the proposed graph-theoretical framework provides a flexible structure that can be recalibrated for different neuroanatomical regions and clinical conditions.

Future work may extend the present model by incorporating larger MRS datasets, EEG and fMRI measurements, Hopfield neural networks, and graph neural network architectures. Furthermore, region-specific indices may be introduced to compare glutamatergic dysfunction across different brain regions.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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