Chapter 1

The Convergence of Glutamate and GABA Dysregulation in Schizophrenia

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/65870

Abstract

Schizophrenia (SCZ) is a heterogeneous neurodevelopmental disorder that afflicts about 1% of the world population, imposing a huge financial and social burden on the community. Schizophrenia is characterized by three core features, positive (e.g., hallucinations, delusions) and negative symptoms (e.g., emotional blunting, reduced motivation), as well as cognitive impairments (i.e., working memory and attention deficits). Current antipsychotic treatments, which primarily target dopamine receptors, are effective at alleviating positive symptoms. However, dopamine-specific therapies are insufficient to relieve negative symptoms and cognitive impairments, indicating other neuronal systems are involved in SCZ. Evidence for hypofunctioning glutamate and gamma-aminobutyric acid (GABA) transmission in forebrain tissue has continued to culminate as major contributors to the onset of SCZ. Furthermore, recent genetic studies reveal disrupted mutations in neurodevelopmental proteins at glutamatergic and GABAergic synapses that are potentially responsible for the synaptic abnormalities seen in the disorder. Therefore, schizophrenia symptomatology is influenced by interactions of several neurotransmitter systems. In this chapter, we focus on how glutamatergic and GABAergic hypofunctioning contribute to the variety of symptoms presented in SCZ and its etiology. We also review the current treatment options with respect to their mechanism of action, side effects, and limitations and provide perspective of where research should be directed to move forward with treating this debilitating disease.

Keywords: neurodevelopment, glutamate, GABA, negative symptoms, cognitive deficits, treatment, schizophrenia

1. Introduction

Schizophrenia is a chronic mental disorder that afflicts approximately 1.1% of the population worldwide. Patients not only experience physical and mental disabilities, but also impose a large financial burden that consumes an estimated over $60 billion in costs per year, including more than $20 billion in treatment in the United States of America alone.

Schizophrenic patients exhibit an array of clinical symptoms that consist of positive symptoms, negative symptoms, and cognitive impairments. Due to the heterogeneity in symptomatology, this disorder is difficult to diagnose and treat. Typically, the onset of symptoms occurs between adolescence and early adulthood, mostly within the age range of 16–30 years old, occurring in men (average 18) earlier than women (average 25). Cognitive and social deficits are the first symptoms to appear and exacerbate over time. Individuals display a lack of attention, short-term and long-term memory loss, as well as lack of executive functions that include disorganized thoughts and planning. In addition, patients have difficulties communicating ideas and notions, consequently leading to social withdrawal. As the individual gets older, negative symptoms appear, including a blunted affect of normal behavior and feelings. For instance, patients will express a lack in motivation and/or pleasure that often leads to depression and mood swings. Positive symptoms develop later and signify an escalated state of mind and altered reality, such as hallucinations, delusions, and false ideas. The amalgamation of these symptoms persist into adulthood and may perhaps lead to other comorbidities such as attention deficit hyperactive disorder (ADHD), depression, anxiety, aggression, and substance abuse [1].

Unfortunately, schizophrenia is challenging to diagnose due to the various signs and symptoms; however, neuroanatomical evidence displays structural aberrations in specific tissues that assist in characterizing the disorder. For instance, postmortem patients show an overall decrease in brain volume and more specifically reduced cortical gray matter in forebrain tissue, such as the dorsolateral prefrontal cortex (dlPFC), superior temporal gyrus, and limbic areas (i.e., hippocampal formation, anterior cingulate cortex). Other anatomical anomalies include enlarged cerebral ventricles, such as the lateral and third ventricles. Lastly, at the cellular level, there are reports of reduced neuronal number and dendritic spine densities in the hippocampus and dorsolateral prefrontal cortex [2, 3], although this observation appears to be controversial. Nevertheless, numerous studies have confirmed a significant decrease in pyramidal dendritic spines within superficial layers of the prefrontal cortex [2, 4].

The neurophysiological changes are equally as detrimental as the structural changes observed in schizophrenic patients. For example, the most prevailing theories describing the etiology of schizophrenia is the “Dopamine hypothesis,” which predicts dopamine imbalances within the mesocortical and mesolimbic pathways underlie schizophrenia pathology. Specifically, dopamine deficiency from mesocortical projecting neurons to the prefrontal cortex results in “hypostimulation” of D1-receptor neurons that contribute to the negative symptoms and cognitive impairments. In contrast, an excess of dopamine to the prefrontal

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cortex and striatum from mesolimbic dopamine pathways induces "hyperstimulation" of D2-receptor neurons, responsible for the positive symptoms [5]. Therefore, current treatments target dopamine receptors, but leave other pathophysiological mechanisms untargeted. Typical and atypical antipsychotics, such as haloperidol and clozapine, respectively, block D2-receptors to alleviate psychotic symptoms. However, dopamine-specific targeted therapy is insufficient to relieve other aspects of the disease; therefore, additional neuronal systems are likely involved.

In recent years, evidence has linked glutamatergic and GABAergic systems to the pathology of schizophrenia. An emerging hypothesis of schizophrenia suggests that N-methyl-D-aspartate (NMDA) receptor hypofunction plays a major role in the dysregulation of GABAergic transmission, thereby contributing to the symptoms [6]. In this chapter, we discuss the structure and function of NMDA and gamma-aminobutyric acid (GABA) receptors, including the effects of genetic abnormalities on them and their associated posttranslational modifications and signal transduction pathways. We will also include the reviewed literature describing the multiple neuronal subtypes and circuits involved in schizophrenia and potential therapeutic options.

2. Glutamate hypothesis of schizophrenia

Glutamate is an excitatory neurotransmitter that can act on four major classes of receptors, which are either metabotropic or ionotropic. Metabotropic receptors are G-protein coupled receptors. Metabotropic glutamate receptors are composed of mGluR1-8 subunits and have seven transmembrane segments that are connected to heterotrimeric G proteins. The remaining three classes are ionotropic receptors, or ion-gated channels, that consist of NMDA, AMPA, and kainite receptors, which are readily distinguished by agonists, antagonists, kinetics, and permeability. Ionotropic glutamate receptors are composed of a tetramer of four subunits, with each representative monomer consisting of three transmembrane segments, a large extracellular glutamate-binding domain, and a cytosolic loop that lines the channel pore (**Figure 1**).

NMDA receptor hypofunction has long been proposed as one of the major hypothesis for the pathophysiology of schizophrenia [6]. NMDA receptors are highly abundant within the forebrain and are responsible for regulating a variety of neuronal pathways; theoretically, damage to the glutamatergic system could underlie many pathologies of the central nervous system. Accordingly, there is an overwhelming amount of evidence illustrating that NMDA receptor dysfunction contributes to the neurophysiology associated with schizophrenia [6, 7]. For instance, in postmortem subjects with schizophrenia, disruptive mutations of NMDA receptor subunits were revealed in the prefrontal cortex, hippocampus, and thalamus [8, 9]. Furthermore, it is well established that administering noncompetitive NMDA receptor antagonists such as phencyclidine (PCP), MK-801 (also known as Dizocilpine), and ketamine can mimic the pathophysiology and behavioral attributes of schizophrenia [10–12]. Therefore, treatments that target to improve NMDA receptor function demonstrate an alleviation of

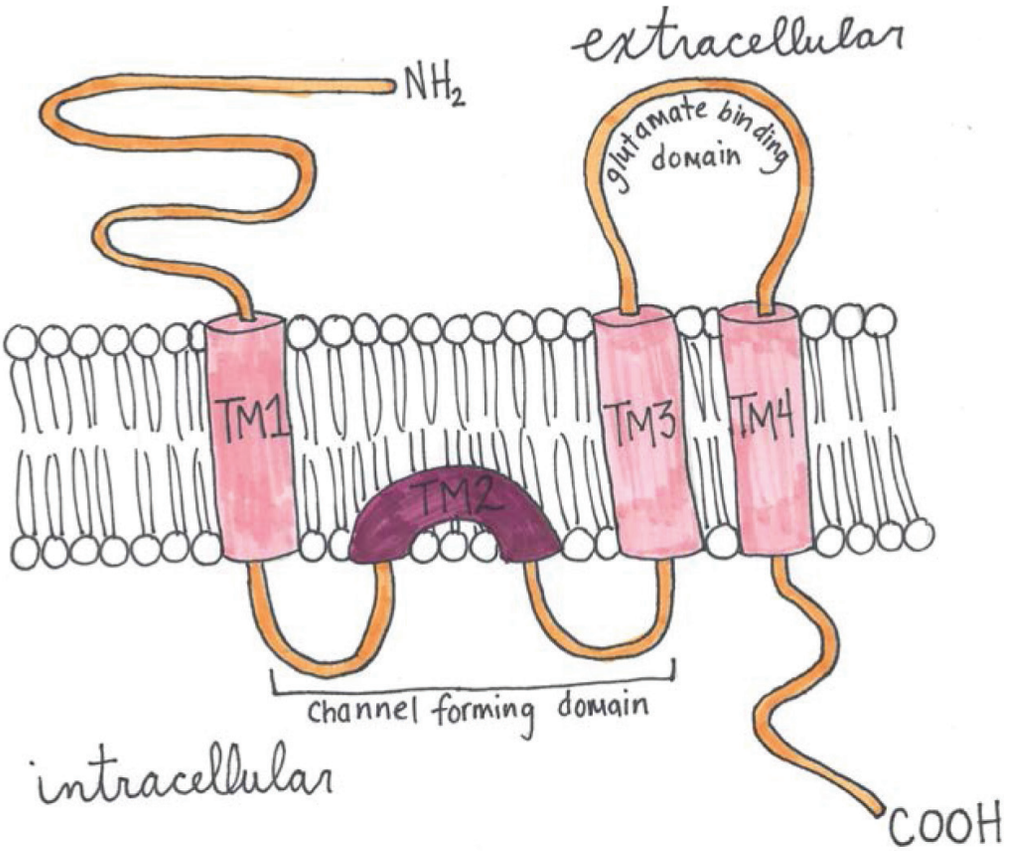

Figure 1. Illustration of prototypic ionotropic receptor subunit. A subunit consists of a large extracellular N-terminus domain, a membrane spanning segment (TM1), a segment that partially enters the membrane (TMII), a glutamate-binding domain, two more membrane spanning segments, and an intracellular c-terminus.

schizophrenic symptoms [13, 14]. Finally, genes implicated in schizophrenia have strong associations with NMDA receptor regulation [15–17].

3. The NMDA receptor structure and function

NMDA receptors are typically located on excitatory glutamatergic synapses, although present in many cell types (i.e., GABAergic neurons, dopaminergic neurons, etc.). NMDA receptors are responsible for synaptic plasticity and cortical development, as well as cognitive processes such as learning and working memory [18]. NMDA receptors are a heterotetrameric complex that consists of an obligatory homodimer of NR1 and homodimers or heterodimers of either combination of NR2A-D or NR3A-D subunits (**Figure 2**). The NMDA channel is voltage-dependent and ligand-gated, and highly permeable to Na^+, K^+, and Ca^{2+}, causing depolarization of a cell and subsequent excitation and activation of intracellular signaling pathways. Although NR1 subunits are required for NMDA receptor function, NR2/NR3 subunits are specialized and critical for functional diversity such as calcium permeability, decay time, open channel time, and pharmacology sensitivity. In addition, NR1 and NR2 subunits

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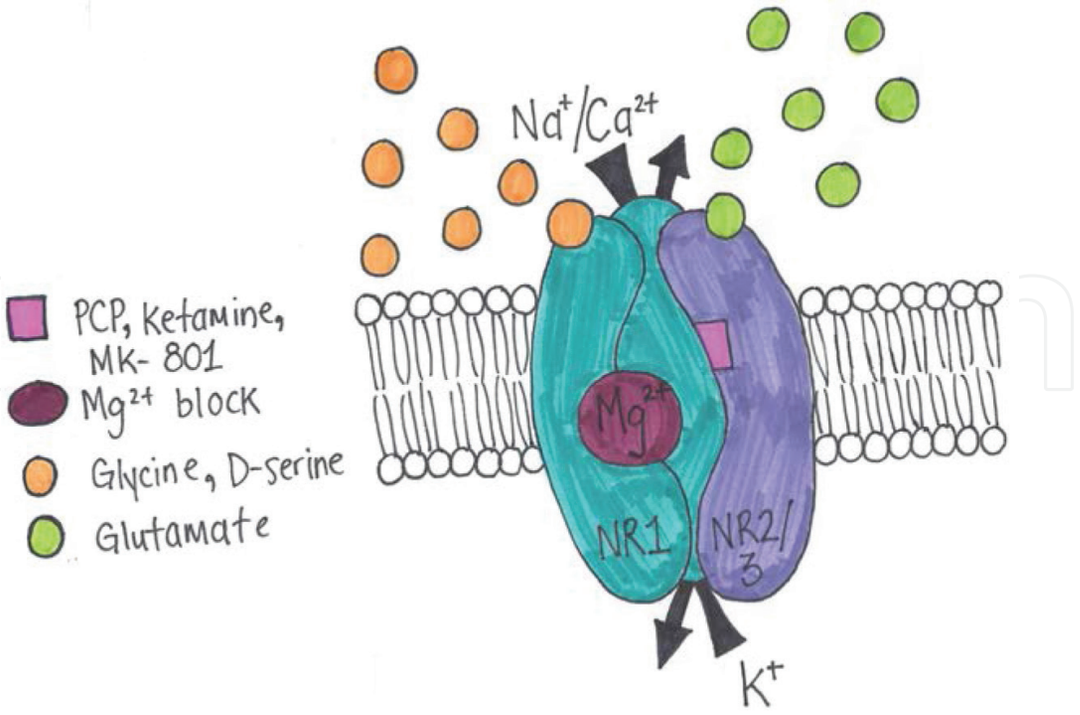

Figure 2. Schematic diagram depicting a NMDA receptor complex. Glutamate binds at NR2/NR3 complex and co-agonist glycine or $_{D}$-serine binds at NR1 complex. Upon depolarization, Mg^{2+} is removed. NMDA receptor permeates Na^{+} and Ca^{+} influx and K^{+} efflux upon activation. Binding sites for PCP, ketamine, and MK801 are included (Figure was modified from Snyder et al. [6] and Cioffi et al. [14]).

contain distinct sites that bind glycine, PCP, and Mg^{2+} that modulate the activity of NMDA receptors (**Figure 2**).

4. The NMDA receptor development

Developmentally, there is an NR2B- to NR2A-subunit switch that occurs from childhood-to-adulthood in most brain regions that facilitate synaptic maturation [19]. NR2B protein expression levels are highly abundant during early development and decline into adulthood; in contrast, NR2A levels begin low and rise in adult. Both subunits are essential for prefrontal synaptic plasticity and function; however, NR2B plays a more dominant role. For instance, in the prefrontal cortex, NR2B levels remain high into adulthood and are important for working memory function [20, 21]. NR2B-containing NMDA receptors play a major role in calcium (Ca^{+}) influx at the postsynaptic membrane, as NR2B receptors have slower kinetics, thus a slower decay time compared to NR2A-containing NMDA receptors. This indicates that NR2B receptors conduct a large amount of Ca^{+} and Na^{+} due to the prolonged open channel state. Although NR2B is essential for cognition processes within the adult, an overabundance may be hazardous due to the significant increase in Ca^{+} conductance that could lead to excitotoxicity and neuronal death [21]. Therefore, NR2B/NR2A composition during development is extremely critical for normal synaptic maturation.

5. NMDA receptor dysregulation and hypofunction in schizophrenia

A major finding discovered by functional imaging studies was reduced activity in the dorsolateral prefrontal cortex (dlPFC) in patients with schizophrenia. The overall reduction in neuronal activity in the dlPFC could explain the cognitive deficits and negative symptoms. There is consensus that NMDA receptor hypofunction is strongly associated with the pathophysiology of schizophrenia. In human studies, single-photon emission computed tomography (SPECT) shows "hypofrontality" patients suffering from schizophrenia [22]. Furthermore, there are genetic implications that show single-nucleotide polymorphisms (SNPs) and a reduction in NR1 protein and mRNA in the dorsolateral prefrontal cortex in postmortem subjects of schizophrenia [9, 23]. Additionally, exome sequencing of patients with schizophrenia also displays disruptive mutations in genes that encode NMDAR subunits and NMDA receptor-associate scaffolding proteins, such as PSD-95 and SAP102 [24, 25]. These findings would suggest a lack of and/or function at the postsynaptic membrane of excitatory synapses that could be responsible for the cellular phenotypes of the disorder.

Noncompetitive NMDA receptor antagonists such as PCP, MK-801, and ketamine have been extensively used to study the symptoms associated with schizophrenia in both human subjects and animal models [26]. Indeed, these studies have shown to mimic the effects of schizophrenia, corroborating the glutamatergic hypofunction hypothesis. Individually, PCP induces psychotic symptoms in healthy humans that resemble schizophrenic-like behavior; MK-801 elicits positive and negative symptoms; and lastly ketamine administration was shown to imitate the positive, negative, and cognitive deficits seen in schizophrenia [11]. In rats, NMDA receptor antagonists cause deficits in working memory, executive functions, and enhanced locomotor activity [27].

6. High-risk genes implicated in schizophrenia

High-risk genes associated with schizophrenia such as DISC1, dysbindin, neuregulin, COMT, and G72/G30 genes, responsible for neurodevelopment, neuronal growth, and migration, have all shown to be involved in NMDA dysfunction leading to schizophrenia [15]. The most prominent of the genes is *D*isrupted in *schizophrenia* 1 (DISC1), which acts as a scaffolding protein involved in the formation of protein complexes important in neurodevelopment, microtubule network dynamics and axonal elongation [28, 29]. Despite the controversy and debate [16, 30], evidence shows that schizophrenic patients contain DISC1-SNPs that cause a decrease in DISC1-interacting protein expression levels, such as NMDA receptors. In DISC1 animal models, mice with point mutations in the gene or truncated forms of DISC1 display molecular, cellular, and behavioral phenotypes that are analogous to schizophrenia. DISC1 is especially susceptible to mutations due to environmental stressors during neurodevelopment that may lead to the pathogenesis of the disorder [31, 32].

7. Other factors affecting NMDA receptor function

Environmental factors during development, such as infection, drug use, parental age, prenatal and early postnatal or childhood stress, have all been linked to the emergence of schizophrenia [33]. In addition, NMDA receptor function is susceptible to the latter environmental risk factors during adolescence, potentially contributing to the onset of the disorder [6, 33, 34]. This could be due to an alteration in NMDA receptor gene expression, as major transcriptional factors such as the cAMP response element binding protein (CREB) are extremely sensitive to environmental stimuli [35]. Previous studies describe that neurodevelopment in the prefrontal cortex is altered in patients with schizophrenia due to a substantial increase in synaptic elimination of glutamatergic excitatory synapses [36].

NMDA receptors are also influenced by posttranslational modifications such as ubiquitination, palmitoylation, and phosphorylation [34]. NMDA receptor phosphorylation is responsible for regulating receptor trafficking, stabilization, kinetics of the channel, and kinase activation. These processes are important for synaptic plasticity during neurodevelopment and if dysregulated could be highly responsible for the pathologies of schizophrenia [7]. NMDA receptor subunits are phosphorylated at serine/threonine and tyrosine residues, providing substrate sites for kinases such as Src family of kinases (SFK), casein kinase 2 (CK2), cAMP-dependent protein kinase A (PKA), cyclin-dependent kinase 5 (Cdk5), protein kinase C (PKC), and Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) [37–40].

Other modification processes such as palmitoylation and ubiquitination have also been directly linked to schizophrenia [41]. There is evidence of NMDA receptor dysregulation due to anomalous modifications that could potentially lead to neuropsychiatric disorders. Palmitoylation is a process that allows the covalent attachment of palmitate group to the cysteine residues of proteins that are facilitated via thioester bonds. Recently, it has shown to be involved in regulating NR2 subunit trafficking during neurodevelopment and synaptic plasticity [42] and is altered in a mouse model of 22q11.2 deletion syndrome. Ubiquitination is a process involved in the targeting and removal of proteins and is responsible for regulating NMDA receptors degradation during development. Specifically, subunits such as NR1 and NR2B undergo polyubiquitination at the synapse [41]. Nonetheless, palmitoylation and ubiquitination require further investigation in its role in NMDA receptor regulation and potential implication in schizophrenia.

8. Intracellular mechanisms affecting NMDA receptor function

Selective intracellular signal transduction pathways, such as the AKT-GSK3β pathway, at excitatory glutamatergic synapses regulate NMDA receptor functions, and are associated with high-risk genes involved in schizophrenia. AKT, also known as protein kinase B, is a serine/threonine kinase involved in neuronal plasticity, migration, protein synthesis, and cell death [43, 44]. Glycogen synthase kinase 3β (GSK3β) is also a serine/threonine kinase that is downstream of AKT and upstream of beta-catenin [45]. Moreover, GSK3β knockdown leads

to a reduction in NMDA receptor current [46]. AKT phosphorylation is a negative regulator of GSK3β activity; similarly, GSK3β phosphorylation induces beta-catenin degradation. High-risk genes such as DISC1, dysbindin and NRG1 are all modulators of the AKT-GSK3β signaling pathway [34]. For instance, reduced DISC1 protein expression causes a decrease in AKT phosphorylation, and thus an increase in GSK3β activity [47]. In addition, reducing GSK3β activity can alleviate the behavioral impairments observed in DISC1 mouse models [48, 49]. These data suggest a link between high-risk schizophrenia genes and intracellular pathways, such as the AKT-GSK3B signaling pathway, that regulate neuronal plasticity. Theoretically, it can be assumed that the high-risk schizophrenia genes would affect the AKT-GSK3β signaling pathway, and thus cause NMDA receptor dysfunction, leading to aberrant neuronal systems that are responsible for the positive, negative, and cognitive symptoms observed in schizophrenia.

9. Drug treatment that targets NMDA receptors

Typically, drug treatment for schizophrenia patients consists of antipsychotics, such as clozapine, that target D2 receptors to relieve the positive symptoms. However, a significant portion of schizophrenia subjects do not respond well to D2 antagonists; moreover, the negative and cognitive impairments are barely affected by treatment with antipsychotic drugs. As a result, medical professionals are testing new pharmacological agents that target NMDA receptors as a therapeutic option. Due to the observed glutamate hypofunction impairment in patients, investigative studies have focused on the enhancement of NMDA receptor function. Therefore, high doses of glycine agonists (60 g/day) that act upon the glycine_B modulatory site are used to increase NMDA receptor function [13]. These agonists have been shown to modestly improve the negative and positive symptoms of schizophrenia and are currently being utilized as an adjunctive treatment to primary therapy with D2 antagonists. An alternative option is to target the glycine transporter-1 (GlyT-1) with the selective inhibitor, sarcosine, to increase glycine availability for NMDA receptor binding [14]. Sarcosine administered at 2 g/day have shown to improve negative and cognitive symptoms of schizophrenia. Other drugs include *d*-Serine and *d*-amino acid oxidase (DAAO) inhibitors to increase *d*-Serine availability, as it is considered a co-agonist to NR1. The effects of the inhibitor were shown to alleviate negative and cognitive impairments in patients when administered at high doses (>2 g/day) and as a supplement to antipsychotic treatments [14]. Kynurenine aminotransferase II (KATII) inhibitors are used to block kynurenic acid (an endogenous antagonist at the NR1 glycine_B site) used to improve negative symptoms. NR2 subtype selective modulators are still under drug development and could prove beneficial to a neurological disorder, such as schizophrenia. Other pharmacological drugs available that affect glutamate transmission are utilized to target AMPA receptors, mGlu5 receptors, and NMDA receptors on GABAergic interneurons. However, many of these new therapeutic interventions are still in clinical trials, whether they are more effective than the typical and atypical D2-related antipsychotic drugs remains to be determined.

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10. Glutamate-GABA association in schizophrenia

It is theorized that NMDA dysfunction in neuronal subtypes of GABAergic and dopaminergic neurons collectively contribute to the neuropathologies of schizophrenia. More specifically, investigators speculate that NMDA receptor hypofunction occurs on GABA interneurons (see **Figure 1** in [6]). Glutamatergic neurons have direct interaction with GABA interneurons, such as basket and chandelier cells, within the cortico-limbic circuitry. These interneurons are responsible for suppressing output from glutamate-releasing pyramidal cells, and due to recurrent collaterals from the two cell types, causes an inhibitory feedback loop. However, if GABAergic activity were suppressed, due to NMDAR dysfunction, it would lead

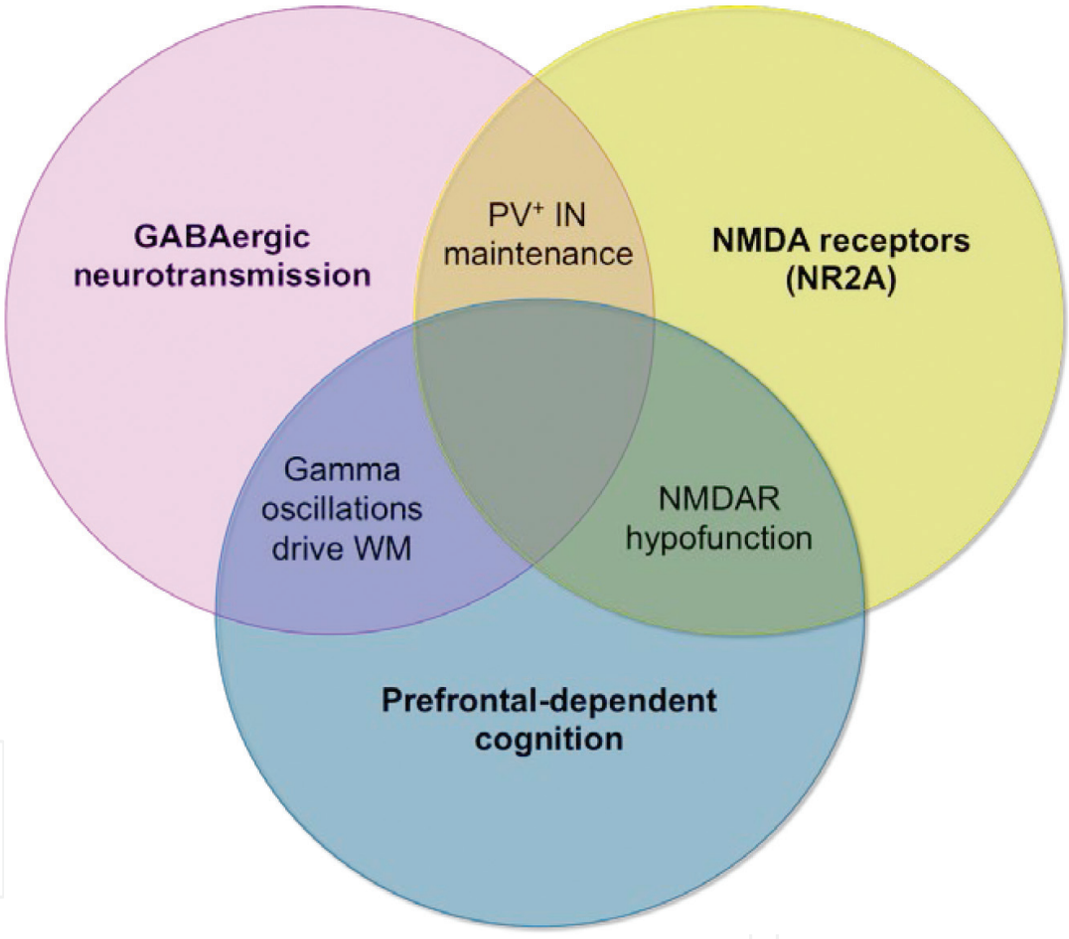

Figure 3. Cross-connections between NMDA receptors, GABAergic neurotransmission, and PFC-dependent cognition. PFC persistent neuronal firing is the foundation of working memory with NMDA receptor activity playing a substantial role in this process [50, 51]. NMDA antagonism in conscious behaving monkeys impairs prefrontal-dependent working memory [52] and induces cognitive impairments in healthy human subjects [11, 53–56], demonstrating a parallel between NMDA hypofunctioning and cognition deficits. This 'online' persistent neural activity is critical for working memory, which is not only NMDAR-dependent, but also requires fast and synchronous inhibition of prefrontal pyramidal neuronal networks by GABAergic interneurons. GABAergic neurotransmission ultimately drives working memory function through the shaping and synchronization of pyramidal cell output. PV cortical interneurons are especially fundamental for generating fast gamma oscillations, which has been demonstrated in humans to be necessary for proper working memory [57]. NMDARs and GABAergic interneurons are interrelated because NMDA receptors play a large role in the maturation [58] and maintenance of interneurons, especially the NR2A subunit [59].

to disinhibition of pyramidal neurons and excessive firing within the cortico-limbic circuit. Physiologically, the excitotoxicity could have multiple effects on circuitry such as changes in membrane potential, receptor desensitization, or cell death. These results would have a twofold effect; first, the GABAergic downregulation would lead to negative symptoms and cognitive deficits. And second, the resulting excess glutamate release of cortico-pyramidal neurons could activate dopaminergic systems that lead to positive symptoms and further cognitive impairments. The glutamate-GABA systems in the forebrain, especially prefrontal cortex, are intertwined to produce prefrontal-dependent cognitive function, as proposed in **Figure 3**. Still, how these two systems interact to induce phenotypes and symptoms in schizophrenia remains to be determined.

11. GABAergic cortical interneurons

Cortical interneurons were first documented with Golgi staining by Santiago Ramón y Cajal and referred to as the "cells with short axons" [60]. Cortical interneurons are typically distinguished by four common attributes: locally projecting, aspiny or sparsely spiny dendrites, small cell soma, and GABAergic. Interneurons exhibit a large diversity and are categorized based on several features including morphology, connectivity, neurochemistry, and physiology [60–62] (**Figure 4**). Due to the heterogeneity of this neuronal population, interneurons can fall into more than one category, showing a great degree of overlap; therefore, interneurons fall more along a spectrum rather than into distinct subgroups. Although this group is very diverse, axonal arborization and the downstream target domain plays a major role in classification and can reveal a lot about a circuitry's function. Essentially, where and how an interneuron synapses onto a target cell ultimately effects neuronal output and therefore function [61], is an essential question for cortical function. Interneurons are crucial for synchronizing and shaping the excitatory activity of pyramidal cells to form a 'task-specific microcircuit' for a particular brain region [61]; the prefrontal cortex contains this microcircuit specialized for working memory [62].

Three common GABAergic neocortical interneurons that will be highlighted and addressed in this chapter are neurochemically defined based on the calcium-binding proteins they express: calbindin (CB), calretinin (CR), and parvalbumin (PV) neurons. Calbindin interneurons (also referred to as somatostatin) makeup ~30% of the cortical interneuronal population and are generally characterized as having either small basket or Martinotti morphology. Commonly, small basket cells target proximal dendrites or the cell soma and electrophysiologically display regular-spiking non-pyramidal (RSNP) activity. Martinotti interneurons exhibit a burst-spiking non-pyramidal (BSNP) firing phenotype and target distal dendrites. Calretinin interneurons are the least prevalent (~15%) and stereotypically have small bipolar morphology. These interneurons target proximal dendrites and also other GABAergic interneurons having either RSNP or BSNP firing. Parvalbumin interneurons are fast-spiking cells and neurochemically the largest group, making up half of the interneuronal population in the cortex. PV interneurons target all along a pyramidal cell, with large basket cells at the proximal dendrites/soma, nest cells at the soma, and chandelier cells targeting the axon initial segment. For the remainder of this section, we will focus on parvalbumin chandelier cells

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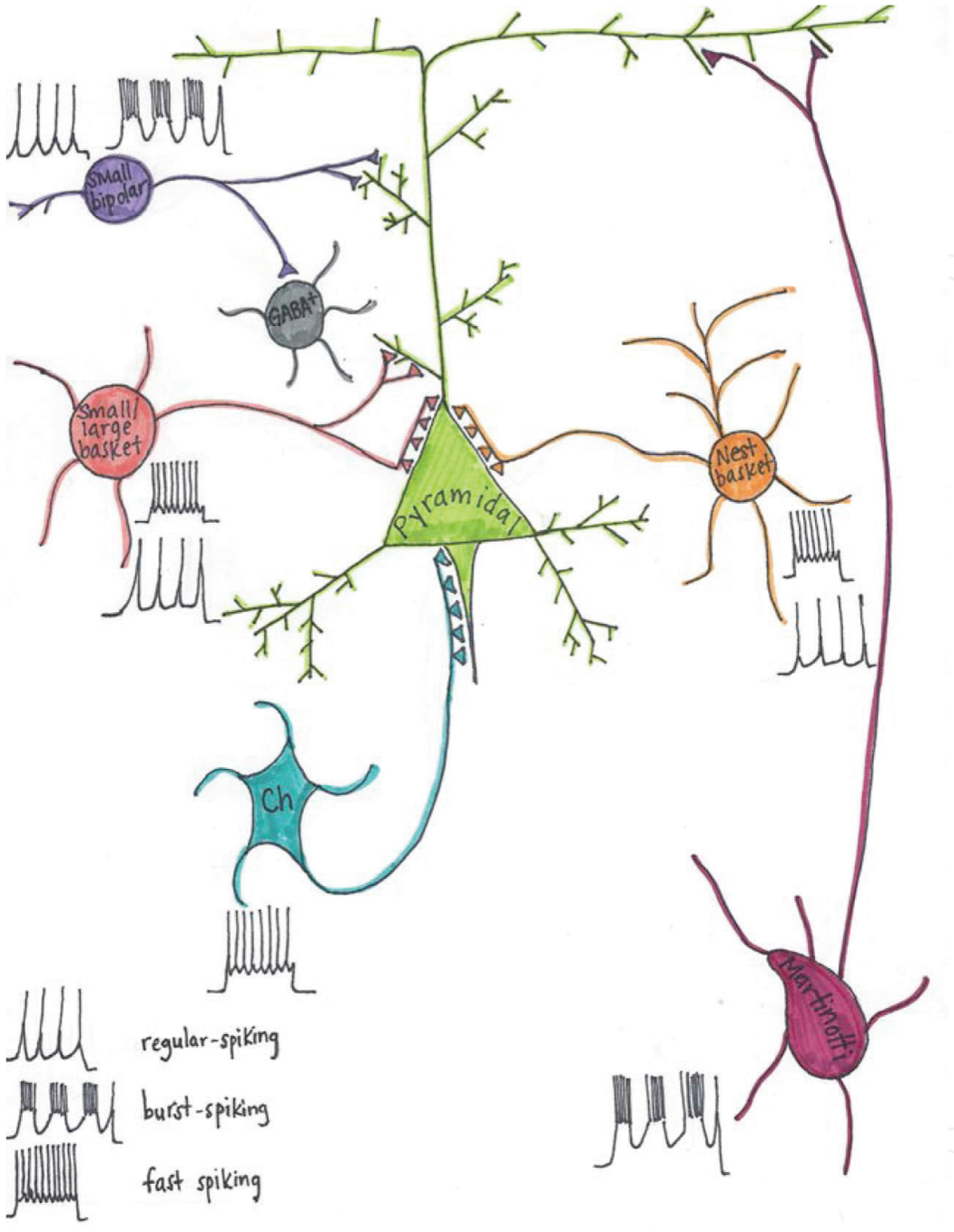

Figure 4. Cortical interneuron connectivity and firing patterns categorized by calcium-binding neurochemical markers. Calretinin small bipolar cells target proximal dendrites and other GABAergic interneurons. Calbindin neurons, small basket cells, and Martinotti cells, target proximal dendrites/soma and distal dendrites. Parvalbumin interneurons are fast-spiking and are further classified into large basket, nest basket, and chandelier (Ch) cells. Large basket cells target proximal dendrites and the soma. Nest basket cells target the cell soma and chandelier cells synapse on the axon initial segment (Modified from Lewis et al. [62]).

since these are the interneurons known to play a major role in prefrontal cortex-dependent working memory and also have been implicated in the pathophysiology of neuropsychiatric disorders such as schizophrenia [60, 62].

12. GABA receptor classification and structure

GABA receptors respond to the ligand GABA, which is the main inhibitory neurotransmitter in the mammalian central nervous system. GABAergic neurons are therefore important for modulating neuronal activity throughout the brain and spinal cord [63–70]. The enzyme L-glutamic acid decarboxylase (GAD) synthesizes GABA in presynaptic terminals through the conversion of glutamate to GABA. GABA is then stored in vesicles waiting for release following neuronal activation [67]. Extracellular GABA can bind to either postsynaptic or extrasynaptic receptors located on presynaptic neurons, leading to hyperpolarization of the target cell [69]. Postsynaptic receptor activation mediates phasic inhibition, whereas extrasynaptic activation mediates a tonic inhibitory state [65, 69]. To remove extracellular GABA in the synaptic cleft, GABA transporters located on the presynaptic terminal and glial cells regulate neurotransmitter uptake; this process is extremely important to retain a balanced circuitry and prevent over inhibition [67].

GABA receptors are classified into two groups, $GABA_A$ and $GABA_B$, with $GABA_C$ receptors recently categorized as a subtype of $GABA_A$ rather than their own distinct class. Receptor characterization is based on structural, biochemical, modulatory, and physiological differences [67–70].

$GABA_A$ receptors are ionotropic chloride channels, conducting fast inhibitory neurotransmission, in which a ligand (i.e., GABA) binds and directly induces pore opening [67, 69]. $GABA_A$ receptors are members of a much larger group referred to as the Cys-loop ligand-gated ion channel superfamily, which also encompasses nicotinic acetylcholine receptors (nAChRs), glycine receptors, and 5-hydroxytryptamine type-3 ($5\text{-}HT_3$) receptors [65, 68–70]. The diverse pharmacology displayed by $GABA_A$ receptors sets them apart from the rest of the family and is clinically relevant targets for anticonvulsant, anxiolytic, and sedative drugs [65, 69]. Typically, $GABA_A$ receptors are heteropentameric structures composed of five different subunits (α1-6, β1-3, Υ1-3 (Υ2S, Υ2L), ϱ1-3, δ, ε, θ, and π), each containing four transmembrane domains (TM1-4) (**Figures 5** and **6**). Five out of twenty-one available subunits comprise the complex, forming a pore from the TM2 segments [67–70]. The top three most common structural compositions in the brain are $\alpha1\beta2\gamma2$, $\alpha2\beta3\gamma2$, and $\alpha3\beta3\gamma2$, with the likely stoichiometry of $2\alpha{:}2\beta{:}1\gamma$ [65, 67, 69].

Benzodiazepines potentiate the inhibitory effects of GABA by allosterically altering the receptor and increasing its affinity for GABA [67]. Benzodiazepine-insensitive receptors are formed when the γ subunit is replaced by δ, ε, or π [69]. Rho (ϱ) subunits are unique because these subunits predominately co-assemble together to form homo- and hetero-oligomers. Previously, ϱ oligomers were classified as $GABA_C$ receptors, but more recently are considered a subclass of $GABA_A$ receptors. Even though $GABA_A$ and $GABA_C$ receptors are structurally very similar to one another, these receptors formally fell into two different groups based on their differential pharmacology and physiology [69, 70]. A major difference between the A and C subtypes are that $GABA_A$ receptors are selectively blocked by bicuculline and modulated by benzodiazepines, steroids, and barbiturates. $GABA_C$ receptors are not sensitive to the same drugs, but rather are blocked by 1,2,5,6-tetrahydropyridin-4-yl) methylphosphinic

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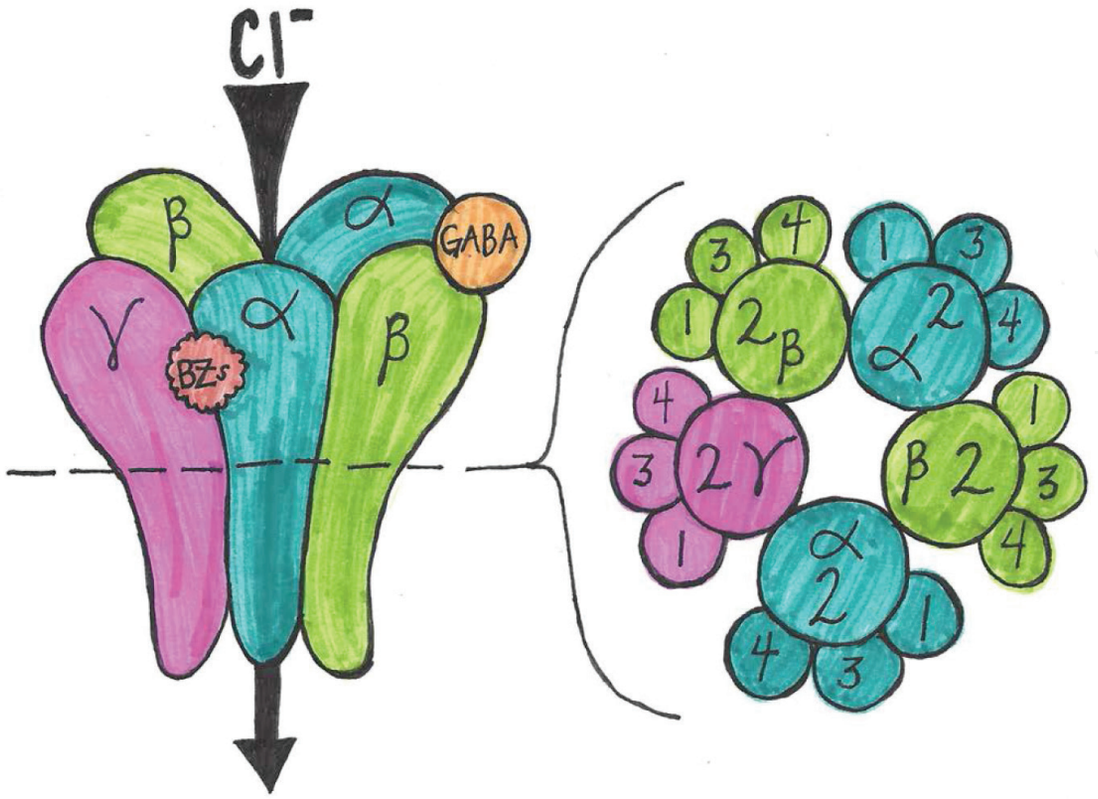

Figure 5. $GABA_A$ receptor structure and cross-section. $GABA_A$ receptors contain five subunits, typically in the ratio of 2α:2β:1γ, with the transmembrane domain 2 (TM2) forming the chloride-permeable pore. Each subunit consists of four hydrophobic transmembrane domains with the N- and C- terminus facing the extracellular side. The GABA binding site is located at the interface between α and β subunit, while the benzodiazepine (BZs) binding site sits at the junction between α and γ. GABA binding triggers channel opening, allowing inward chloride ion flux, whereas benzodiazepine binding potentiates the GABA-induced chloride influx [65, 69] (Modified from Jacob et al. [65] and Vithlani et al. [69]).

acid (TPMPA) and activated by Z-4-amniobut-2-enoic acid [cis-aminocrotonic acid (CACA)]. Additionally, $GABA_C$ receptors exhibit a higher sensitivity to GABA, conduct less current, have longer channel opening times, and desensitize slower in the presence of an agonist. $GABA_C$ receptors, however, are no longer classified as a separate division, but are now considered a $GABA_A$-ρ subclass because they are exclusively constructed of ρ subunits [70].

$GABA_B$ receptors are metabotropic Ca^{2+} or K^+ channels, conducting slow inhibitory neurotransmission, in which a ligand (i.e., GABA) binds and indirectly induces pore opening through G-protein coupling activation and second messenger signaling [64, 67, 68] (**Figure 7**). Functional $GABA_B$ receptors exist as heterodimers composed of one $GABA_{B(1)}$ (1a-g) and one $GABA_B$ subunit [70]. The $GABA_{B(1)}$ subunit binds to GABA and is mandatory for functional receptors, whereas the $GABA_{B2}$ subunit is responsible for G-protein coupling and signaling. The most prevalent $GABA_B$ isoforms are $GABA_{B(1a)}$ and $GABA_{B(1b)}$, which are highly conserved across species. Other isoforms, 1c-g, have also been identified, but are either species-specific or do not exist naturally [64]. Baclofen, clinically used as a muscle relaxant, stimulates $GABA_B$ receptors, which are otherwise insensitive to drugs that modulate the $GABA_A$ receptors [67].

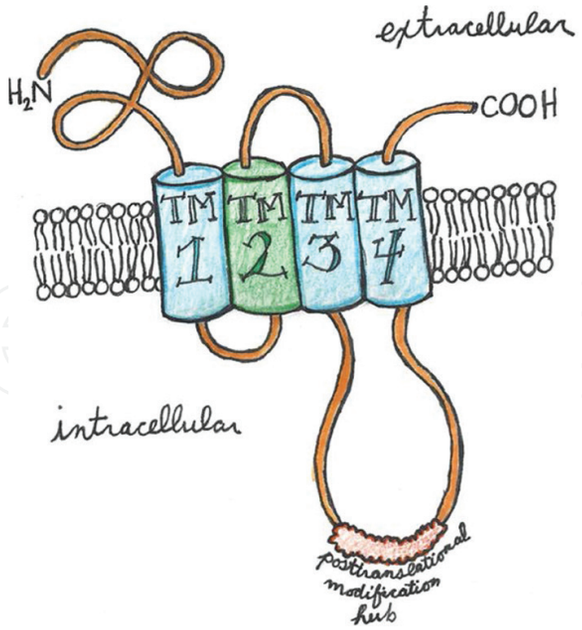

Figure 6. $GABA_A$ receptor transmembrane topology. Each subunit consists of four transmembrane domains. The N- and C-terminus lie on the extracellular side, with the N-terminus being the site of action for several drugs. A large intracellular domain exists between TM3 and TM4, providing a hub for a majority of the protein-protein interactions as well as posttranslational modifications (palmitoylation, ubiquitination, phosphorylation) [65, 69].

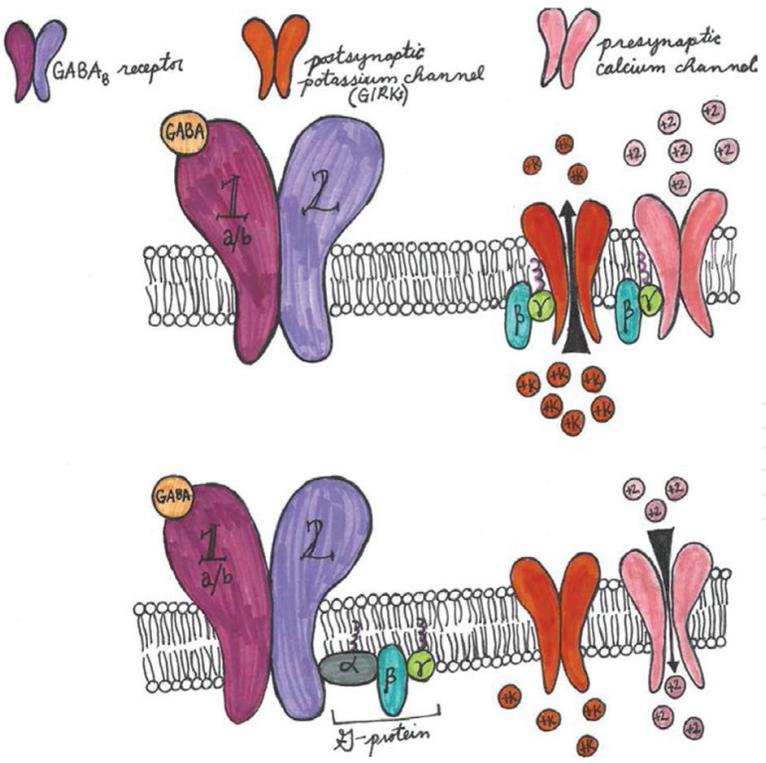

Figure 7. $GABA_B$ receptor structure. $GABA_B$ receptors are heterodimers composed of either a 1a or 1b subunit and a mandatory 2 subunit. $GABA_B$ receptors are G-protein coupled and are activated by the ligand GABA, which binds to the 1 subunit. Following GABA ligand binding, G-protein activation induces opening of postsynaptic potassium channels and closing of presynaptic calcium channels, hyperpolarizing the target cell (Modified from Emson [64]).

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13. Distribution

$GABA_A$ subunit expression has been well characterized in the rat brain [66]. Several subunits exhibit broad expression throughout the nervous system, fluctuating across development and regions. However, a few subunits demonstrate regional or cell-type specificity. For example, $\alpha 6$ subunit is exclusively expressed in cerebellar granule cells and the ρ subunit is largely restricted to the retina. Peripheral expression of $GABA_A$ receptors has been demonstrated in the liver, smooth airway muscles, the lung, immune cells, and the intestines [68]. $GABA_B$ receptors are localized in the striatum, brainstem, thalamus, hippocampus, cerebellum, and cortex. The 1b subunit is the most prevalently expressed across all brains regions, except for the striatum in which the 1a subunit is the most abundant [64].

14. Parvalbumin interneurons and the prefrontal cortex

The prefrontal cortex (PFC) is the neuroanatomical hub for executive functions such as working memory, which can be metaphorically thought of as the brain's blackboard [21, 71]. Incoming stimuli are transiently stored, manipulated, updated, and guide goal-directed behavior [72]. Working memory is dependent on prefrontal circuitry involving the unique balance between pyramidal Delay excitatory neurotransmission and GABAergic interneuronal inhibition [57, 62, 71]. Excitatory Delay cells become activated upon presentation of a salient cue and sustain neuronal activity throughout a delay period, essentially 'remembering' the cue, and allowing an appropriate response. For instance, **Figure 8** represents an

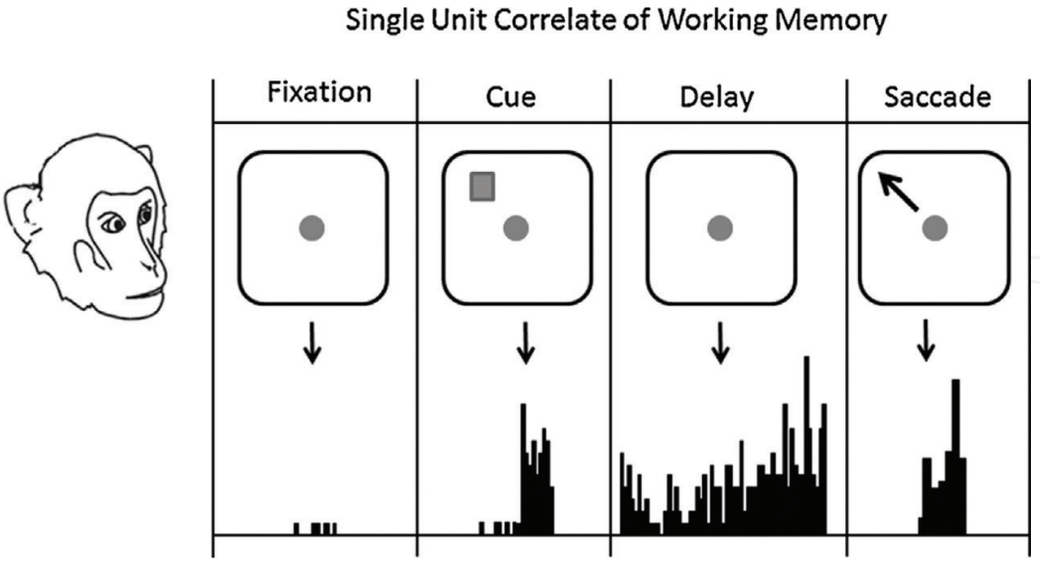

Figure 8. Single unit electrophysiological activity of a Delay cell in the primate DLPFC during a working memory task. The onset of Delay cell activity is triggered by the presence of relevant stimuli, or a cue. In the absence of a visual cue, Delay cells persistently fire during the delay period and allow for the generation of a goal-directed response (e.g., saccade). The sustained neuronal firing during the delay period is hypothesized to be the neural correlate of working memory and depends on both excitatory pyramidal activity as well as fast-spiking GABAergic interneurons in the DLPFC [21, 71, 73, 74] (Modified from Monaco et al. [21]).

example of single unit prefrontal Delay cell activity in the primate dorsolateral prefrontal cortex (DLPFC) during an oculomotor delayed-response task. In this working memory task, subjects are trained to fix their gaze at the center. A single cue is presented somewhere in the 360° perimeter, followed by a brief delay period in which the cue is absent. After the delay period, an appropriate response would be an eye saccade in the direction that the cue was first presented.

Working memory, the sustained neuronal activity that occurs during the delay, is not only dependent on prefrontal pyramidal cells, but also fast-spiking GABAergic interneurons [57, 62, 71]. Pharmacological evidence supports the importance of fast-spiking interneurons in the DLPFC for working memory function. Administration of a $GABA_AR$ antagonist, bicuculline, lead to impaired mnemonic tuning during an oculomotor delayed-response task. Therefore, working memory, particularly sustained neuronal activity during the delay period, depends on $GABA_A$ receptors. Furthermore, GABAergic hypofunctioning in the DLPFC partly contributes to working memory deficits [62, 75]. GABAergic neuronal activity and its role in working memory function are also connected to gamma oscillations. Gamma oscillations, which fall in the band range between 30 and 60 Hz, are required for working memory function. A research study conducted in 2003 reported that gamma band oscillations increased proportionally with working memory load [57, 62, 76]. More specifically, fast-spiking PV interneurons are a crucial input for gamma rhythm generation. Inhibition of PV interneurons attenuates gamma oscillations, whereas driving PV neuronal activity initiates gamma-frequency rhythms [62]. Excitatory pyramidal output in the prefrontal cortex is modulated by inhibitory gamma oscillations, largely driven my PV-interneurons, essentially fine-tuning the circuit and allowing for proper working memory function. Conclusively, PFC-dependent working memory involves a symbiotic balance between excitatory pyramidal output and fast inhibitory activity of PV-interneurons, which shapes and fine-tunes the circuit.

15. Parvalbumin interneuronal hypofunctioning in schizophrenia

Schizophrenia is a debilitating neurodevelopmental disorder in which afflicted individuals suffer from cognitive impairments, working memory deficits being a core feature. Unfortunately, available medications poorly treat cognitive symptoms albeit cognitive performance most strongly determines functional outcomes. Working memory function requires fast and synchronous inhibition of pyramidal neuronal networks within the prefrontal cortex, which is regulated by GABAergic neurotransmission. Because individuals afflicted with schizophrenia display reduced frontal cortical gamma oscillatory power in the DLPFC during a working memory task and cognitive impairments are a core feature, disrupted GABAergic signaling is highly implicated in the pathology of this disorder [57, 62]. Glutamic acid decarboxylase (GAD), the enzyme that synthesizes GABA and PV prefrontal expression is reduced in schizophrenia, further demonstrating a GABA deficit in this neuroanatomical region [57, 62, 77–79].

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NMDARs have been demonstrated to be vital throughout neurodevelopment, with NR2A specifically involved in the maturation and maintenance of GABAergic PV interneurons. A previous study showed that NR2A hypofunction leads to reduced GAD67 expression and PV immunoreactivity [59]. It is important to note that the reduction in parvalbumin is not due to density (i.e., interneuronal cell number), but rather a decrease in protein level expression. Researchers hypothesized that this suppressed expression in GAD67, and therefore PV, leads to GABAergic malfunctioning or hypofunctioning [57, 59, 62, 77]. Interestingly, GAD65, the other isoform, does not demonstrate such impairments. Cortical levels of GABA remained unaltered in animals without GAD65, thus demonstrated specificity to the GAD67 isoform [57, 62, 80]. Reductions in GAD67, however, are associated with decreased GAD enzymatic activity as well as GABA levels in the cortex [62, 81]. Individuals suffering from schizophrenia were also reported to have increases in the α_2 subunit of $GABA_A$ receptors and decreased GABA transporter 1 (GAT1) levels. GAT1 are proteins important for the removal of GABA from the synaptic cleft, while the $GABA_A$ α_2 subunit is highly concentrated at the axon initial segment of pyramidal neurons and mediate fast synaptic inhibitory neurotransmission (**Figure 9**). Therefore, this

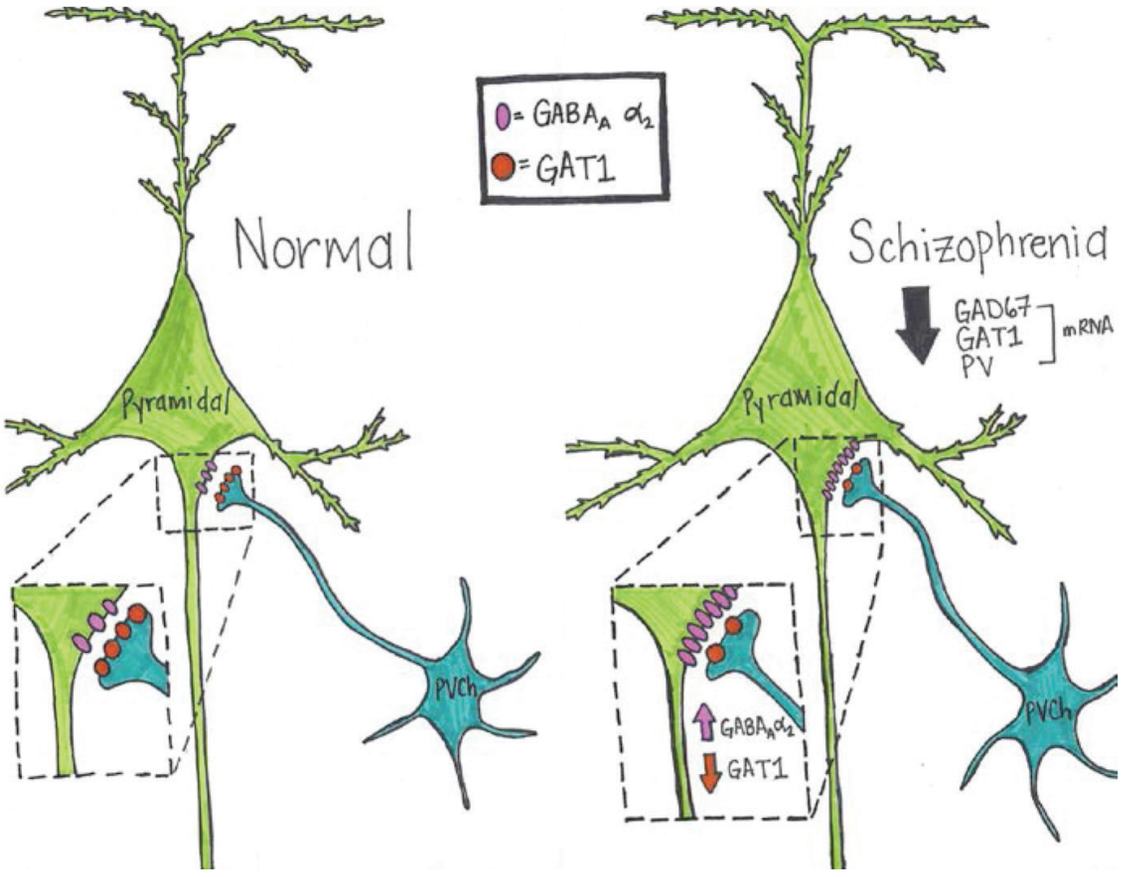

Figure 9. Comparison of normal and schizophrenia synaptic connection at the junction between a parvalbumin chandelier interneuron (PVCh) and a pyramidal axon initial segment. A core feature of schizophrenia is GABergic deficits; in the rebalanced circuitry, presynaptic expression of GABA transporter 1 (GAT1) on the axonal terminals of the GABAergic interneurons is decreased, while the expression of $GABA_A\alpha_2$ receptors at the axon initial segments of pyramidal neurons is increased (Modified from Lewis et al. [62] and Lewis et al. [57]).

inverse correlation is speculated to act as a compensatory mechanism to increase the effect of GABA on postsynaptic cells and return the circuitry back to homeostatic conditions [57, 62, 82].

However, what remains to be unanswered is which proceeds which: NMDA receptor hypofunctioning or GABAergic deficits. In order to understand how cognitive impairments in schizophrenia emerge, we must first uncover the molecular underpinnings that lead to the root of these dysfunctions.

16. Current GABA-targeted therapeutics

In individuals afflicted with schizophrenia, a compensatory mechanism to balance the circuit naturally gets set into motion. In order to offset the shift towards excitation, GAT1 is reduced presynaptically and $GABA_A\alpha_2$ receptors are increased postsynaptically. These changes result in levels of GABA remaining in the synaptic cleft longer and more postsynaptic receptors available for activation. $GABA_A\alpha_2$ receptor agonists offer as a promising therapeutic to pharmacologically target the pathophysiological inhibitory deficit in the DLPFC [62]. $GABA_A\alpha_2$ receptors are predominately located at the axon initial segment of pyramidal neurons and therefore should exhibit limited off-target effects on other domains [83]. $GABA_A\alpha_2$-selective benzodiazepines are a likely candidate because these agents would only activate and potentiate $GABA_A\alpha_2$ receptors in the presence of GABA, preventing dysregulated inhibition that would otherwise result from direct activation of these receptors. Treatment with $GABA_A\alpha2$-selective benzodiazepines might also offer an additive benefit of reducing anxiety in patients, due to the anxiolytic effects that are mediated by $GABA_A\alpha_2$ receptors [62, 84]. In aims to provide better treatment options, further research is warranted to elucidate the underlying mechanism of GABAergic hypofunctioning, which largely contribute to working memory deficits seen in schizophrenia.

17. Summary

Working memory is a key executive function that guides an organism's response by filtering out important information from the external environment and applying relevant details towards a goal-directed behavior. This process requires the output of a specialized circuit localized within the prefrontal cortical circuits. The synchrony between excitatory pyramidal Delay cells, which produce the necessary persistent neuronal activity, and fast-spiking GABAergic neurotransmission, which in turn shape and fine-tunes the pyramidal cell output, underlies working memory. Both the excitatory and inhibitory components (such as NMDARs and $GABA_A$Rs) are crucial in the maintenance of this delicate process, and dysregulation of either likely serves as a pathophysiological process in schizophrenia. Working memory deficits are a core feature of schizophrenia with NMDA and GABA hypofunctioning highly implicated in the etiology of the disease. Future research is warranted for further deciphering whether NMDA hypofunctioning precedes GABAergic deficits or vice versa.

Acknowledgements

This work was supported by NIH R01MH085666, R21MH110678, and NARSAR Independent Investigator Award 2016 from the Brain and Behavior Research Foundation to W.J. Gao.

Declarations/Competing interest

The authors claim no conflicts of interest.

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