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Emerging therapeutic targets for schizophrenia: a framework for novel treatment strategies for psychosis

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Abstract

Introduction: Antipsychotic drugs that target the dopamine system have been central to the treatment of schizophrenia, but their limitations in efficacy, tolerability, and precision necessitate improved treatment strategies. Multiple lines of research have implicated glutamatergic dysfunction in the hippocampus as an early source of pathophysiology in schizophrenia. Novel compounds have been designed to treat glutamatergic dysfunction, but they have produced inconsistent results in clinical trials.

Areas Covered: This review discusses how the hippocampus is thought to drive psychotic symptoms through its influence on the dopamine system. It offers the reader an evaluation of proposed treatment strategies including direct modulation of GABA or glutamate neurotransmission or reducing the deleterious impact of stress on circuit development. Finally, we offer a perspective on aspects of future research that will advance our knowledge and may create new therapeutic opportunities. PubMed was searched for relevant literature between 2010–2020 and related studies.

Expert Opinion: Targeting the aberrant excitatory-inhibitory functioning observed in the hippocampus and its related circuits has the potential to both alleviate symptoms and reduce the risk of transition to psychosis if implemented as an early intervention. Longitudinal multimodal brain imaging combined with mechanistic theories generated from animal models can be used to better understand the progression of hippocampal-dopamine circuit dysfunction and factors related to heterogeneity in treatment response.

Keywords

Schizophrenia; Antipsychotic; Dopamine; Glutamate; GABA; Hippocampus; D2; Early Intervention

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Declaration of Interest

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1.0 Introduction

Schizophrenia is most characteristically defined by psychotic symptoms, which include hallucinations and delusions. Psychosis in schizophrenia typically emerges in late adolescence and early adulthood (1). The first episode of psychosis (FEP) is often preceded by a prodromal period as sub-threshold symptoms develop, including attenuated psychotic symptoms, and deterioration in social and cognitive functioning (2). Some patients experience sustained symptom remittance with treatment and fully recover functional capability following FEP, However, many patients remain chronically ill with exacerbations and remissions of symptoms over time (3–5).

Current antipsychotic drugs are generally effective at dampening psychotic symptoms, but they often leave a high level of disease burden (6, 7), and numerous side effects that contribute to treatment nonadherence (8). Considerable heterogeneity exists in symptom profiles and treatment response. Up to 30% of patients display persistent symptoms despite multiple trials of antipsychotic drugs, referred to as treatment resistance (9, 10). There are few options available to patients with treatment resistance because all antipsychotic drugs produce their therapeutic effect via a common mechanism, by blocking D_2 receptors (11). Blockade of D_2 receptors reduces dopamine (DA) transmission, in line with the DA hypothesis, which postulates that increased presynaptic DA transmission in the striatum underlies the expression of psychosis (12, 13). However, it has been proposed that patients who do not respond to current drugs may either not display this hyperdopaminergic phenotype, which would be apparent from the start of treatment, or they may develop DA supersensitivity over time following prolonged D_2 antagonist treatment (14–16). These situations highlight the need for alternative treatment strategies.

Although DA hyperactivity plays a critical role in schizophrenia, it is not the only neurotransmitter involved in the development of psychosis and multiple lines of research have demonstrated that it is secondary to dysregulation of excitatory and inhibitory neurotransmission (17, 18). In addition, current DA antagonist drugs fail to effectively address cognitive and negative symptoms of this disorder (19). Numerous novel target mechanisms have been tested in clinical trials, yet none have proven sufficiently effective to be approved for clinical practice (20, 21). This review will focus on promising strategies for treating DA dysfunction in schizophrenia through targeting upstream pathophysiology in the hippocampus, with a focus on targeting excitatory-inhibitory dysregulation through 1) drugs that act therapeutically to regulate glutamate, GABA, or inflammation 2) approaches that are preventative in nature, such as mitigating the effects of stress or early behavioral intervention (Table 1).

2.0 Neurotransmitter Dysregulation in Schizophrenia

2.1 Dopamine

Neuroimaging studies have demonstrated that psychotic symptoms are associated with increased presynaptic DA signaling in the striatum, including measures of synthesis capacity and release (22–27). Higher DA synthesis capacity is also observed in clinically high risk (CHR) individuals, which correlates with greater severity of prodromal symptoms (28, 29).

DA synthesis capacity progressively increases as CHR individuals transition to psychosis and it may be able to predict likelihood of conversion (28–31). These findings support the hypothesis that presynaptic DA dysfunction in subcortical projections, particularly to the associative striatum (26), is closely linked to the onset and expression of psychotic symptoms. The DA hypothesis has held up to decades of research, but it has also been modified based on evidence that the nature of DA dysregulation varies based on brain region (13). Specifically, blunted DA release has been reported in prefrontal cortical regions in patients with schizophrenia, which is suggested to contribute to cognitive symptoms (32). Potential therapeutic options for modifying cortical DA transmission have been discussed elsewhere (33, 34), and this review will focus on treatment of psychosis associated with the subcortical DA dysregulation and other target structures.

All current antipsychotics target the DA system by blocking D_2 receptors (11). Animal research has shown that D_2 antagonists reduce the number of spontaneously active DA neurons (i.e. population activity) (35–37). Blockade of both presynaptic and postsynaptic D_2 receptors results in overexcitation-induced depolarization block, leading to a broad reduction in DA signaling (38). The majority of antipsychotic drugs act as D_2 antagonists; however, D_2 partial agonists, such as aripiprazole are also available. D_2 partial agonists produce a “normalizing” effect on DA neuron population activity depending on the state of the DA system (39, 40). In contrast to D_2 antagonists, D_2 partial agonists do not induce depolarization block in vivo, and instead may functionally act as an agonist on presynaptic D_2 receptors to downregulate DA neuron activity (41). Although current antipsychotics directly target the DA system, there is little evidence for dysfunction within the DA system itself. Its hyperresponsiveness is instead proposed to be a consequence of excitatory-inhibitory imbalance in afferent structures (42).

2.2 Glutamate and GABA

One strategy to address DA dysfunction in schizophrenia is to modulate the upstream abnormalities in glutamate and GABA neurotransmission. Schizophrenia is associated with altered excitatory-inhibitory transmission in several brain regions, and some studies have shown these abnormalities are present in CHR individuals (43). The hippocampus displays a hypermetabolic state in patients with schizophrenia (44–49). Increased perfusion has also been observed in CHR individuals in the CA1 region (50–52), which spreads to the subiculum, the predominant output structure of the hippocampus, upon onset of psychosis (48). Elevated hippocampal glutamate levels have been observed in patients diagnosed with schizophrenia (43, 53–55), and reported in CHR individuals in some studies (50, 53), although not all (56). There is evidence that glutamate levels in CHR individuals may predict conversion to psychosis (53, 57), although this is also not a consistent finding (50, 56). It is possible that these changes in the hippocampus relate to a general psychosis spectrum that may or may not reach diagnostic criteria for schizophrenia, which may contribute to inconsistencies in longitudinal studies looking at CHR individuals. Additionally, there are different indices of glutamate functioning, including glutamate itself, its metabolite, glutamine, and Glx (glutamate + glutamine). Some studies have found increases in glutamate, whereas others have reported increases in glutamine, Glx (43, 58), or

the ratio of glutamine to glutamate (59, 60), which has been suggested to be a more sensitive measure of glutamate release (59)

The increased metabolism of the hippocampus is associated with a loss of local GABAergic parvalbumin (PV+) interneurons that normally regulate pyramidal neuron activity, and local atrophy, which is believed to reflect loss of the interneurons and neuropil (61–63). More research is needed to understand the relationship between these pathophysiological findings, how they relate to vulnerability to psychosis in the high-risk state, and their relative progression over time. Ultimately, the resulting loss of GABA interneuron function is proposed to lead dysregulation of excitatory neurotransmission within the hippocampus, and thereby a disruption of a polysynaptic circuit that regulates DA transmission.

The methyazoxymethanol acetate (MAM) neurodevelopmental rodent model (64, 65) has demonstrated that increased pyramidal neuron activity in the hippocampus leads to an increased number of spontaneously active DA neurons available for phasic DA release. The offspring of pregnant females that receive an injection of MAM at gestational day (GD) 17 develop adult phenotypes relevant to schizophrenia, in contrast to the offspring of pregnant females that receive a saline (SAL) injection (64, 66, 67). Similar to findings in schizophrenia patients (17), MAM rats show loss of PV+ interneurons in the hippocampus (63), resulting in an increase in pyramidal cell activity and a baseline hyperactive state (68). The subiculum of the hippocampus extends glutamatergic projections to the nucleus accumbens, which in turn inhibits the ventral pallidum. (69, 70). The ventral pallidum holds a variable proportion of DA neurons in the VTA in a hyperpolarized state. As a consequence of hippocampal hyperactivity, greater inhibition of GABAergic neurons in the ventral pallidum results in reduced inhibitory hold on DA neurons in the VTA and an increase in the number of spontaneously active DA neurons compared to control rats (68). This circuit is normally adaptive to environmental stimuli to set the gain of DA neurotransmission. However, with abnormally increased activity of the hippocampus, the DA neuron population activity is proposed to be set at a high gain state, allowing for increased release of DA in the striatum, consistent with clinical studies in patients with schizophrenia (42, 63, 68) (Figure 1).

3.0 Promising Antipsychotic Drug Targets

Numerous novel target compounds for the treatment of schizophrenia have shown promise in preclinical research, but to date, none have shown sufficient efficacy in phase 3 clinical trials to enter clinical practice (34). However, the increased striatal DA signaling targeted by current antipsychotics is a consequence of upstream anomalies that are implicated in both the development and expression of psychotic symptoms (71). Indeed, the induction of DA supersensitivity by prior treatment with current antipsychotic drugs may interfere with the efficacy of such novel target agents (72). These targets are derived from a well-supported framework and still show promise, but future studies are required to better understand their mechanisms of action and optimal methods for clinical trial design and ultimately treatment.

3.1 GABA

Compounds that target the GABA system aim to restore normal patterns of PV+ interneuron activity. Indeed, transplants of GABA interneuron precursor cells into the hippocampus of MAM rats has been shown to normalize hippocampal pyramidal neuron activity and DA neuron population activity, demonstrating that restoring GABA function is sufficient to normalize the aberrant hippocampus-DA circuit (73). Increased GABA signaling can also be accomplished through direct modulation of GABA receptors. Broad action GABA modulators, such as benzodiazepines are problematic due to their sedative actions, risk of dependency and inferiority in reducing psychotic symptoms compared to current antipsychotics in patients with chronic schizophrenia (74), but other, more localized options, have been studied for their potential therapeutic value.

One target that has shown promise is the α5 subtype of the $GABA_A$ ($\alpha5GABA_A$) receptor, which is highly expressed in limbic brain regions, including the hippocampus (75). $\alpha5GABA_A$ receptors are involved in generating a tonic inhibitory current to pyramidal neurons, which may help coordinate spike timing (76–78). A positive allosteric modulator (PAM) that acts at $\alpha5GABA_A$ receptors has been tested in the MAM model, and reduced DA neuron population activity and amphetamine-induced hyperlocomotion to control levels when administered either systemically or directly infused into the ventral hippocampus. $\alpha5GABA_A$ PAM administration also reduced evoked responses in hippocampal neurons (79). The $\alpha5GABA_A$ receptor may be an effective antipsychotic target to normalize hippocampal activity, but it has yet to be tested in patients.

The mood stabilizer valproate has also been studied as a potential antipsychotic that affects the GABA system. Valproate inhibits histone deacetylation and can increase GABA synthesis at high concentrations (80–83). As a treatment for schizophrenia, some clinical trials found that valproate could enhance the rate of improvement of symptoms when used as an adjunct to current antipsychotics, but results were inconsistent (84–86). More recently, valproate has been studied for its potential in reinstating critical periods of plasticity in adulthood (87–89), and thus might provide additional value in conjunction with other therapies.

3.2 Glutamate

Evidence from preclinical and clinical studies have supported the role of glutamate system dysfunction in the pathophysiology of schizophrenia, including elevated levels of glutamate in the hippocampus of unmedicated patients (43). Thus, another promising option for the treatment of schizophrenia is inhibition of glutamate release.

Numerous glutamate-targeting compounds have been evaluated in clinical trials. NMDA receptor co-agonists, including D-cycloserine, D-serine, and glycine, were among the earliest studied in an effort to enhance NMDA-mediated interneuron function (90), thereby increasing inhibition of pyramidal neurons. Despite initial promise in clinical trials, none of these compounds passed phase 2 or phase 3 clinical trials as either a monotherapy or adjunct to current treatments (91, 92). Selective glycine transporter 1 (GlyT1) inhibitors, such as sarcosine and biopertin have also been tested as an alternative method to increase the

availability of glycine at NMDA receptors (93). Sarcosine has demonstrated success in clinical trials as an adjunct treatment in early clinical trials in improving positive, negative, and cognitive symptoms (94, 95) with some evidence for greater efficacy than NMDA receptor agonists (96). However, not all trials have shown significant results with GlyT1 inhibitors, such as when added to clozapine or tested as a monotherapy (97–99). D-amino acid oxidase (DAAO) inhibition with compounds such as sodium benzoate, has also recently been explored as a method of enhancing NMDA receptor activation by blocking D-amino acid metabolism. Sodium benzoate has produced promising results as an adjunctive therapy in early clinical trials (100–102). Larger clinical trials are needed to better assess the potential benefits of NMDA receptor-targeting drugs.

Group II metabotropic glutamate receptor (mGluR2/3) agonists were another target that garnered interest as a novel treatment for schizophrenia. mGluR2/3 are expressed in limbic brain regions and localized presynaptically on glutamatergic terminals to negatively regulate glutamate release (103). Preclinical research produced extensive support for mGluR2/3 agonists and PAMs (104–109). The mGluR2/3 agonist, pomagluemtad methionil, was shown to reduce hippocampal pyramidal neuron hyperactivity in the MAM model, resulting in the downstream normalization of DA neuron population activity and improvement in a hippocampal-dependent task, which were not observed in normal rats (110).However, while pomaglumetad methionil demonstrated efficacy in a phase 2 clinical trial (111) it subsequently failed to show efficacy in other phase 2 trials as a monotherapy or adjunct therapy (112–114) and as a monotherapy in a phase 3 trial (115). It has been suggested that it may be most effective early in the disease (116) or that the dose used in clinical trials was not adequate (117). Another possibility is that withdrawal from current D_2 antagonist drugs leaves a state of DA receptor supersensitivity, impeding the efficacy of non-D_2 drugs at reversing the hyperdopaminergic state, as suggested in animal models (72). This could also account for why patients that had not been treated as long with D_2 antagonists show greater efficacy. Additional trials are needed in FEP and CHR populations for clarification and further research is needed to understand why certain groups may respond better to glutamate-targeting drugs.

3.3 Inflammation

Another potential means of early intervention in schizophrenia is through targeting neuroinflammation and immune system dysregulation (118). Prenatal inflammatory events, such as infections, illicit maternal immune activation that may cause deleterious effects on neurodevelopment. In combination with other risk factors, it may lead to disrupted synaptic plasticity and impaired development of PV+ interneurons from oxidative stress that leave the brain vulnerable to additional hits of stress (119, 120). In animal models, early life immune activation, such as through injecting double-stranded RNA poly(I:C) or bacterial lipopolysaccharide (LPS), alter cytokine levels in the placenta, amniotic fluid and fetal brain (121–125). This leads to increased vulnerability to stress-induced increases in inflammatory markers in adulthood (126), consistent with findings in patients with schizophrenia (127, 128). Risk of transition to psychosis is also associated with increases in inflammatory markers (129, 130). Some anti-inflammatory compounds have demonstrated prophylactic effects in maternal immune activation rodent models, including N-acetylcysteine and

sulforaphane (131, 132). Antioxidants that reduce inflammation, such as omega-3 fatty acids (133) have produced mixed success in reducing transition rates in patients (2, 134, 135), but investigation of other anti-inflammatory compounds may be warranted. For example, some studies have demonstrated a deficit in glutathione in patients with schizophrenia, which is a prominent cellular antioxidant. Glutamatergic dysfunction and subsequent atrophy may be most apparent in the presence of insufficient glutathione, and it has been proposed that interventions that increase glutathione may be beneficial in preventing the detrimental effects of oxidative stress (136, 137).

3.4 Stress

Based on the diathesis-stress model, early disruption in brain development can lead to heightened vulnerability to stress (138, 139). Increased vulnerability to stress implies that there does not need to be a difference in the acute stress exposure, but in vulnerable individuals stress may trigger the first episode and precede relapses (140, 141). Dysregulated hypothalamic-pituitary-adrenal (HPA) axis activity is implicated the development of schizophrenia (142). In CHR individuals, salivary cortisol levels are correlated with severity of anxiety, suspiciousness, and impaired stress tolerance (142, 143) and also higher in individuals who transition to schizophrenia compared to those who do not (144). It is specifically distressing psychotic-like experiences in adolescence that are most indicative of CHR state and greater risk of developing a psychotic disorder (145). Compared to healthy controls, patients with active psychosis and those at CHR demonstrate greater stress-induced DA release, associated with an elevated cortisol response to the stressor (146).Together, these findings suggest a close link between stress sensitivity and the development of DA dysfunction.

The hippocampus is highly susceptible to stress (147, 148) and the influence of the HPA axis on hippocampal circuits may serve as a critical mediating link between environmental stressors and the development of psychosis, as these systems can act synergistically to stimulate subcortical DA (149). Early neurodevelopmental insults and other factors that increase response to stress early in life may increase the vulnerability of the hippocampus to HPA activation. The prelimbic prefrontal cortex (plPFC) normally limits the impacts of stress on basolateral amygdala activation in rats (150, 151), which holds a robust modulatory influence on DA neuron activity (152). For example, plPFC lesions performed in naïve rats shortly post-weaning (postnatal day 25) caused the rats to show increased anxiety-like behaviors as adults. When exposed to stressors during puberty do not result in increased DA neuron population activity in adulthood in control rats, the plPFC-lesioned rats exhibit the hyperdopaminergic phenotype as adults (153). However, a combination of prepubertal stressors can lead to increased DA neuron population activity, increased hippocampal pyramidal neuron activity, and a loss of hippocampal PV+ interneurons even in naïve rats that have not experienced plPFC lesions (87, 153). Similarly, MAM rats exhibit a greater response to stress and amygdala hyperactivity pre-pubertally prior to the emergence of the hyperdopaminergic state in adulthood (154, 155). Prepubertal environmental enrichment was sufficient to prevent DA hyperresponsivity in MAM rats through normalizing ventral hippocampal pyramidal neuron activity; however, it was not sufficient to reduce anxiety-like behavior in an elevated plus maze nor hyperactivity of the basolateral amygdala (156). Thus,

treatments that reduce stress, and more specifically, protect PV+ interneurons in the hippocampus, may be particularly effective when administered during adolescence.

Taken together, these studies suggest that severe stress or heightened stress responsivity during adolescence may exacerbate the impact of inflammation, leading to impaired development of PV+ interneurons in the hippocampus, and ultimately impaired DA system function that may reciprocally impact stress (157, 158). The hippocampus is a particularly promising target for reducing the effects of stress because PV+ interneurons in the hippocampus continue to mature through late adolescence (159), creating a potential window of opportunity for intervention. The interaction between stress and neurobiological changes indicates that psychological treatments, such as cognitive remediation, cognitive behavioral therapy, or psychosocial therapies, have the potential to be disease modifying. Psychotherapy can be implemented to mitigate stress reactivity and promote social integration, which could have beneficial effects in protecting circuits from disruption. Hybrid treatments with the use of psychotherapy alongside pharmacotherapy may be the most successful in reducing the impact of stress on the neurodevelopment schizophrenia and related disorders (160–162).

4.0 Timing of Treatment

The prodromal phase of schizophrenia is characterized by a period of functional decline, including the emergence of sub-clinical psychotic symptoms that generally begin after puberty and progress in severity (163). It is unclear to what extent schizophrenia is progressive following the prodromal period (164, 165), due to confounding variables such as antipsychotic medication (166–170). The duration of untreated psychosis is a critical factor in determining prognosis, suggesting that active psychosis may be progressively detrimental until treated and alterations in brain structure and neurophysiology may already be established by the time of diagnosis (163). Early interventions may thus provide greater benefits (171).

The developmental changes that occur during puberty have been suggested to be a critical period surrounding the onset of psychosis, such that targeting pathophysiological processes during this time may provide long-term amelioration of symptoms (158). This period of plasticity to allow for maturation may contribute to the vulnerability of the developing brain to environmental factors, including psychological stress, social isolation, and drug abuse, that can lead to the emergence of psychiatric disorders (126, 172). Critical period closure following puberty is marked by the development of perineuronal nets that surround PV+ interneurons to stabilize synapses (173). Oxidative stress may disrupt the formation of perineuronal nets, leading to impaired PV+ interneuron function (87, 174). Antioxidants and glutamate modulating agents have been shown to prevent damage to the perineuronal nets in rodent studies (175). Pharmacological treatments administered during puberty in the MAM model have also been shown to prevent PV+ interneuron loss and circumvent the emergence of schizophrenia-relevant phenotypes in adulthood. Furthermore, peripubertal administration of the anxiolytic drug diazepam prevented the increase in DA neuron population activity, increased anxiety-like behavior and the higher neuronal firing rates within the basolateral amygdala normally present in adult MAM rats, compared to adult SAL rats (154, 155). Long

term administration of benzodiazepines is not a feasible intervention due to issues including dependency (74), but these findings indicate that alleviating anxiety and abnormal stress responsivity during puberty may preserve PV+ interneurons and prevent the progression of abnormalities associated with psychosis.

5.0 Heterogeneity in Treatment Response

Due to the substantial variability in symptoms and treatment response, in addition to overlap with other disorders, schizophrenia is not likely to be a distinct disease entity. Its clinical presentation displays better conformity with the concept of a syndrome that lies upon a spectrum and potentially encompass multiple subtypes (176, 177). The heterogeneity is likely reflected in individual differences in the underlying neurobiology that are not adequately treated by current antipsychotics.

PET studies have demonstrated that some patients with treatment resistant schizophrenia do not display striatal hyperdopaminergic activity that is observed in treatment-responsive patients. In contrast, treatment resistant patients displayed increased levels of glutamate in the anterior cingulate, which is present from the first episode (14, 15, 178–180). Differences in glutamate have also been observed in patients who respond to clozapine, the antipsychotic that currently has the highest efficacy for refractory symptoms (181). Clozapine-responsive patients displayed higher levels of glutamate and glutamine in the putamen compared to patients who respond to first-line treatment and those who are resistant to clozapine (“ultra-treatment resistant”) (182). Whether this is indicative of a different disease pathophysiology or differences in system responsivity is unclear. For example, rapid antipsychotic drug-induced induction of depolarization block of DA neurons requires the presence of a hyper-excited DA system at baseline. If the DA system function is attenuated, addition of antipsychotics may be subthreshold for inducing depolarization block and preventing abnormal DA system activation (35, 183). Further research is needed to determine whether treatment resistance from the first psychotic episode lies on a spectrum or represents multiple distinct subtypes. A greater understanding of how individual patterns of network dysfunction contribute to differences in symptoms and clinical outcomes is critical to developing personalized treatments.

6.0 Summary

Current D_2-targeting antipsychotics alleviate certain symptoms in patients, but given their central role in the pathophysiology of schizophrenia (17, 63, 68, 184), GABAergic and glutamatergic targets still hold promise as an effective therapy to regulate glutamate activity and downstream dopamine hyperactivity. Additionally, they may provide options for individuals who are resistant to current antipsychotics and display glutamate hyperactivity, as demonstrated by neuroimaging studies. Early interventions that protect excitatory-inhibitory circuits, such as by reducing stress and neuroinflammation, have the potential to modify illness progression. Additional research on the development of psychosis and factors that contribute to heterogeneity in treatment response is needed to best implement these novel strategies.

7.0 Expert Opinion: A Framework for Future Research

The findings discussed in this review support the hypothesis that targeting prodromal and early phase schizophrenia has the potential to limit the pathophysiological progression that leads to a chronic illness state. The implementation of early intervention strategies for CHR individuals requires reliable biomarkers to predict disease course and treatment response. Potential candidates include striatal DA concentrations, metabolic activity and glutamate and GABA concentrations in regions including the hippocampus and anterior cingulate, resting state connectivity, salivary cortisol, and serologic markers of oxidative stress and inflammation (10, 163, 185–188). More research is needed to understand the relative reliability of these options, how different trajectories progress, whether current clinical trial designs are effective at identifying novel non-D_2 agents, and whether treating general psychopathology at the CHR state is beneficial across psychiatric disorders (189). It is also imperative to accurately predict the risk of transition to schizophrenia to avoid consequences, such as stigma, unnecessary treatment, and related adverse effects (190). Treatment of CHR individuals may reduce their risk of transition to schizophrenia, but they may remain at risk for other psychiatric disorders, such as depression or anxiety (189). A greater understanding of the neurobiology underlying the heterogeneity in schizophrenia will help to determine which therapeutic strategies are most effective for preventing or minimizing psychotic symptoms for an individual. We propose that the most promising avenues of research for novel antipsychotics and early intervention strategies are compounds that normalize excitatory-inhibitory transmission and either reduce stress or mitigate its effects.

Targeting excitatory-inhibitory processes, particularly compounds that regulate hippocampal activity, may avoid the side effects associated with D_2 antagonist treatment and may also alleviate more symptoms of the disorder, including negative and cognitive symptoms. Indeed, a hyperactive hippocampus can impact more than the DA system; its dysrhythmia may also interfere with functions in its other targets related to cognition and affect/negative symptoms (119). Clinical trials of excitatory-inhibitory-targeting agents have yielded disappointing results, but further research is needed to understand why these compounds failed, what impact prior treatments may have had on novel compound response, whether there are additional variables that must be considered, and how to more effectively target symptoms. There is evidence to suggest that these compounds may not be effective in patients with chronic schizophrenia who have already received prior D_2 antagonist antipsychotic drug treatment (72). However, some of these treatments may be effective in appropriate circumstances, such as in antipsychotic-naïve patients or those who are early in the disease (116). In addition to their prophylactic potential, treatments that normalize glutamate in the hippocampus may provide much-needed options for patients resistant to current antipsychotics (10, 14).

Additional longitudinal studies in clinical populations and neurodevelopmental animal models are needed to characterize the pathophysiological progression of the hippocampus-DA circuit over time and its relationship with changes in symptoms. Additional time points in large samples may provide clarity to the interplay between hippocampal glutamate levels, increased metabolism, and atrophy and how these factors relate to changes in the DA system

(191). A timeline of whether a strategy may be most effective in the high-risk state, and to what extent it remains beneficial following the first episode could provide valuable insight into early intervention strategies.

Compounds that treat schizophrenia closer to the site of pathology by modulating glutamate and GABA transmission and/or mitigating the effects of stress hold promise for improving outcomes in patients with schizophrenia. Future research must focus on improving our understanding of the heterogeneity of the disease to determine which patients are most likely to respond to a given intervention. Additionally, a more detailed timeline of the progression of pathophysiological changes involved in schizophrenia is required to determine the optimal window for treatment. Targeted research questions from clinical studies and animal models that move toward the goal of a more reliable and individualized process of treatment, driven by a more informed understanding of the variables at hand, will ultimately help break the status quo and improve clinical outcomes.

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Article Highlights

- Developmental animal models relevant to schizophrenia are an effective approach to examine how neurotransmitter systems interact and change over time, which can provide valuable information about potential targets for early intervention and treatment.
- Animal models have demonstrated that stress during puberty can impair perineuronal nets around interneurons and have long-lasting impacts on dopamine neuron activity.
- Modulating excitatory-inhibitory dysregulation is promising as an alternative therapeutic strategy to D_2-targeting antipsychotic drugs, and merits further research as a potential early intervention.
- Targeting hippocampal pathophysiology upstream of dopamine neuron dysfunction has the potential to both normalize dopamine neuron activity and alleviate other symptoms of schizophrenia.
- Future research must focus on categorizing subtypes to determine which patients may benefit most from a treatment, adapting clinical trial design for non-dopaminergic agents, and employing animal models to study changes that may not be apparent in normal rodents.

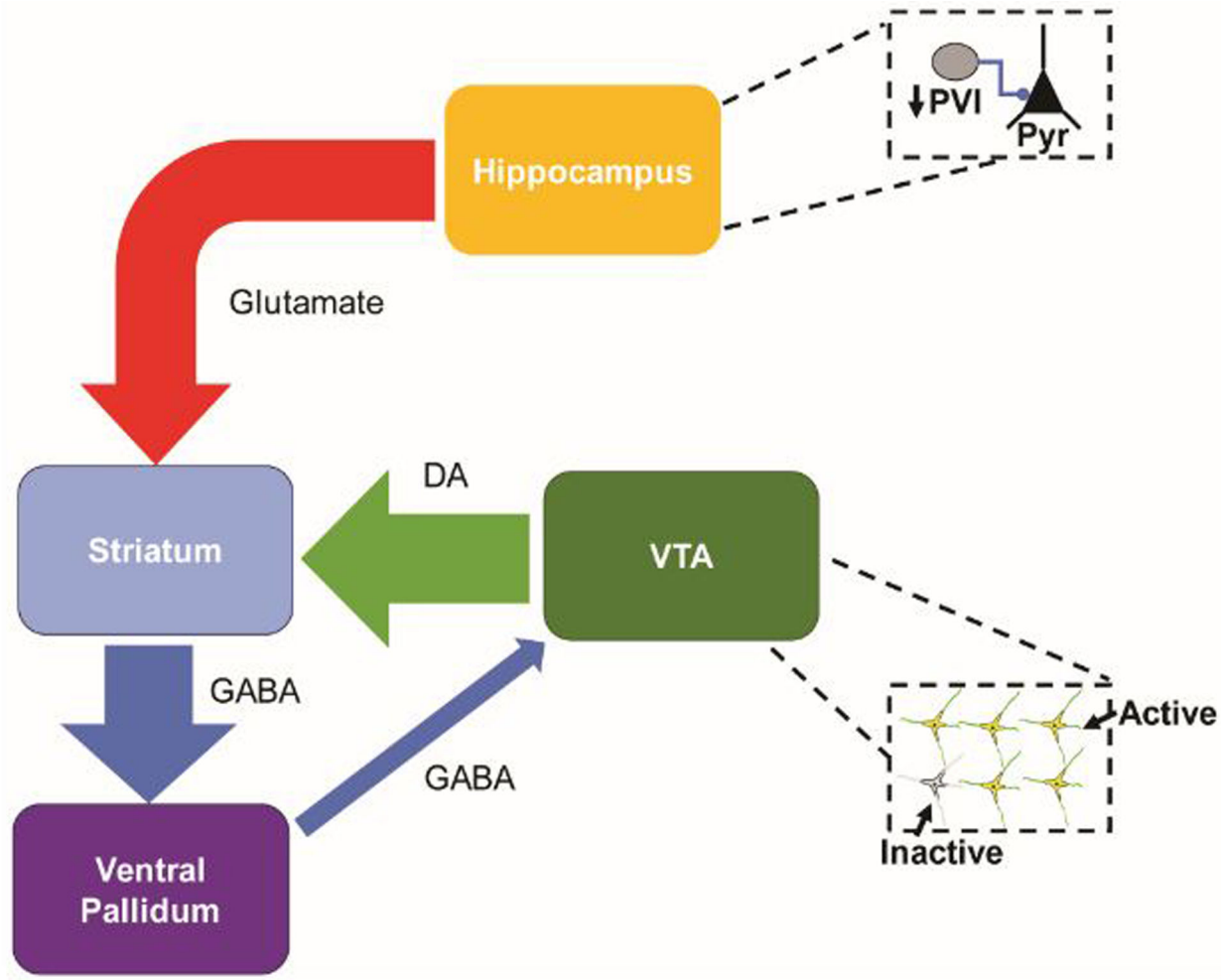

Figure 1. The hippocampus regulates DA neuron population activity through a polysynaptic circuit.

Pyramidal neurons (Pyr) in the subiculum of the hippocampus send excitatory projections to neurons in the nucleus accumbens that, in turn, inhibit activity in the ventral pallidum. The ventral pallidum holds a variable subset of DA neurons in the ventral tegmental area (VTA) in an inhibited state. Through this circuit, activation of the hippocampus modulates the number of spontaneously active DA neurons. In schizophrenia, hyperactivity of Pyr in the hippocampus, following a loss of PV+ interneurons, drives an increase in DA neuron population activity. The increased gain results in increased phasic striatal DA release.

Table 1.

A summary of potential targets for the treatment of psychosis.

Approach	Therapeutic/ Preventative	Putative Clinical Effect	Examples
GABA receptors	Therapeutic	Increase GABA signaling to increase inhibition of pyramidal neurons	• $\alpha 5GABA_A$ PAM • Valproate
NMDA receptors	Therapeutic	Enhance NMDA-mediated interneuron function to increase inhibition of pyramidal neurons	• GlyT1 • DAAO inhibitors
mGluR2/3 receptors	Therapeutic	Normalize glutamate release to reduce pyramidal neuron hyperactivity	• mGluR2/3 agonists
Inflammation	Both	Prevent oxidative stress to protect PV+ interneurons	• Glutathione
Stress	Preventative	Protect hippocampal circuits from environmental stressors/excessive HPA activation	• Psychotherapy to reduce stress reactivity