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Damage To N-Methyl D-Aspartate Receptors Following Perinatal Hypoxia-Ischemia and Its Relation to Schizophrenia

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ABSTRACT

The role of NMDAR hypofunction in schizophrenia has garnered significant attention due to its involvement in cognitive and emotional regulation. Interestingly, recent research reveals a strong correlation between obstetric complications and neuropsychiatric disorders. This review aims to synthesize findings on mechanisms of perinatal hypoxic-ischemic injury and its relevance to NMDAR hypofunction in schizophrenia. Findings regarding the role of NMDAR in memory, cognition, and emotion are explored in conjunction with morphological and functional impacts of perinatal hypoxia on NMDARs and deficits in NMDAR activity observed in schizophrenia. Evidence suggests perinatal hypoxic-ischemic insult disrupts NMDAR activity in cognition and social behavior and contributes to positive, negative, and cognitive symptoms found in schizophrenia, establishing NMDARs as a potential mechanism explaining the link between obstetric complications and neuropsychiatric disorders. Understanding the development of NMDAR dysfunction following perinatal hypoxia offers pathways to early diagnosis and intervention in the development of schizophrenia.

Introduction

Schizophrenia (SCZ) is a debilitating and complex mental disorder, affecting approximately 25 million people worldwide.[1] Its symptoms, according to the DSM -V diagnostic criteria, include delusions, hallucinations, a restricted range of emotions, cognitive deficits, social dysfunction, psychosis, and disorganized speech and behavior that last over 6 months. These are often classified as positive, negative, or cognitive symptoms. [2]

In the glutamate hypothesis of schizophrenia, N-methyl-D-aspartate receptors (NMDARs), glutamatergic ligand-gated ion channels, have been implicated in the development of not only positive, but also negative and cognitive symptoms in SCZ.[3,4,5,6] In healthy individuals, NMDARs are notably involved long term potentiation and depression, playing a crucial role in synaptic plasticity[7,8,9] and, in turn, neural development throughout cortical regions[10]. Though NMDARs have a relatively ubiquitous presence throughout the brain, they have been found to be particularly significant in the functions in regions such as the prefrontal cortex, hippocampus, amygdala, and thalamus.[11, 12,13,14,15]

Consequently, the glutamate hypothesis of schizophrenia identifies NMDAR hypofunction and subsequent dysregulation of functions in relevant regions as a major contributing factor to SCZ pathogenesis. [16,17,18]

Nevertheless, the exact etiology of SCZ is complex, with an abundance of research investigating the numerous relationships between morphological abnormalities, metabolic pathways, neurotransmission, and genetic susceptibility to environmental stressors in SCZ.[19,20,21,22,23]

One such relationship is the strong correlation between perinatal hypoxia-ischemia (PHI) and later onset of SCZ, with papers citing as much as a two-fold risk of developing SCZ in infants that experience perinatal hypoxia-ischemia. [24,25,26,27]

Perinatal hypoxia-ischemia, characterized by insufficient oxygen and blood flow that may occur between the 28th week of gestation until the 28th day after birth, induces multiple harmful biochemical downstream pathways. [28*]

However, despite the clear correlation, the exact steps and mechanisms between perinatal hypoxia-ischemia (PHI) and SCZ pathogenesis remain unclear. This review will discuss how perinatal hypoxic-ischemic injury may be mediated by NMDAR hypofunction as a potential mechanism that correlates perinatal hypoxia-ischemia and N-methyl-D-aspartate receptor hypofunction in schizophrenia pathogenesis.

The NMDA Receptor: A Brief Overview of Physiological Structure, Activation, Regulation and Regional Functions

Structure, Activation, and Regulation

NMDARs are heterotetrameric complexes, consisting of two obligatory GluN1 subunits in addition to two GluN2 and/or GluN3 subunits[29].

These subunits are each further comprised of an extracellular amino-terminal domain(ATD), an extracellular ligand binding domain(LBD), a transmembrane domain(TMD), and an intracellular carboxy-terminal domain(CTD).The ATD plays a regulatory role, containing the binding sites for ligands such as Zn2+. The LBD plays a central role in activation, containing the binding sites for the agonist glutamate on the GluN2 and the coagonists D-serine or glycine on both the GluN1 and GluN3 subunits.The TMD plays a significant structural role, each TMD of the receptor's constituent subunits forming the ion channel. Additionally, the channel harbors a binding site for Mg2+ that blocks the ion channel until depolarization. Once the necessary agonists bind and depolarization occurs, the ion channel opens, allowing Ca2+ influx. The Mg2+ only unblocks the channel at higher frequencies. This, in conjunction with the requisite of glutamate and D-serine or glycine agonists permits precisely controlled activity [30,31,32,33,34,35,36].

Lastly, the intracellular CTD provides intracellular binding sites for protein phosphorylation and regulation. For instance, protein kinase C (PKC) and casein kinase II (CKII) potentiate GluN2A currents and regulate GluN2B surface expression through intracellular signaling cascades, respectively. Another kinase Fyn, an Src Family kinase, has been found to phosphorylate tyrosine residues on GluN2B. The CTD also interacts with PSD-95, a protein that stabilizes the receptor's structure on the postsynaptic membrane. [37,38,39,40,41]. CTD's arbitration of diverse and specific relationships between NMDAR subunits and regulatory proteins may explain its ability to mediate functions in various brain regions.

Nevertheless, the NMDAR still has defining features where it is only optimal in specific functions. Compared to other glutamatergic receptors, NMDARs have relatively slower deactivation kinetics and higher permeability to Ca2+, which produces a strong and long lasting postsynaptic calcium transient and shapes the central role of NMDARs in long term potentiation (LTP), long term depression (LTD), and synaptic plasticity. [42,43,44]

Subunits

The NMDAR's activity is also influenced by subunit composition. In both the developing fetal brain and adult brain, NMDARs constituted with GluN2B or GluN2A subunits are the most prevalent, with high concentrations in areas such as the hippocampus, cortex, and basal ganglia. [45,46]

However, in the postnatal weeks following birth, multiple changes occur in NMDAR subunit distribution. Notably, GluN2A expression is significantly upregulated above levels of GluN2B, which dominates in the prenatal brain. [47] This developmental switch is accompanied by distinct pharmacological properties of the subunits as GluN2A-containing NMDARs have been found to have faster decay times and demonstrate lower sensitivity to

selective antagonists.[48] Moreover, GluN2A's faster kinetics makes the subunit fundamental in LTP and depotentiation, though GluN2B still plays a significant role in LTD due to its slower kinetics.[49,50]

Taken together, GluN2A and GluN2B dynamically regulate the strength of neural connections, which allows precise regulation of multiple processes that involve memory, including learning, cognition, sensory processing, and emotional regulation.

Regional Functions

Hippocampus

In the hippocampus, NMDARs have been heavily studied and found to be highly prevalent. In human tissue, NMDARs are suggested to influence hippocampal volume [51]. Through studies involving mice where subunits of the NMDAR in the hippocampus are antagonized, deleted or observed, NMDAR activity is demonstrated to mediate important functions such as sensory processing [52]; spatial learning[53,54,55,56,57]; non spatial learning [58]; temporal associations[53, 59]; episodic memory [60]; memory consolidation [53,55,57,61]; memory acquisition [62]; memory plasticity, including extinction [63], decay [64], destabilization and reconsolidation[65]; and fear memory [66].

In a study observing treatment of anti-NMDAR encephalitis, bilateral hippocampal functional connectivity and verbal episodic memory was significantly improved in patients who received both first and second-line immunotherapy compared to patients who only received first-line immunotherapy. In fact, there was little discrepancy between patients who received both first and second-line immunotherapy and healthy controls [67]. Anti-NMDAR encephalitis impairs NMDAR functions; thus, improvements in connectivity and episodic memory following treatment reveal the NMDAR's crucial role in the hippocampus and its functions.

Through distinct LTP induction thresholds and properties, the switch in dominance from GluN2B to GluN2A adds a layer of complexity. GluN2A-containing NMDARs, possessing faster kinetics and a lower LTP threshold and magnitude is associated with enhanced context learning and acquisition, while GluN2B - containing NMDARs play an important role in memory consolidation [55,61].

NMDARs in the hippocampus also operate on distinct neuron types. Evidence has shown that NMDARs are relevant in hippocampal interneurons. In the dentate gyrus and CA3 pyramidal layer, NMDA regulates the synaptic activity and survival of interneurons that construct new neural circuits and potentially new memories. [68] GluN2B-containing NMDA particularly are indicated in mediating signals in parvalbumin positive (PV+) interneurons [69,70], which regulate balanced firing in pyramidal cells by releasing GABA [71] and have been found to influence spatial and working memory [72], prepulse inhibition [73], and anxiety [69]. NMDARs' expression in both pyramidal neurons and interneurons of the hippocampus points to a very involved role in memory formation and behavior.

In the hippocampus, research even indicates NMDARs operate outside of synapses and influence LTP induction in synaptic NMDARs [74]. Moreover, a study evaluating memory in aged mice found that reduced trafficking to extrasynaptic locations and accumulation at synapses for GluN2B-containing NMDARs in particular are associated with impairment of memory storage and consolidation [59]. Taken together, evidence highlights the importance of NMDARs in locations outside of the synapse.

In brief, NMDARs are shown to be significantly involved in the functions of the hippocampus.

Similar NMDAR involvement in memory is found outside of the hippocampus.

Prefrontal Cortex

For instance, multiple studies analyzing NMDAR activity in the prefrontal cortex find that it is crucial for working memory [75,76], delayed responding [77], trace fear conditioning [78], social recognition memory [79], aversive memory acquisition [80], and anxiety [81,82]. In response to stress, NMDAR activation is implicated in plasticity and retraction of dendrites [83]. Like in the hippocampus, NMDARs in the prefrontal cortex shape learning that is fundamental to cognition and social behavior.

In adult human cortical tissue, protein levels of GluN2A, and particularly GluN2B, as well as the NMDAR

contributions in neural activity decline [84], which may correlate with decline in cognition in aging humans and indicate the role NMDARs in human memory. A separate study done on healthy human volunteers found that the NMDAR antagonist ketamine reduced connectivity in the dorsolateral prefrontal cortex and impaired spatial working memory [85]. Both studies highlight the importance of NMDAR activity in the prefrontal cortex to cognition and memory.

Also similar to the hippocampus, NMDARs in the prefrontal cortex influence interneuron activity. Research suggests NMDARs play a role in interneuron expression [86,87] , inhibition of pyramidal neuron activity [87], synchronization of spikes [88] and functions such as reversal learning [86].

NMDARs play a crucial role in the prefrontal cortex's activity.

Amygdala and Thalamus

A third region where NMDARs play a notable role is the amygdala, where NMDARs are found to be important in fear response formation and extinction [89,90,91,92]; fear memory destabilization, reconsolidation, and long term consolidation [93]; aggression [94]; thalamic-lateral amygdala connections [91,95]; and temporal associations [96].

In a study evaluating extinction of emotional cues with healthy adults and monetary wins and losses as stimuli for appetitive and aversive learning, administration of an NMDAR agonist, D-cycloserine, before extinction training was associated with reduced amygdala activation compared to a control group who received a placebo [97]. As amygdalar activity is heavily involved in fear memory, a reduction in activation indicates a diminished fear or emotional response. In other words, increased NMDAR activity encouraged the extinction of reward associations, highlighting the receptor's role in the amygdala and the plasticity of fear memory.

In the basolateral amygdala, interneuron activity is also mediated by NMDARs, especially GluN2A-containing NMDARs [95], making them crucial to inhibitory regulation of excitation in the amygdala.

Additionally, subunit composition in the amygdala has been found to be important. Overexpression of GluN2A-containing NMDARs in relation to GluN2B-containing NMDARs impairs fear memory consolidation and extinction [92,93], which can potentially be explain by findings suggesting their distinct roles: GluN2A-containing NMDARs mediate LTP are more involved in initial memory formation while GluN2B-containing NMDARs mediate LTD are more involved in extinction [89].

Taken together, the evidence of involvement in fear acquisition and extinction emphasizes stable NMDAR expression in the amygdala, and the thalamus, as crucial to establishing lasting and responsive fear memory and subsequent emotional behavior based on sensory input.

Perinatal Hypoxia and How It Affects NMDAR Function

Mechanisms of PHI Injury

During hypoxia-ischemia, inadequate levels of oxygen and blood flow causes brain tissue to rely on anaerobic respiration. In turn, ATP is depleted and cellular homeostasis is severely disrupted as lactic acid accumulates, causing inflammation and damaging membranes. Furthermore, disrupted cell homeostasis contributes to imbalanced and increased levels of glutamate.[98,99,100]

Overactivation of NMDARs by glutamate then results in excessive Ca2+ influx into neurons where NMDARs are present. The neurotoxic cascades, such as excessive Ca2+ influx, brought about by energy failure during PHI are in part mediated by NMDARs and disrupt NMDAR function through neuronal damage and disturbed NMDAR subunit development and expression. Brain regions with high NMDAR involvement experience drastic impacts on morphology and function.

Impact on NMDA Function

Hippocampus

In the hippocampus, PHI was correlated with reduced NMDAR expression and binding ability [101, 102], reduced complexity in dendrites and LTP [103], decreased neuron numbers and Ki-67 proliferation index [104], inflammation and subunit dysregulation [105]. Moreover, inflammation and damage done to hippocampal neurons could be mitigated with NMDAR antagonist memantine [104], illuminating the role of NMDARs in, not only experiencing impairments to their activity, but also mediating PHI damage.

Functional implications following PHI damage in the hippocampus are disrupted learning and memory later in life [106, 107, 102]. In an study involving children with HIE and controls, children born with HIE had smaller hippocampal volumes and impaired visuospatial memory compared to the controls [108]

Prefrontal Cortex

Similar detriment following PHI is found in the prefrontal cortex, such as reduced neuronal density and impaired synaptic plasticity[109], cortical dysmaturation [110], inflammation and impaired cellular metabolism [111], and abnormal firing in connections to the hippocampus [112]. Pretreatment with the NMDAR antagonist ketamine reduced inflammatory responses during PHI and attenuated damages to neuronal structures, indicating the role of NMDARs in initiating neurotoxic pathways that ultimately harm its own activity and functions [111].

Damage in the prefrontal cortex caused by PHI correlated with multiple cognitive impairments, such as depressive-like behavior [109], deficits in recognition memory [112], and impaired short-term spatial memory [113]. In fact, in a study assessing cognitive composite scores, children who experienced PHI performed poorer compared to healthy controls [114].

PHI influenced PV+ interneurons in the prefrontal cortex as well, where one study found impaired inhibitory density and resulting activity, evidenced by increased excitatory glutamatergic transmission. Elevations in tonic inhibition were also observed, indicating a compensation in extrasynaptic receptors in response to elevated excitation [110]. These changes in excitation and inhibition are paralleled in a separate study; administration of the NMDAR antagonist ketamine resulted in reduced PV+ interneurons inhibition on pyramidal cells, increased glutamatergic activity, and compensatory upregulation of NMDARs on interneurons [87]. Taken together, these studies implicate NMDARs in mediating PHI's influence on the activity of interneurons and indicate the changes are caused by PHI damage to NMDAR activity. Moreover, loss in PV+ interneuron expression is correlated with anxiety-like behavior [115].

In brief, NMDARs mediate neural inflictions in the prefrontal cortex during PHI; subsequent detriments to morphology are associated with impaired cognition and behavior.

Amygdala

Like the hippocampus and prefrontal cortex, the amygdala also experiences morphological and functional impairments following PHI. Decreased glucose metabolism [116], reduced interregional connectivity [117], and decreased expression of Nrxn1: a protein associated with social behavior [118]. Hypoxic stress is also correlated with reduced amygdala volumes in humans [119]. Moreover, cell death following PHI is attenuated by NMDAR antagonists [120], suggesting NMDARs in contributing to structural deficits in the amygdala.

Structural deficits are correlated with cognitive deficit, impaired spatial memory [116], and impaired fear memory [121]. In patients with bipolar disorder, who experience symptoms such as psychosis, perinatal hypoxia-ischemia was associated with smaller amygdala volumes [122], associating abnormal morphology and behavior in the amygdala following PHI. In short, PHI and NMDAR hypofunction contribute to morphological and functional deficits in the amygdala.

Thalamus

In the thalamus, analogous deficits in synaptic function and PSD-95 expression [123] and glutamatergic signaling protein vGluT1 [124] were observed following PHI. Both PSD-95 [125] and vGluT1 are indicators of NMDAR activity, and their reduced levels suggest harm to NMDAR activity in the thalamus. Moreover, structural deficits in thalamus were associated with impaired spatial learning [123]; and poor social interaction, anxiety, and memory [126]. Taken together, this evidence highlights PHI's disturbances to NMDAR function throughout the brain.

NMDAR Hypofunction in Schizophrenia Pathogenesis

Hypofunction of NMDARs has been implicated in SCZ pathogenesis, with phencyclidine, a non-competitive NMDAR antagonist, has been administered to create accurate animal models of SCZ. This is due to its reproduction of positive, negative, and cognitive symptoms of SCZ, such as hyperlocomotion, social behavioral deficit, and inhibited performance in learning and memory. [127]

Additionally, it has been demonstrated that the NMDAR antagonist ketamine produces SCZ symptoms in healthy individuals and reproduces pre-existing symptoms in stabilized SCZ patients [128]. Positive, negative, and cognitive SCZ symptoms - including impaired verbal fluency, perception, and recall - after administration of ketamine strongly implicates NMDAR hypofunction in the development of SCZ

As a result, various studies have further explored the role of NMDARs in SCZ.

Hippocampus

Aberrant morphology and behavior associated with SCZ is found to be correlated with NMDAR activity in the hippocampus.

In a mice study, reduced GluN1 levels in the hippocampus led to increased excitatory glutamate transmission at Mossy fibers-CA3 synapses and CA3 pyramidal neurons. Hyperactivity from CA3 pyramidal neurons and their projections in the hippocampus were then correlated to deteriorated social memory, reduced prepulse inhibition, and increased fear conditioning [129]. GluN1 deletion in the CA3 also contributes to increased impulsive behaviors and decreased social behaviors in mice[130]. These results parallel a human study where CA3 pyramidal cells show increased spine density on CA3 pyramidal cell apical dendrites and thorny excrescences in SCZ patients compared to healthy controls [131].

Taken together, elevated excitatory activity in mice with less NMDAR structures and elevated presence of inputs into the CA3 sublevel in patients with SCZ suggest that a reduction in NMDAR expression or activity leads to the structural abnormalities seen in SCZ patients. Once NMDAR activity is lowered, the excitatory signals it mediates are also lowered. Synapses between the dentate gyrus and the CA3 sublevel may have compensated by increasing their density and excitability, contributing to hyperactivity and positive symptoms of SCZ.

Moreover, research on postmortem tissue of SCZ patients has found lower levels of GluN1 in the dentate gyrus [132, 133] as well as reduced hippocampal volume and cell number [134], further connecting NMDAR hypofunction to behavioral abnormalities.

Prefrontal Cortex

In the prefrontal cortex, NMDAR hypofunction is found to contribute to SCZ symptoms.

In a post mortem study of SCZ patients, significantly reduced mRNA levels of GluN1 have been found [135]. GluN21 deletion in the prefrontal cortex of mice increased compulsive behavior and tendency toward social novelty [136], indicating NMDAR involvement in the development of impaired social behavior. Administration of ketamine to healthy volunteers resulted in hyperconnectivity that resembled clinical groups of individuals with high risk of SCZ

or early course SCZ [137].

NMDAR hypofunction on cortical networks and PV+ interneurons are also notable. Compared to controls, patients with psychosis and, to a lesser extent, unaffected relatives experience increased excitability in the prefrontal cortex [138].

Increased excitability, psychosis, and other SCZ symptoms may be explained by a reduction in NMDAR activity on PV+ interneurons. A meta-analysis of SCZ models, including post mortem studies of SCZ patients, found that PV levels are significantly reduced in both the prefrontal cortex and the hippocampus. Moreover, genetic and pharmacological models relied on NMDAR antagonism [139], and reduced GluN1 levels are found in SCZ patients[135], highlighting the role of NMDAR in influencing morphology and PV+ interneurons. A decrease in NMDAR activity that mediates inhibitory signals through PV+ interneurons onto excitatory pyramidal cells leads to disinhibition. In an attempt to reach normal levels of excitation and inhibition, excitability is increased, especially of NMDARs on PV interneurons [87].

Amygdala and Thalamus

NMDARs mediate morphological and behavioral changes related to the amygdala as well.

In mice injected with the NMDAR antagonist MK-801, the expression of SCZ-like symptoms – such as hyperactivity, social withdrawal, and impaired memory – correlated with activity in the amygdala – increased cFos expression and calcium signaling, reduced calcium signaling, and reduced cFos expression and calcium signaling, respectively [140]. In a separate study involving the NMDAR antagonist ketamine, social withdrawal was associated with abnormally increased brain activity in the amygdala [141]. Both suggest that NMDARs play an important role in mediating amygdalar functions and disruption of such activity mirrors SCZ symptoms. Furthermore, in a study analyzing NMDAR antibodies in participants at clinical high risk for psychosis and healthy volunteers, high risk individuals with NMDAR antibodies had larger amygdala volumes compared to high risk individuals with no NMDAR antibodies as well as higher levels of depression and performed significantly poorer in auditory verbal memory and IQ tasks [142]. These findings highlight how NMDAR hypofunction is central to structural and functional deficits associated with SCZ found in the amygdala.

Lastly, in the thalamus, inhibition of NMDAR activity through deletion or antagonization results in increased cell death and reduced size within the amygdala [143], indicating NMDARs as essential to vitality in the thalamus. In patients with schizophrenia, decreased expression of NMDAR-related postsynaptic density protein transcripts was found [144], potentially contributing to NMDAR hypofunction and SCZ symptoms. In fact, in mice where the postsynaptic density protein-95 (PSD-95) is knocked out, there are impairments in PFC-related functions such as sociability and cognition, potentially influenced by disrupted signaling between regions [145] .

Perinatal Hypoxia as a Contributing Factor to Schizophrenia Pathogenesis

As reviewed, NMDARs are crucial to activity in the hippocampus, prefrontal cortex, amygdala, and thalamus. As a result, damage to NMDARs leads to disruptions in memory, cognition, fear, and sociability. Thus, not only do NMDAR's play a role in mediating PHI, but also NMDA receptor activity is influenced by PHI by experiencing harm and resulting in structural and functional deficits that align with abnormalities seen in SCZ.

In the hippocampus, PHI reduces neuron number and hippocampal volumes and leads to impaired memory, mirroring the reduced neuron numbers, hippocampal volumes, and disrupted memory found in the hippocampus of SCZ patients. Moreover, a prominent link between the abnormalities seen in patients who experienced PHI and patients with SCZ is that they are both mediated by NMDAR dysfunction.

The same link of NMDAR dysfunction can be found in the parallels of disrupted connectivity, disinhibited pyramidal neurons, and the reduced cognition in the prefrontal cortex of both PHI and SCZ patients; decreased

signaling in social situations and impaired memory in the amygdala of both PHI and SCZ patients; and reduced PSD-95 and reduced sociability in the thalamus of both PHI and SCZ patients.

In short, PHI's correlation with SCZ is potentially explained by NMDAR hypofunction as a result of PHI insult.

Discussion

This review aimed to synthesize recent findings on the role of PHI in the development of SCZ, focusing on its impact on NMDAR structure and function.

PHI was generally found to cause abnormalities in NMDAR activity. However, the NMDAR's role in plasticity and multiple dynamic processes can make it difficult to draw conclusions on specific changes on NMDAR following PHI, especially in terms of activity of particular NMDAR subunits. For instance, one study suggests levels of GluN2A levels decrease following hypoxia and observe no changes in GluN2B [48], while another suggests GluN2B levels decrease and no changes in GluN2A [107]. It is even indicated that GluN2B levels increase [105]. As NMDAR subunits possess distinct characteristics in the brain, mixed findings make implications for function and behavior unclear.

Variations in these findings regarding PHI to NMDAR may arise from differences in the method of study. Discrepancies in length, severity, and timing in natal development of the PHI as well as the timing of data collection all influence how damage through inflammation and energy failure occurs, potentially contributing to differing impacts on NMDARs.

Ultimately, though, later impairments seen in PHI patients are consistent with overall NMDAR dysfunction. Moreover, despite its complex involvement, NMDAR activity, and dysfunction following PHI, is most prominently found in memory, where it influences learning, cognition, and social behavior.

In SCZ patients, aberrant activity due to NMDAR hypofunction parallels that is observed in individuals after PHI. Across studies, deficits in NMDAR function correlate with SCZ. Notably, not only are there decreases in neural activity and complexity observed, but also there is evidence hyperactivity due to NMDAR hypofunction on inhibition, contributing to positive SCZ symptoms. Thus, negative, positive, and cognitive symptoms of SCZ correlates with NMDAR impairments seen following PHI.

Nevertheless, gaps and questions regarding the development of SCZ remain, including its delayed onset. Only 8% of SCZ patients are diagnosed before 18 [146], leaving approximately 92% of SCZ experiencing symptoms later in life at 18 or older. Moreover, mechanisms that explain the delayed onset are unclear. It can potentially be explained by disruptions to NMDAR subunits. In healthy individuals, there are changes in NMDA subunit composition with maturation and age [47, 84]. However, as reviewed, subunit composition is disrupted in both PHI and SCZ patients. Disruptions to certain subunit activity may not become more prominent until after natural changes in composition are supposed to occur and cause a more severe abnormality. Yet, that remains to be more thoroughly researched and explored. Additional uncertainty regards limited understanding of NMDA activity in brains of schizophrenic patients during specific tasks, which would help pinpoint specific areas of disruption and potentially illuminate characteristics on NMDAR dysfunction in schizophrenia.

Further areas of potential discussion are suggested by the link between PHI and SCZ through NMDAR dysfunction reviewed. The fact that damage to NMDAR function is largely due to inflammation and energy failure suggests that other forms of birth complications involving inflammation in the natal brain, such as maternal infection, may correlate with SCZ as well.

Additionally, experiences of PHI in an individual could warrant increased monitoring of cognitive and behavioral abnormalities. To better understand how PHI may contribute to aberrant symptoms, future research could include longitudinal studies observing individuals who experienced perinatal hypoxia, identifying changes in NMDA activity or other biomarkers, and evaluating those changes in correlation with the development of SCZ. Findings may reveal mechanisms that contribute to early diagnosis, intervention, and prevention.

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