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Review Article

The role of netrin G1-netrin-G-ligand-1 in schizophrenia

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Abstract

Schizophrenia (SCZ) is a chronic psychotic disorder that profoundly alters an individual's perception of reality, resulting in abnormal behavior, cognitive deficits, thought distortions, and disorientation in emotions. Many complicated factors can lead to SCZ, and investigations are ongoing to understand the neurobiological underpinnings of this condition. Presynaptic Netrin G1 and its cognate partner postsynaptic Netrin-G-Ligand-1 (NGL-1) have been implicated in SCZ. This review article emphasized the structure and expression of Netrin G1/NGL-1 in the brain, its dysregulation in SCZ patients, and its role in synaptic plasticity, synaptic interaction, learning and memory, microglia neurotrophic activity, and possible signaling between Netrin G1/NGL-1, postsynaptic density protein 95, and cyclin-dependent kinase-like 5 in synaptic morphogenesis. Pharmaceutical targets and the potential use of Netrin G1/NGL-1 as treatment targets or biomarkers for SCZ were also discussed.

Keywords: *Microglia, Netrin G1/Netrin-G-ligand-1, Schizophrenia, Synaptic plasticity*

Introduction

Schizophrenia (SCZ) is a debilitating mental disorder that causes perturbations in the processing of thoughts and disorientation in emotions, perceptions, and social interactions [1,2]. It is characterized by a psychotic mental display of alterations in thinking, hallucinations, abnormal behaviors, cognitive impairment, motor deficits, emotional disorder, inability to complete given tasks, and deficits in social relationships, which tend to worsen over time due to genetic and environmental factors like childhood trauma and substance abuse [2]. Hence, SCZ is regarded as a neurodevelopmental mental illness [3,4].

Treatments of SCZ have been loop-sided toward positive symptoms, using dopaminergic antagonists and leaving out negative symptoms such as cognitive decline. Cognitive impairment in SCZ usually does not respond to antipsychotics. Furthermore, these treatments do not address the underlying biological mechanisms contributing to synaptic dysfunction, hence the critical need for exploring novel therapeutic pathways. Several risk variants that regulate synaptic pathways responsible for synapse development, plasticity, and microglial-associated synaptic pruning have been identified, like the Netrin G1/Netrin-G-Ligand-1 (NGL-1) pathway, which is integral to synaptic development and plasticity [5]. The Netrin G1/NGL-1 pathway depicts a promising target due to its critical role in early neuronal synapse development, maintenance, and plasticity. Previous studies indicate that Netrin G1 and its receptor NGL-1 are essential for neuronal network formation and synaptic stability. Alterations in this pathway could potentially contribute to the synaptic deficits observed in SCZ. Targeting this novel biological pathway may lead to the development of treatments that more effectively impact the full spectrum of SCZ symptoms, improve patient outcomes, and reduce the side effects associated with current therapies [6]. Therefore, early intervention, preventive measures, and exploring the Netrin G1/NGL-1 pathway is essential for advancing our understanding of SCZ and enhancing personalized treatment approaches [4,7,8].

Prevalence and classification of schizophrenia

SCZ manifests between the late teens and early thirties, with males experiencing its emergence earlier than females during the late teens to early twenties and early twenties to early thirties, respectively [9]. According to the World Health Organization, SCZ affects about 24 million people worldwide, that is, 1 in 300 persons are diagnosed with the disorder [2]. It is ranked as one of the 15 leading causes of disability globally [2,10]. Schizophrenic patients have an increased risk of early mortality [11-13] and may later develop Alzheimer's disease due to the similarity of excessive prunning of synaptic

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connections caused by microglial activation [14]. The prevalence of SCZ varies globally, and this has been attributed to the differential standard of diagnosis, sampling method, and demographic factors. In Asia, approximately 7.8 million Chinese suffer from SCZ, and 100,000 new cases of SCZ are recorded yearly.

SCZ is classified into the following two categories of symptoms: positive and negative. According to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition [15], these symptoms must persist for at least 6 months, causing interference in daily life as well as social and occupational events for clinical diagnosis [4]. Positive symptoms depict the overexpression and exaggeration of actions, ideas, and perceptions, whereas negative symptoms refer to the decline in usual and common mental activities and functions, such as anhedonia, avolition, and alogia. It has been reported that these symptoms are linked to perturbations in the brain neurotransmitters, with dopamine being the main culprit, in the frontal and temporal regions and the mesostriatal system of the brain [16].

The current treatment of schizophrenia

Treatments of schizophrenic conditions have been focused more on positive symptoms, and this has been characterized by adverse side effects, but negative and cognitive symptoms remain untreated [17,18]. The current treatment modes of schizophrenic patients are summarized in Table 1. The treatment interventions summarized have their benefits and limitations [19-22], and more research is needed in the development of therapeutic interventions. Despite the use of clozapine and several antipsychotic medications, including therapies for negative symptoms and cognitive disorders, the clinical demand for suitable treatment is still unmet. Therefore, alternative drugs that target cellular and molecular puncta are highly needed for the treatment of SCZ.

Neurotransmitter dysregulation in schizophrenia

Neurotransmitter dysregulation has been shown to play a role in positive, negative, and cognitive symptomology of SCZ. The dopamine hypothesis of presynaptic dopamine disorder and the increase in subcortical and striatal dopamine levels leads to delusion and psychosis in SCZ patients [16,23,24]. A recent review showed that dopaminergic neurons release cotransmitters such as glutamate (excitatory) and gamma-aminobutyric acid (GABA) (inhibitory) to the striatal system causing positive and negative SCZ symptoms [25]. In addition, it was reported that the N-methyl-D-aspartate (NMDA)-receptor antagonist such as ketamine can cause disruption in the thalamic circuit and lead to psychotic disorder and cognitive deficit [25]. The dopaminergic hypothesis, as shown in Figure 1, suggests that increased levels of dopamine transmission in the subcorticolimbic region contribute to positive symptoms, while dysregulation and decreased dopamine in the prefrontal cortex are associated with negative and cognitive symptoms [26]. Several antipsychotic drugs have been employed in the treatment of SCZ; however, they have limitations and adverse side effects impacting the central nervous system, metabolism, cardiovascular, and endocrine system [27-29]. Besides, the treatment intervention has focused majorly on positive symptoms.

Table 1: Current treatment modes of schizophrenic patients

Type of treatment	Description of intervention	Limitations	References
Pharmacotherapy	Antipsychotic medications, both first- and second-generation, have been widely used to reduce positive symptoms First generation - dopamine D2 receptor antagonists Second generation - consists of multi-target antagonists, targeting serotonin 5-HT2A receptors more, compared to dopamine D2 receptors Third-generation antipsychotics, exemplified by aripiprazole, brexpiprazole, cariprazine, and lumateperone	The efficiency of treatment is limited to a few patients. They reduce majorly positive symptoms. Negative symptoms remain untreated. They cause severe neurological and metabolic side effects and may result in sexual dysfunction	[17,18]
Psychosocial interventions	The RAISE: It is effective in treating ongoing symptoms and improving daily functioning for those with SCZ	Lacks a built-in comparison group	[19]
Digital therapeutics	Smartphone apps and virtual reality programs empower SCZ patients with self-help resources, symptom tracking, and cognitive training	Research is still at the infancy stage and faced with the need for standards for clinical health assurance that include measures of efficacy, mental health risk, engagement, and data privacy	[20]
Personalized medicine	Pharmaco (epi) genetic research helps clinicians identify genetic markers or treatment response variations, enabling personalized medication choices and dosages, minimizing side effects, and optimizing therapeutic outcomes	The focus has been on DNA methylation, but there is a paucity of data for other modifications such as hydroxymethylation, histone modifications, and noncoding microRNAs	[21]
TMS	TMS is a noninvasive procedure that uses magnetic fields to stimulate specific regions of the brain. Recent studies have reported improvement in negative symptoms and cognitive functioning	Some adverse effects, such as neck pain, headache, and a mild reduction in diastolic blood pressure, have been reported. Conflicting results exist regarding the length of the cortical silent period	[22]

5-HT2A: 5-hydroxytryptamine receptor 2A, RAISE: Recovery after an initial SCZ episode, TMS: Transcranial magnetic stimulation, SCZ: Schizophrenia

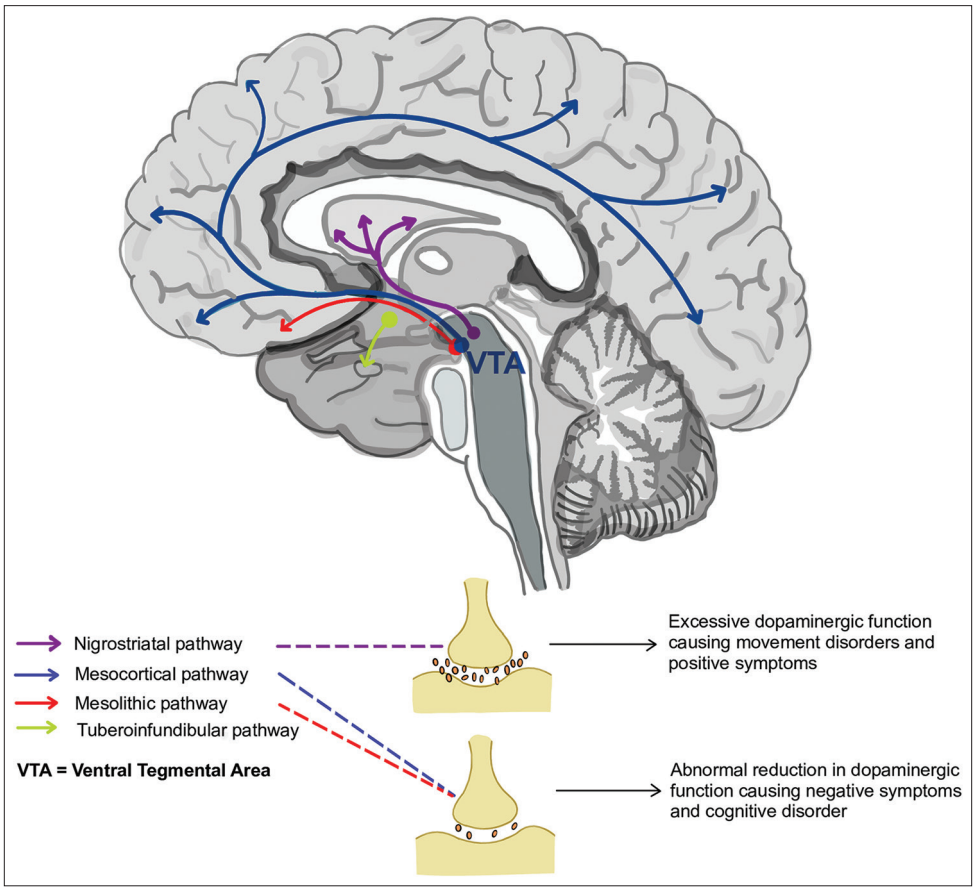

Figure 1: Dopaminergic hypothesis in schizophrenia. The nigrostriatal pathway is formed by projections from the substantia nigra pars compacta to the dorsal part of the striatum, its disruption results in excessive dopamine release, which impairs movement and increases positive symptoms. The mesocortical and mesolithic pathway is formed by projections from the ventral tegmental area to the cortical region, mostly the frontal cortex, and the nucleus accumbens. Disorder in this pathway is associated with a decrease in dopaminergic functions, causing negative symptoms and cognitive disorder. VTA: Ventral tegmental area

Genes and environmental implication in the pathophysiology of schizophrenia

Compelling growing evidence suggests that environmental risk factors such as migration, childhood adversities, trauma, urban dwelling, infection, obstetrics, and substance abuse are associated with SCZ [30]. Psychosocial stressors such as daily stressors, major life events, and childhood trauma have been associated with the development and increase of the progression of psychotic disorders [31,32]. SCZ is an inheritable psychotic disorder with a percentage of 60%–80% inheritability [33]. Genetic factors contribute largely to the pathophysiology of SCZ, and a recent genetic study review revealed that SCZ is highly pleiotropic and polygenic [5]. Genes encoding synaptic proteins, such as the postsynaptic density (PSD) molecules [34], glutamate receptors, and dopamine receptor D2, have been identified by genome-wide association studies (GWAS) with common variations [23]. Genome-wide enrichment analysis from a genome-wide association studies (GWAS) showed that protein-coding genes such as the Netrin receptor deleted in colorectal cancer (DCC) and leucine-rich repeat (LRR) containing 4B (LRRC4B) are associated with postsynaptic pathology in SCZ [33]. However, direct links between genetic and environmental factors with SCZ are still missing. Therefore, understanding how genetic and environmental risk factors contribute to the development of SCZ is necessary.

Netrin-G-ligand 1 and netrin G1

Netrin is a word derived from the Sanskrit word *netr*, which implies "a guide." Netrins are extracellular proteins that play a functional role in guiding cells and axonal migration during the embryogenesis of the central nervous system [35,36]. Identified in mammals, they are categorized into secreted netrins (netrins 1, 3, and 4) and glycosylphosphatidylinositol-linked membrane proteins (netrin G1 and G2). Netrins elicit the activation of cell signaling, chemotropic response, migration, and adhesive mechanisms by binding to different receptors. Netrin Gs do not interact with secreted netrin protein receptors [35]; they bind to transmembrane (TM) proteins with extracellular domains composed of LRRs and immunoglobulin (Ig) domains known as NGLs-1, 2, and 3 to regulate neuronal synaptic interactions [35,37]. The physiology, early formation, maintenance, and development of neuronal synapses have been reported to be regulated by cell adhesion molecules (CAMs) such as the NGL/LRRC4 family of proteins [37]. NGL-1/LRRC4C was first identified as a member of the LRR family and was isolated as a protein to selectively interact with the presynaptic netrin G1 [38]. In humans, the gene that encodes NGL-1 is in chromosome

11p12, and due to its small number of total and coding exons, the possible alternative splicing is highly limited; therefore, NGL-1 diversity is unlikely to occur. However, the netrin G1 gene, which encodes NGL-1 is susceptible to alternative splicing [37,39]. As shown in Figure 2, the domain structure of NGL-1 and other NGLs is similar; their extracellular region consists of nine LRRs capped at their N-terminal and C-terminal lateral ends by cysteine-rich domains (LRRNT and LRRCT) and a C2-type Ig domain, which is followed by one transmembrane (TM) domain and a cytoplasmic region that terminates with a PDZ domain-binding motif [37].

Expression of netrin G1/netrin-G-ligand-1 in the brain

A detailed review by Woo *et al.*, 2009, reported that NGLs are primarily located at the postsynaptic ends of the excitatory synapse, and they also interact with the presynaptic ligands, netrin G1, and netrin G2. Netrin G1 is primarily found in mouse thalamic axons, while NGL-1 is more abundant in the striatum and cortex, playing a crucial role in dendrite differentiation and final recipients of the thalamocortical axons [37,40]. NGL-1 is densely located in the dendrite segments that correspond to the termination of the lamina-specific netrin G1-positive axons in the hippocampus and cortex (parietal and piriform) [40]. In addition, NGL-1 is expressed in the superior and inferior colliculus, lateral septum, and amygdala [41]. However, it is highly expressed in the thalamic reticular nucleus, hypothalamus, and habenula. The subspecific regional expression of NGL-1 is high in the somatosensory cortex and CA1 region of the hippocampus [41]. Netrin G1 has been reported to be differentially expressed in the dorsal thalamus and localized to the thalamocortical axons in the mouse-developing brain [42]. The specific receptor–ligand interaction between netrin G1 and its cognate partner NGL-1 has been reported in several studies, and they do not bind other classical netrin receptors such as the DCC and uncoordinated 5 receptors [37,38,40].

Functions of netrin G1/netrin-G-ligand-1

Netrin G1 and NGL-1 functionally modulate axon outgrowth and the segmentation of lamina-specific dendrites in the hippocampus and cortex [40]. These diverse roles imply that their interaction is crucial for axonal, dendritic, and synaptic development and regulation of excitatory synapse formation [43]. A study revealed that netrin G1 expressed in thalamocortical axons is an axonal receptor for the ligand NGL-1 and that they interact to promote thalamocortical axonal outgrowth. It was reported that the NGL-1 and netrin G1 interaction is highly specific within the netrin family [38]. It was reported that netrin G1-deficient mice show normal axonal pathfinding; however, NGL-1 segmental distribution is disrupted selectively and diffused in line with the dendrites [40]. Notably, a previous study showed that mice lacking NGL-1 displayed marked hyperactivity and anxiolytic-like behavior and impaired spatial and working memory [44]. Whether the observed behavioral phenotypes after NGL-1 loss or Netrin G1/NGL-1 are associated with the dopaminergic, GABAergic, and glutamatergic pathways under schizophrenic conditions remains undetermined. Emerging findings suggest that a few pharmaceuticals may have an effect on Netrin G1/NGL-1 function [45,46]. These potential pharmaceuticals are summarized in Table 2.

Evidence of netrin G1/netrin-G-ligand-1 dysregulation in schizophrenia patients

Netrin G1/NGL-1 has been implicated in neurodevelopmental disorders. Netrin G1/NGL-1, which are highly expressed in the thalamus and cortical areas, may play a role in maintaining neuronal plasticity critical for sensory and cognitive functions. In SCZ, abnormalities in brain regions such as the frontal cortex and, specifically, the dorsolateral prefrontal cortex (DLPFC) have been implicated in the disease progression [47]. Disruptions in the DLPFC circuit can alter both intrinsic and extrinsic functional connectivity, potentially contributing to SCZ's symptoms. Changes at the transcript level of Netrin G1/NGL-1 could exacerbate SCZ symptoms like neurocognitive impairment. In addition, this study found that certain genetic variations in the frontal cortices (Brodmann's Areas 11 and 46) and the temporal cortex (Brodmann's Area 22) of postmortem brains from

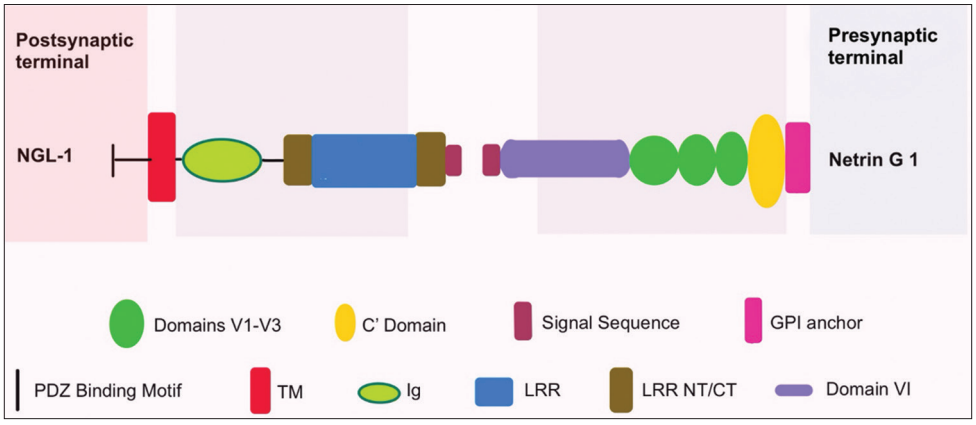

Figure 2: Domain structure of netrin G1 and Netrin-G-Ligand (NGL-1). Netrin G1 is located at the presynaptic end and consists of a signal sequence bridged with protein domains VI-V3 and a C' domain anchored by a GPI link. Its partner NGL-1 is located at the postsynaptic end, and it is a transmembrane protein with extracellular domains composed of leucine-rich repeats and immunoglobulin domains that terminate with a PDZ binding motif. NGL-1: Netrin-G-Ligand, TM: Transmembrane, LRR: Leucine-rich repeat, Ig: Immunoglobulin

schizophrenic patients, compared to healthy subjects, affect the splicing of Netrin G1 haplotypes and are associated with SCZ. Furthermore, they showed that splicing of Netrin G1 involves exons 5 through 9, with aberrant processing possibly linked to its genetic role in SCZ. Moreover, splice variants Netrin G1c and G1d were found in significantly lower levels in the DLPFC of SCZ patients compared to the control subjects, with these isoforms specifically binding to NGL-1, underlining their potential involvement in SCZ pathology [47]. In another study, the expression level of Netrin G1c mRNA was found to be decreased in SCZ patients, which underscores alterations in the synaptic protein in the temporal lobe [48]. The different Netrin G1 isoform expression levels are summarized in Table 3. The primary expression of Netrin G1 mRNAs in excitatory neurons indicates that a decrease in their levels in SCZ might predominantly influence glutamatergic synapses. The expression of Netrin G1 mRNA in certain hippocampal interneurons also points to its potential involvement in the GABAergic alterations seen in the disorder [48]. However, the specific postsynaptic neuronal populations impacted by Netrin G1 changes remain unidentified due to the lack of data on the cellular distribution of NGL-1 in the human brain. Further investigations are required to delineate whether Netrin G1 and NGL-1 interact in these neuronal circuits. Moreover, a study showed that Netrin G1 and NGL-1 functionally promote neurite outgrowth in the thalamus [38], which has been reported to be affected in SCZ patients, leading to attentional deficits and cognitive impairment [49-52]. A disorder in the Netrin Gs, such as Rett syndrome, bipolar disorder, and neurodegenerative disease, has been linked with SCZ [48,53-55], and it is characterized by loss of intentional hand movement and lack of social interaction in humans [56], acoustic stimuli dysfunction [57], and learning and memory impairment. These findings further suggest that Netrin G1/NGL - 1 may play a role in social interaction, movement deficits, and cognitive impairment in schizophrenic patients.

Role of netrin-G-ligand-1 in synaptic plasticity

NGLs interact with the abundant PSD95 protein and NMDA receptors. These interactions are thought to couple synaptic adhesion events to the assembly of synaptic proteins. In addition, NGL proteins regulate axonal outgrowth and lamina-specific dendritic segmentation, suggesting that the NGL-dependent adhesion system is important for developing axons, dendrites, and synapses. NGL-1 is a TM protein, as a member of the NGLs family [38]. NGL-1 is located in the postsynaptic membrane of neurons. It interacts with netrin G1 in the presynaptic membrane to form complexes across the synapse [58]. NGL-1 can bind to lipid-anchored netrin-G1 especially, as a ligand of netrin-G1 [43], leading to the recruitment of presynaptic LAR (a protein) to the complex [59]. All NGLs can trigger presynaptic differentiation in axons that encounter them when cocultured with neurons [37,43]. This family of (LRR)-LRR-containing CAMs actively engage in synapse formation and associations in brain dysfunctions [37].

Previous findings have reported the synaptogenic role of netrin G and NGL mRNAs, which were expressed in the developing brain at postnatal day (PD), 14, a period for possible synaptogenesis [43]. It was found that netrin G2 and NGL-2 mRNA are expressed in the CA3 and CA1 regions of the hippocampus. In contrast, netrin G1 and NGL-1 mRNA are expressed in the thalamus and cortex (thalamocortical axon area) [38], which corresponds to the same expression

Table 2: Pharmaceuticals that influence Netrin G1/Netrin-G-Ligand-1

Pharmaceutical	Effect of treatment	Model	References
PDBu and combination of forskolin and IBMX	Decreased representative fEPSP potentiation at TA-CA1 synapses, no change in fEPSP potentiation	Netrin-G1 knock out mice	[45]
Bis I	Blocked PTP evocation	Netrin-G1 knock out mice	[45]
NetG1 monoclonal antibody	Transient blocking of netrin-G1 Decreased activity of kinases p38, AKT, and its downstream targets FRA1 and 4E-BP1	Human samples and mice cancer-associated fibroblasts under PDAC condition	[46]

PDBu: Phorbol 12, 13-Dibutyrate, IBMX: 3-Isobutyl-1-methylxanthine, Bis: Bisindolylmaleimide I, NetG1: Netrin G1, fEPSP: Field excitatory postsynaptic potentials, PTP: Posttetanic potentiation, FRA-1: Fos-related-antigen 1, 4E-BP1: Eukaryotic initiation factor 4E-binding protein 1, PDAC: Pancreatic ductal adenocarcinoma, TA-CA1: Temporoammonic - CA1

Table 3: Netrin G1 genetic expression in schizophrenic patients

Netrin G1	Gender (male:female)	Age of onset (years)	Level	Clinical symptoms	Brain region	Method of assessment	References
Netrin G1c, G1d	20:7	63.67±10.86	Decreased	DSM-IV criteria	Temporal cortex, orbitofrontal cortex, DLPC	FISH and RT-PCR	[47]
Netrin G1 mRNA	26:9	21.3±6.1	Decreased	Psychosis	Medial and inferior temporal lobe	FISH and RT-PCR	[48]
Netrin G1c Isoform	26:9	21.3±6.1	Decreased	Psychosis	Medial and inferior temporal lobe	FISH and RT-PCR	[48]
Netrin G1a, m, d, e Isoforms	26:9	21.3±6.1	Unchanged	Psychosis	Medial and inferior temporal lobe	FISH and RT-PCR	[48]

FISH: Fluorescent *in situ* hybridization, RT-PCR: Real-time polymerase chain reaction, DLPC: Dorsolateral prefrontal cortex, mRNA: Messenger ribonucleic acid, DSM: Diagnostic and statistical manual of mental disorders

levels in the mouse brain at PD 20–21 [43]. These studies support the notion that netrin G1 and NGL-1 may play crucial roles in synaptic formation and dendritic and thalamocortical axonal outgrowth in the developing brain. An investigation revealed that deletion of NGL-1 in the brain of mice suppressed hippocampal synaptic function and development modestly [41]. In addition, the interaction between Netrin G1 and NGL-1 is crucial for the synaptic processing of auditory inputs in the brain [57].

The role of netrin G1/netrin-G-ligand-1 in synaptic interactions

Synaptic connections are crucial for neuronal survival and transmission of electrical impulses throughout the brain. A compromise in synaptic interactions within different regions of the brain has been shown to cause schizophrenic disorder [60]. It has previously been reported that NGL-1 expressed in the CA1 region is localized and maintained at the stratum lacunosum-moleculare (SLM) layer via a trans-synaptic interaction with presynaptic netrin-G1 [40]. On the other hand, it has been shown that postsynaptic NGL-1 is required for the presynaptic localization of netrin-G1 [45]. These observations suggest that the function and synaptic signaling in the SLM layer are likely dependent on the crucial trans-synaptic interaction between NGL-1 and netrin-G1. NGL-1 predominantly interacts with the PSD protein 95, PSD95 [41,43], and NMDA receptors as well [43].

Furthermore, the deletion of NGL-1 in the mouse brain caused a decrease in the density of excitatory synapses and PSD levels located close to the presynaptic axon terminals in the ventral CA1 hippocampal region. However, this moderate decrease in PSDs was not fully observed in the dorsal CA1 region, suggesting a mild reduction in synaptic densities. Furthermore, the loss of NGL-1 suppressed short-term synaptic plasticity in the temporoammonic-CA1 and Schaffer collateral-CA1 pathways [41]. Several studies have revealed the role of PSD95 in learning, memory, and synaptic plasticity; therefore, NGL-1 might be a promising therapeutic target for memory function in SCZ.

The role of netrin G1/netrin-G-ligand-1 in learning and memory

Netrin G1/NGL-1 have been implicated in cognitive function impairments observed in SCZ, through various mechanisms and associations with genetic variants. Studies have shown that dysregulation of Netrin G1/NGL-1 may contribute to the symptoms of SCZ, especially those related to cognitive functions.

The specific mechanisms by which Netrin G1 and NGL-1 influence learning and memory are speculated to involve the modulation of synaptic plasticity. Synaptic plasticity, including short-term synaptic plasticity, long-term potentiation, and long-term depression, are fundamental to the brain's ability to encode and store information [61]. The interaction between Netrin G1 and NGL-1 is essential for the development of functional neural and synaptic circuits that support learning and memory [45]. Recent evidence suggests that disrupting this interaction can lead to deficits in synaptic plasticity, such as impaired short-term synaptic plasticity (short-term potentiation and post-tetanic potentiation), a cellular mechanism of learning and memory required for information processing [41]. A study on NGL-1/LRRC4C-mutant mice demonstrated that these mice exhibited spatial and working memory impairments along with hyperactivity and anxiolytic-like behavior. These behavioral changes were associated with suppressed baseline and stress-induced limited neuronal activation in various brain regions, including areas critical for cognitive function, such as the anterior cingulate cortex, motor cortex, and hippocampal dentate gyrus. These findings indicate that NGL-1 plays a significant role in regulating specific behaviors, neural circuits, and synaptic properties, which are essential for learning and memory [44]. Considering the hippocampus's central role in learning and memory, alterations in NGL-1 function could significantly impact cognitive functions. In addition, genetic studies in the human population have identified associations between certain genetic variants and the risk of developing SCZ [48,53,62]. In Japanese families, a link has been established between Chromosome 1p13 and SCZ, with the Netrin G1 gene at 1p13.3 identified as a key candidate gene in this association [53]. Single-nucleotide polymorphism (SNP) is a critical genetic factor that significantly influences susceptibility to the development of SCZ. The rs2021722 SNP, located within the human leukocyte antigen locus on chromosome 6, was found to be significantly associated with SCZ risk in a Han Chinese population [62]. These findings suggest that genetic variants affecting the expression or function of proteins like Netrin G1 and NGL-1, or related pathways, may potentiate SCZ development, including its cognitive symptoms.

Cyclin-dependent kinase-like 5 stablize interaction between netrin-G-ligand-1 and postsynaptic density protein 95

Cyclin-dependent kinase-like 5 (CDKL5) deficiency disorder has been related to several neurodevelopmental disorders, including synapse dysfunction. Some studies have shown that netrin G1-NGL1 promotes synaptogenesis, neurite development, and excitatory synapse maintenance, with opposed interaction with PSD95 [38,43]. An investigation revealed a regulatory phosphorylation process in NGL-1. The findings showed that CDKL5 could mediate and phosphorylate NGL-1 binding to PSD95, ensuring stability in the NGL-1-PSD95 interaction in *in vitro*, mouse brain, and human cells, respectively [63]. These findings may be useful in understanding synaptic morphogenesis in the development of SCZ. Furthermore, the role of this possible signaling in schizophrenic pathology remains unexplored, thus indicating that NGL-1 may be a promising therapeutic target.

Netrin-G-ligand-1-netrin G1 and microglia neurotrophic activity

Microglia are known as the resident brain immune cells, responding to infiltration of the brain under pathological conditions. Hyperactivation of the microglia cells has

been associated with neuroinflammation, which has been tagged in the pathogenesis of SCZ. Sustained microglia activation has been associated with neuronal loss and brain dysfunction in neurodegenerative diseases such as Alzheimer's disease, Parkinson's disease, and ataxia, and it has been noted that microglia activation may be involved in the pathogenesis of SCZ in human patients [64,65]. Recent accumulating evidence has revealed that dendritic loss and aberrant synaptic pruning by microglia potentiate SCZ [66,67]. Netrin G1 gene knockdown or deletion leads to a decrease in microglia neurotrophic activity around the subcerebral projection axons and results in cortical neuronal loss [68]. Similarly, the deletion of microglia NGL-1 caused a decrease in microglia puncta around the internal capsule, where NGL-1 is highly expressed in the mouse postnatal brain. These findings postulate that NGL-1-netrin G1 signaling mediates the aggregation of microglia around the axons for neuronal survival [68]. Based on these findings, Netrin G1/NGL-1 might be a promising therapeutic target in mitigating neuroinflammation under schizophrenic conditions. It may also be necessary for homeostatic regulation of microglia activity and neuronal maintenance; thus, its loss or reduction may exacerbate schizophrenic pathologies. More studies are warranted to elucidate the molecular mechanisms underlying microglia activity and cortical neuronal interaction with Netrin G1/NGL-1 and to determine its therapeutic role.

Conclusion

SCZ is a mental disorder resulting from synaptic dysfunction, cognitive deficits, and abnormal behavior. Microglia, the resident brain immune cell, plays a critical role in SCZ; however, there is limited knowledge about its role in the onset and progression of SCZ pathologies. Unfortunately, the current SCZ treatment has debilitating side effects and focuses more on the positive symptoms, neglecting cellular and molecular mechanistic targets for negative symptoms. In this review article, we have reviewed the possible implication and role of Netrin G1/NGL-1 in SCZ and enumerated the basic structure and functions, brain regional expression, and their signaling, which mediates the aggregation of microglia around the axons for neuronal survival and promotes axonal outgrowth, synaptogenesis, neurite development, and excitatory synapse maintenance. Since Netrin G1/NGL-1 associates with synaptic molecules required for learning and memory, understanding its role in cognition under SCZ conditions might be beneficial to clinicians. Further investigations are needed to unravel the functions of Netrin G1/NGL-1 at the cellular and molecular levels in humans. There is the possibility that NGL-1 and its binding partner Netrin G1 are connected with the disruption of synaptic synergy, and their loss or reduction may exacerbate schizophrenic pathologies. Future clinical studies can be directed toward understanding its role in neuroinflammation as this is part of the central core of brain diseases. Hopefully, Netrin G1/NGL-1 might be a potent and promising target for SCZ and other neurological disorders.

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Data availability statement

Data sharing does not apply to this article as no datasets were generated or analyzed during the current study.

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Conflicts of interest

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