Schizophrenia: Genetics, neurological mechanisms, and therapeutic approaches

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From the Contents

Abstract

Schizophrenia is a complex psychiatric disorder marked by positive and negative symptoms, leading to mood disturbances, cognitive impairments, and social withdrawal. While anti-psychotic medications remain the cornerstone of treatment, they often fail to fully address certain symptoms. Additionally, treatment-resistant schizophrenia, affecting 30%-40% of patients, remains a substantial clinical challenge. Positive, negative symptoms and cognitive impairments have been linked to disruptions in the glutamatergic, serotonin, GABAergic, and muscarinic pathways in the brain. Recent advances using genome-wide association study and other approaches have uncovered a significant number of new schizophrenia risk genes that uncovered new, and reinforced prior, concepts on the genetic and neurological underpinnings of schizophrenia, including abnormalities in synaptic function, immune processes, and lipid metabolism. Concurrently, new therapeutics targeting different modalities, which are expected to address some of the limitations of anti-psychotic drugs currently being offered to patients, are currently being evaluated. Collectively, these efforts provide new momentum for the next phase of schizophrenia research and treatment.

Key Words: neuroinflammation; neuropsychiatric disorders; neurotransmitter pathways; schizophrenia risk genes; treatment resistance

Introduction

Schizophrenia (SCZ) is a complex psychiatric disorder characterized by a broad range of symptoms, including positive symptoms (hallucinations, delusions, disorganized speech, and behavior), negative symptoms (deficits in motivation and pleasure, and expression), and cognitive impairments (deficits in attention, working memory, and executive function) (Jauhar et al., 2022; **Figure 1**). Globally, SCZ accounts for a substantial disease burden with 13.4 million years of life lived with disability (95% UI: 9.9–16.7) based on Global Burden of Disease (GBD) study in 2016 (Murray et al., 2020). A recent comprehensive analysis of 396 medical conditions, which included major mental health disorders, reported an increase in the burden of SCZ experienced by individuals between the ages of 25 and 49 (Diseases and Injuries, 2020). A follow-up report from the GBD 2019 Mental Disorders Collaborators group, which specifically examined twelve mental disorders, ranked SCZ fifth as a cause of burden in individuals aged 15 to 24 years. Among individuals aged 25 to 69 years, SCZ was ranked third (following depressive and anxiety disorders, which have higher prevalence), and fourth among individuals over 70 years old (Collaborators, 2022).

The manifestation of SCZ-spectrum disorders is usually seen in early adulthood from ages 14–30 years, with a peak age of 20.5 years and a median age of onset of 25 years (Solmi et al., 2023). The lifetime occurrence of SCZ is approximately 1%, while the employment rate among individuals with the disorder is poor, at only 10%–15% (Dixon, 2017). Individuals with schizophrenia commonly face a range of physical comorbidities (He et al., 2022), engage in unhealthy lifestyle choices (Firth et al., 2020), and display numerous risk factors for cardiovascular and other medical conditions (Rossom et al., 2022). The primary approach in current pharmacotherapy for the treatment of SCZ involves the use of antipsychotic (AP) drugs. However, these medications have limited effectiveness in addressing negative and disorganized symptoms. They are also ineffective in approximately 30% of the cases when it comes to treating psychosis and is associated with a noteworthy incidence of adverse effects such as drug-induced parkinsonism (e.g., haloperidol) or weight gain or predisposition to metabolic conditions such as diabetes and hyperlipidemia (e.g., olanzapine; Pillinger et al., 2020).

The boundaries delineating SCZ from other psychiatric syndromes are overlapping. No single symptom is pathognomonic of SCZ; symptom overlaps are commonly observed with other psychotic and mood conditions, and childhood neurodevelopmental disorders (Lewine and Hart, 2020). The diagnosis of SCZ is based on the conceptualization of the disorder in the International Classification of Diseases (ICD) and Diagnostic Statistical Manual (DSM). These diagnostic guidelines are developed by the World Health Organization and American Psychiatric Association, respectively. To evaluate the patient, a thorough analysis of their background is conducted, including a detailed history and a mental status examination. It is crucial to assess the potential risks of self-harm or harm to others, as well as to consider the impact of substance use during this evaluation process. According to DSM-5-TR, the diagnostic criteria of SCZ comprise two or more presentations of delusions, hallucinations, disorganized speech and grossly disorganized or catatonic behavior, negative symptoms (i.e.,

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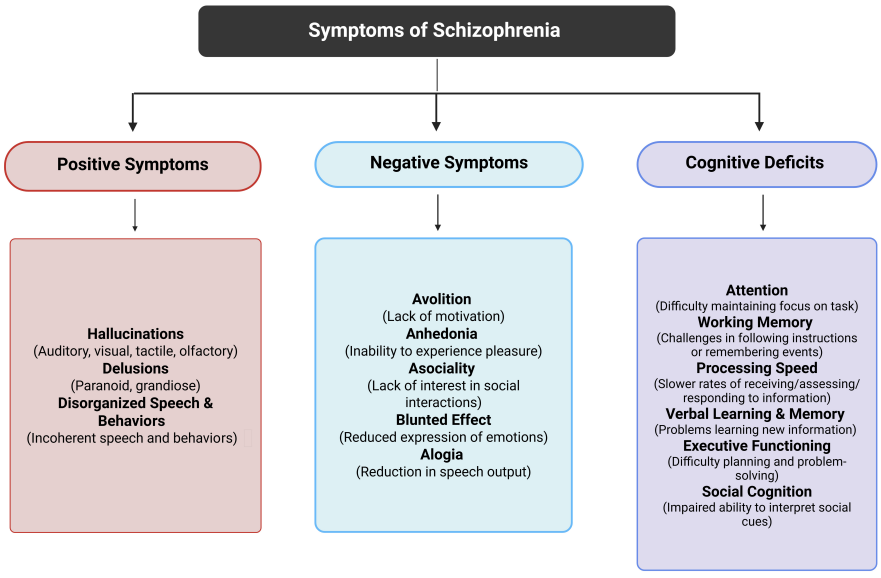

Figure 1 | **Positive, negative, and cognitive symptoms of schizophrenia.**
Positive symptoms encompass a range of experiences, such as hallucinations, delusions, and disorganized thinking in speech and behaviors. Negative symptoms refer to a reduction or absence of normal emotional responses and behaviors, including avolition, anhedonia, asociality, blunted effect, and alogia. Cognitive deficits involve impairments in mental processes, such as divided attention, poor working memory, slow processing speed, problems learning new information, and impaired ability to interpret social cues. Created with BioRender.com.

diminished emotional expression or avolition) for a substantial period during a month. Similarly, ICD-10 states that a patient must portray at least one of the positive symptoms or at least two of the negative symptoms coupled with catatonic behavior for a period greater than or equal to a month (First, 2024). Contrasting to DSM-5-TR, ICD-10 classifies SCZ into different subtypes based on the prominent symptoms observed in the individuals. These subtypes include paranoid SCZ, hebephrenic SCZ, catatonic SCZ, undifferentiated SCZ, post-schizophrenic depression, residual SCZ, simple SCZ, SCZ, other, and SCZ, unspecified. Although the use of ICD and DSM has allowed the general diagnosis and treatment decisions, the frameworks limit the comprehensive study of the disorder (Deacon, 2013).

There is no diagnostic biomarker for SCZ. Hence, diagnosis of SCZ requires both subjective reports and behavioral observations since there is no existing exhibit of clinical and biological diversity (Butcher et al., 2020; Bakken, 2021). On top of that, there is currently inadequate progress in developing diagnostic schemes and treatments based on its underlying pathophysiology. Despite extensive studies, conclusive pathological alterations similar to the presence of senile plaques and neurofibrillary tangles observed in Alzheimer's disease have not been detected in the postmortem brains of SCZ patients. Understanding the pathogenesis underlying SCZ is crucial to making progress in developing diagnostic approaches that are rooted in the underlying pathology and developing therapeutic options (Zhuo et al., 2019; Kimura et al., 2021).

SCZ is highly heritable, with 60%–80% heritability based on twin studies (Föcking et al., 2019; Cheng et al., 2021). By utilizing a large-scale genome-wide association study (GWAS) and leveraging single nucleotide polymorphism-based heritability estimates to dissect the genetic architecture of SCZ, significant genetic loci, and pathways associated with SCZ susceptibility have been identified, shedding light on the genetic underpinnings of the disorder (Trubetskoy et al., 2022). Therefore, by taking into account all detectable common genetic variants, even those with minimal or unsubstantial statistical correlation, researchers were able to elucidate over 20% of the susceptibility to SCZ (Nakamura and Takata, 2023). In this review, we will present recent clinical aspects of SCZ, summarize affected neurological pathways and mechanisms and specific genes involved, discuss leading therapeutics, and highlight upcoming drug targets in clinical trials.

Search Strategy

A comprehensive literature review on schizophrenia was conducted by utilizing databases such as PubMed, EMBASE, PsycINFO, and Medline, employing a multifaceted search strategy. Keywords related to the condition (schizophrenia, psychosis), symptoms (delusions, hallucinations, cognitive deficits), clinical outcomes (hospital admission, functional outcomes), clinical progression (first episode psychosis), drug targets (dopamine receptors, glutamate receptors), treatment strategies (antipsychotic medications, psychosocial interventions, clinical trials, drug targets), neurotransmitter systems (dopaminergic, glutamatergic, serotonergic) using "OR" within each category and "AND" to link categories.

Clinical Course, Trajectories, and Diagnosis of Schizophrenia

The majority of people with SCZ experience a prodromal period lasting several years, accompanied by notable psychosocial impact (Verdolini et al., 2022). The extent of both positive and negative symptoms are crucial determinants of patients' clinical progression, where cognitive deficits and other non-clinical factors (e.g., family support and social stigma) may also play a role (Harvey and Strassnig, 2012; Galderisi et al., 2014; Galderisi et al., 2020).

Positive symptoms

Awareness and concern about positive symptoms, also commonly referred to as psychosis, (delusions, hallucinations, and thought disorder) are presumably more distressing to the patient and often the reason they seek help. Psychotic experiences can vary in intensity and severity, occurring at different levels across a range. These symptoms usually occur during adolescence to early adulthood, between ages 18 to 25 years. In a short-term study performed on young patients with SCZ, positive symptoms were observed to be greatly reduced at discharge and remain stabilized (Arndt et al., 1995; de Winter et al., 2023). While there were some studies conducted on SCZ patients that reported persistent positive symptomatology (Maïza et al., 2011; Cobia et al., 2012), others reported progress during the study period (Gur et al., 1998; Reske et al., 2007). These contrasting results may have stemmed from the sample size used in the studies, where a smaller cohort of patients was used in studies that concluded persistent positive symptoms, and larger sample sizes were utilized in most of the studies that found favorable progress in symptom remission (Heilbronner et al., 2016).

Furthermore, long-term course studies that followed SCZ patients after 15 years found that while their negative symptoms remained stable, there was a significant decrease in paranoid and hallucinatory (positive) symptoms (Möller et al., 2010). Two separate studies assessed data from the Chicago Follow-up Study on the long-term course of positive symptoms with intervals of up to 20 years. The first study included patients with SCZ and bipolar disorder for the occurrence of Schneiderian first-rank symptoms, such as delusional perceptions and commenting voices found that 44% of patients with SCZ experienced these symptoms 2 and 4.5 years after their initial admission (Rosen et al., 2011). However, the prevalence decreased to 30% at the 10-year follow-up, only to increase again to 44% at the 20-year follow-up (Rosen et al., 2011). Another study examined hallucinations alone over time and found approximately 80% of patients with SCZ experienced these symptoms during their initial hospitalization (Goghari et al., 2013). This percentage consistently decreased to around 30% at the 15-year follow-up and demonstrated only a slight increase at the final measurement point of 20 years (Goghari et al., 2013). These studies make it challenging to draw definitive conclusions about the impact of medication status. However, it seems that a greater number of unmedicated individuals tend to experience longitudinally fluctuating positive symptoms.

Negative symptoms

Negative symptoms of SCZ often manifest during the prodromal phase of the disorder, preceding the first acute psychotic episode (An der Heiden et al., 2016; Correll and Schooler, 2020). It was previously found that the majority (70%) of

individuals experiencing negative symptoms had them prior to the onset of positive symptoms, while 20% of them showed negative and positive symptoms concurrently within the same month (An der Heiden et al., 2016). Hence, the emergence of negative symptoms during the prodromal stage has been identified as a potential risk factor for the transition to psychosis and healthcare providers are urged to remain vigilant regarding the presence of positive symptoms accompanied by lack of emotional expression, extensive social isolation, and signs of cognitive dysfunction (Goff, 2021).

Moreover, negative symptoms are harder to diagnose and treat (Kirkpatrick et al., 2023). Indeed, up to 60% of patients suffering from prominent negative symptoms are left untreated (Correll and Schooler, 2020), denoting an area of critical unmet medical need. This in part stemmed from the emphasis on positive symptoms and the notion that improvements in positive symptoms will extend beneficially to negative symptoms. Additionally, the clinical overlap between cognitive function and negative symptoms might lead clinicians to prioritize treatment for the former (Kirkpatrick et al., 2006; Skiba et al., 2024). To circumvent these issues, progress in developing valid scales for assessing and identification of negative symptoms has been made, even as efforts are still being made to develop interventions (Galderisi et al., 2021). Negative symptoms can be further categorized into primary (directly associated with SCZ) or secondary. The latter can be caused by positive symptoms, depression, extrapyramidal side effects of AP drug therapy, or other contributing factors such as substance abuse. As per the recommendations provided by the European Psychiatry Association regarding the management of negative symptoms, various interventions have demonstrated positive effects on alleviating these symptoms. These interventions include the use of second-generation AP drugs (i.e., risperidone, cariprazine, and olanzapine), antidepressant medications, psychosocial rehabilitation programs (such as social skills training), cognitive remediation techniques, and incorporating exercise into the treatment regimen (Galderisi et al., 2021). Nonetheless, the psychopathologic mechanisms driving negative symptoms remain poorly understood compared to those underpinning positive symptoms, which are more comprehensively studied (Habtewold et al., 2023; Wang et al., 2023).

In a study conducted to track long-term trajectories of first episode psychosis to investigate symptom course based on longitudinal clinical data, it was reported that the majority of participants in the study experienced a decrease in positive symptoms that eventually stabilized over time (Starzer et al., 2023). Furthermore, changes in negative symptoms were less pronounced, with more than half of the participants showing minimal or no significant changes from their initial levels (Starzer et al., 2023). The findings of this study align with the existing research on negative symptoms where patients with these symptoms are likely to experience them throughout the illness course (Butcher et al., 2020; Okada et al., 2021) and remain unresponsive to current treatments (Remington et al., 2015a; Mosolov and Yaltonskaya, 2021). Additionally, the extent of these symptoms has a direct impact on overall long-term functioning and recovery rates (Kalisova et al., 2023). These results suggest that compared to positive symptoms, negative symptoms result in a more persistent, deteriorating ramification of illness progression in SCZ patients.

Cognitive impairment

Cognitive impairment is a fundamental characteristic of SCZ that persists throughout the illness. Nevertheless, due to the challenges associated with investigating cognitive decline in individuals before the onset of the illness, the long-term trajectory is not completely comprehended. The period onset of cognitive impairment remains tricky to determine, and much of whether these intellectual inabilities predate psychosis as well as the degree of decline throughout the illness course remain unclear.

Impairment in cognitive function typically commences during adolescence in individuals who subsequently develop SCZ (MacCabe et al., 2013; Sakurai and Gamo, 2019). The current available evidence regarding the advancement of impairments after the onset of illness shows varying levels of consistency. There is a clear indication of a decline in cognitive function from the period prior to the onset of psychotic symptoms to the period following it (Karr et al., 2018; Sheffield et al., 2018). Although cognitive deficits often accompany psychosis, AP drugs do not effectively address or improve these cognitive impairments (Nielsen et al., 2015; McCleery and Nuechterlein, 2019). In fact, AP drugs show limited effectiveness in enhancing daily functioning, and studies indicate that functional impairment is more strongly linked to cognitive deficits rather than the severity of psychotic symptoms (Velligan et al., 1997; Harvey et al., 2022). As a result, addressing cognitive deficits becomes a crucial focus for enhancing the well-being of individuals living with psychotic disorders such as SCZ.

A cognitive function study performed two years after patients who exhibited the first episode psychosis observed improvement in verbal learning, and other aspects of cognitive functioning remained stable (Amoretti et al., 2021). Tapping onto the Chicago Follow-up Study, a group studied a subsample of the cohort and discovered that SCZ patients demonstrated declining performance over time in a test of executive function, specifically verbal fluency, while maintaining stable performance in most other cognitive domains (Burdick et al., 2006; Harrow et al., 2017). In short, SCZ sufferers commonly display significant deficits in overall cognitive function, usually averaging around two standard deviations below that of individuals without the condition (Keefe et al., 2011; McCutcheon et al., 2023).

Overall, late-onset SCZ patients may portray signs of dementia based on a five-year follow-up study where almost half of the patients met the criteria for dementia (Brodaty et al., 2003; Yang et al., 2023), identifying potential neurodegenerative changes in SCZ that develops later in life or suggesting the presence of concurrent dementia. The decline in cognitive function may be a common characteristic of SCZ in older individuals as they tend to experience a gradual decline in cognitive function as indicated by the Mini-Mental State Examination (Friedman et al., 2001). However, most studies do not provide enough details about the medication status of the participants to make any definitive conclusions about the impact of psychopharmacology on the collected results.

There is substantial evidence suggesting a decline in cognitive function prior to the emergence of psychotic symptoms, continuing into the period that follows. A recent study of the genetics underlying treatment-resistance SCZ (TRS) uncovered genes related to glutamatergic synaptic transmission and regulation embedded in the TRS genetic signal (Lim et al., 2023). This suggests the involvement of neurodevelopmental pathways in the development or risk predisposition to TRS. However, pinpointing the exact timing of this onset remains challenging. Conversely, a significant majority of patients as previously discussed report experiencing negative symptoms before the appearance of positive symptoms. **Figure 2** illustrates the variability in drug responses to AP drugs among patients and can be categorized into three distinct categories (antipsychotic responsive, primary TRS, and secondary TRS). Notably, the antipsychotic responsive group consists of patients who respond favorably to AP medications, achieving a reduction in positive symptoms that falls below the diagnostic threshold (**Figure 2A**), primary TRS patients show no response to AP drugs from the outset and continue to exhibit a lack of improvement even after two treatment trials (**Figure 2B**), and secondary TRS patients may initially respond well to the first administration of AP drugs but later develops resistance to the drugs over time (**Figure 2C**).

Current treatment practices and their limitations

The treatment of SCZ has evolved. First-generation antipsychotics (FGAs), such as chlorpromazine and haloperidol, were the mainstay of treatment for several years. However, since the 1990s, the introduction of second-generation antipsychotics (SGAs) has led to changes in the approach to treatment. These newer medications, also known as atypical antipsychotics, have become more commonly prescribed due to their potentially reduced side effects. 10 years later, conclusions from a comprehensive analysis, including a systematic review and meta-regression of 52 randomized controlled trials involving 12,649 patients comparing the effects of FGAs with SGAs, suggested that the initial perspective of SGAs having marginally better effectiveness, improved tolerability, and a decreased likelihood of causing extrapyramidal symptoms was overly simplistic (Geddes et al., 2000). In comparison to a specific group of patients who were administered 12 mg/day or less of haloperidol (or its equivalent), they observed that there was no distinction in efficacy or overall tolerability between FGAs and SGAs. Moreover, they found that SGAs were only marginally better at causing fewer extrapyramidal symptoms (Geddes et al., 2000; Zhang et al., 2013). Despite this, it is acknowledged that numerous patients with chronic illnesses continue to display an inadequate response to both FGAs and SGAs (AP drugs) treatment, categorized broadly as treatment resistance SCZ (TRS) (Buckley, 2020).

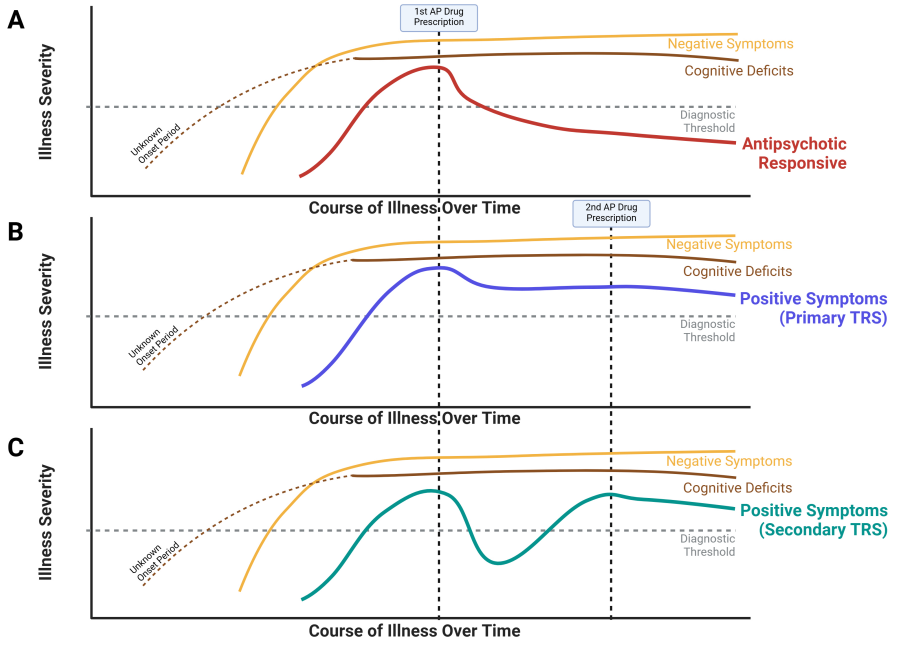

Figure 2 | **Treatment response to AP drugs by different groups of patients.**
There is a clear indication of a decline in cognitive function prior to the onset of psychotic symptoms to the period following it, albeit the period of onset is difficult to determine. Most patients (~70%) experience negative symptoms prior to the onset of positive symptoms. Current drug treatments are mainly focused on treating the positive symptoms of SCZ. As a result, negative symptoms and cognitive deficits are often left untreated. However, there are differences in response to AP drugs as well, which can be categorized into three categories. (A) Antipsychotic responsive is the group of patients that responds well to AP drug, showing a reduction in positive symptoms to below the diagnostic threshold. (B) Primary TRS is the group of patients that do not show any response to AP drugs right from the very start and exhibit a lack of response even after two trials of AP drugs. (C) Secondary TRS is the group of patients that initially had good responses to the initial AP drug administration but exhibited resistance to the AP drug after a period. Created with BioRender.com. AP: Antipsychotic; SCZ: schizophrenia; TRS: treatment-resistance schizophrenia.

TRS occurs in 30%-40% of patients and remains a major clinical challenge (Meltzer et al., 1997; Lally et al., 2016; Demjaha et al., 2017). The exact cause for the ineffectiveness is currently unknown although studies have shown contributory causes from both genetics and environmental factors (Takeuchi et al., 2019; Zoghbi et al., 2021; Lim et al., 2023). Based on the definition by the Treatment Response and Resistance in Psychosis (TRRIP) Working Group, TRS is often defined by the lack of response after two trials of AP drugs prescribed for a substantial amount of duration, dose, and usage compliance. Initial resistance to treatment with AP drugs is observed at the inception of therapy (primary TRS), whereas a group of patients may exhibit resistance to the medication only after a period of treatment (secondary/late onset), frequently following relapses (Correll and Howes, 2021). Primary TRS is associated with neurodevelopmental origins and patients generally show greater severity in symptoms (Demjaha et al., 2017). Patients with secondary TRS may suffer from more relapses or have prior interruptions in their antipsychotic treatment, i.e. non-adherence or treatment discontinuation (Emsley et al., 2012; Takeuchi et al., 2019) or other comorbidities.

At present, there exists a knowledge gap with regard to primary and secondary TRS. It remains unclear how to identify them, whether early intervention is effective, if early use of clozapine is significant, or if there exists a distinct neurobiological subtype for which we lack treatment options. The development of SGAs is also geared toward long-acting injectables to minimize nonadherence, management of the disease and outcomes (Brasso et al., 2023; Fernandez-Miranda et al., 2024). However, while medication adherence plays a role in treatment response, there may also be elements of AP drug tolerance and dopamine super-sensitivity – where prolonged treatment with AP can lead to an upregulation of dopamine receptors in the brain, which may result in increased dopamine activity when the medication is withdrawn or reduced (Chouinard et al., 2017). Even with the introduction of SGAs, up to 60% of patients with TRS may not respond positively to clozapine, underscoring the pressing requirement for the development of therapeutics utilizing novel mechanisms of action (Potkin et al., 2020).

Neurotransmitter Systems Driving Positive, Negative, and Cognitive Symptoms

SCZ is a multifaceted psychiatric disorder characterized by cognitive deficits, hallucinations, and delusions, with key neurobiological involvement from the prefrontal cortex, midbrain, and hippocampus (**Figure 3**). The interplay between various neurotransmitter pathways, dopaminergic, glutamatergic, serotonergic, and GABAergic, is central to understanding the complex pathophysiology of SCZ. Research indicates that these systems do not operate in isolation. Rather, they interact in ways that significantly influence the symptoms and development of the disorder.

In the prefrontal cortex, dysregulation of glutamatergic, serotonergic, and muscarinic signaling pathways through glutamate, GABA, and acetylcholine contributes to impaired cognitive functions such as decision-making and memory. Glutamatergic pyramidal neuron communicates with medium spiny neurons in the nucleus accumbens and dopaminergic neurons in the midbrain through the flow of glutamate and dopamine. There is extensive evidence suggesting that dysregulation in dopamine transmission is closely linked to alterations in glutamatergic signaling. For example, N-methyl-D-aspartate (NMDA) receptor hypofunction (a glutamatergic pathway) is thought to lead to increased dopaminergic activity, particularly in the mesolimbic pathway, which correlates with positive symptoms of SCZ. Conversely, insufficient activation of dopaminergic transmission in the prefrontal cortex can contribute to cognitive and negative symptoms (Deng and Dean, 2013; Buck et al., 2022). GABAergic neurons play a crucial role in modulating excitatory glutamatergic signaling. In SCZ, reduced GABA synthesis has been observed, which can lead to increased glutamate levels and further exacerbate excitatory transmission. This imbalance may contribute to the hyperactivity of dopaminergic pathways, leading to psychotic symptoms (Buck et al., 2022).

On the other hand, the interaction between serotonin and dopamine systems is considered a viable mechanism for enhancing therapeutics in SCZ (De Deurwaerdère et al., 2021). Serotonin-dopamine activity modulators may improve negative symptoms by helping to control the activity of serotonin and dopamine (Brasso et al., 2023) The serotonin system inhibits dopaminergic function in the midbrain and forebrain, and serotonergic antagonists release the dopamine system from this inhibition (Courtiol et al., 2021). This disinhibition may alleviate neuroleptic-induced extrapyramidal symptoms and ameliorate negative symptoms (Courtiol et al., 2021). However, combined serotonergic-dopaminergic blockade benefits may be observed in a narrow dose range and lost with suprathreshold dopaminergic blockade. Current research is exploring the possibility of using specific serotonergic treatments as flexible adjuncts to typical neuroleptics. Beyond dopamine, increasing evidence implicates serotonin and glutamate networks in the pathophysiology and treatment of some forms of psychosis (Stahl, 2018). Besides the prefrontal cortex, the muscarinic pathway in the hippocampus is also implicated, where cholinergic neurons send signals to CA1 pyramidal neurons through acetylcholine (**Figure 3**). We discuss the different signaling pathways in greater detail in the next section.

Dopamine pathways

It is hypothesized that patients with SCZ who respond to treatment and those who are resistant to treatment represent distinct subtypes (Demjaha et al., 2014). Additionally, the neurobiology of patients who initially respond to therapy but later develop resistance during the treatment course is also distinct (Takeuchi et al., 2019). The dopamine hypothesis posits that an imbalance in dopaminergic neurotransmission contributes to the positive symptoms of SCZ. Specifically,

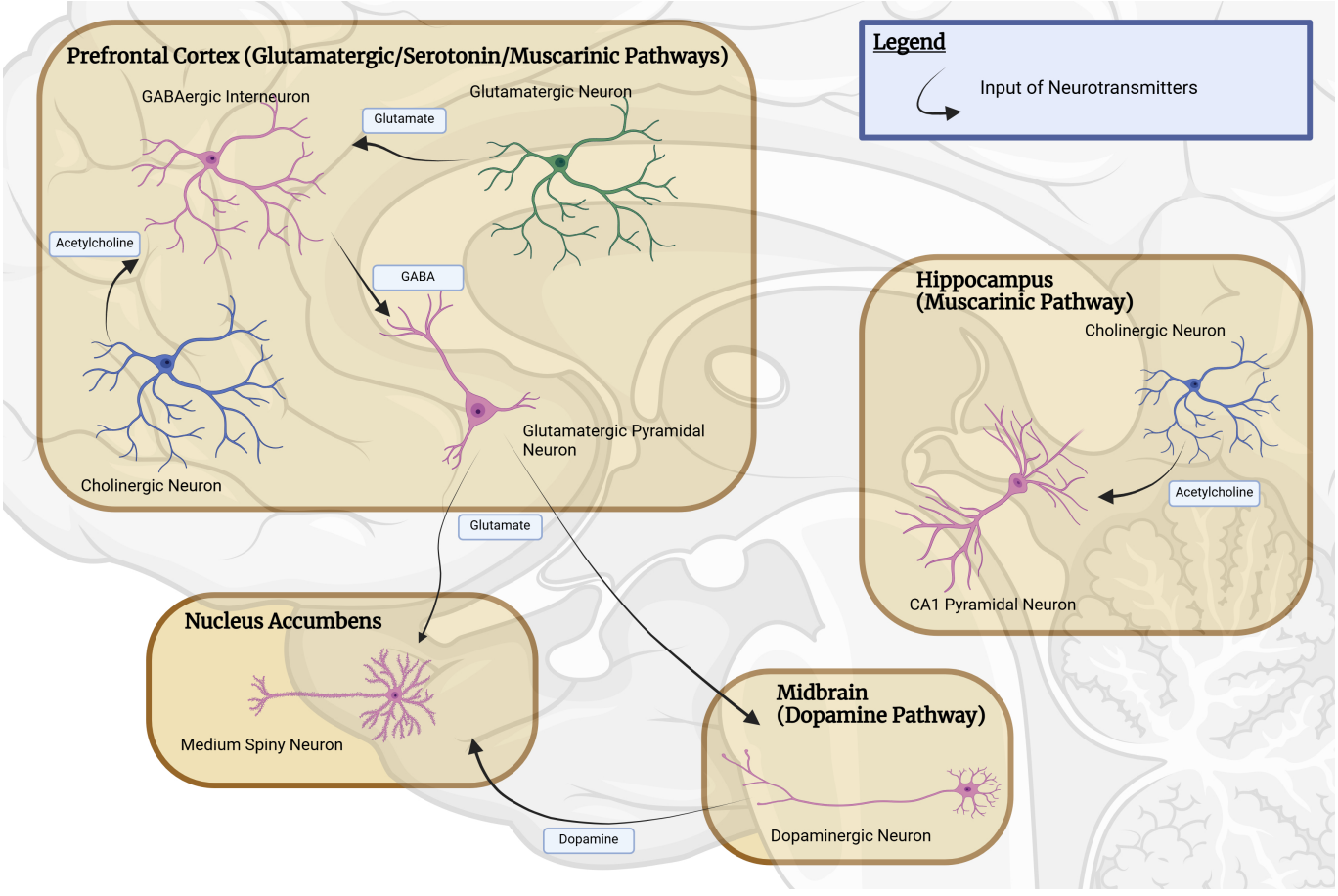

Figure 3 | **Overview of neurotransmitter systems implicated in schizophrenia.**
Schizophrenia is associated with dysfunction in specific brain regions, notably the prefrontal cortex, midbrain, and hippocampus. Within the prefrontal cortex, several neurotransmitter signaling pathways, including glutamatergic, serotonergic, and muscarinic systems, are involved. Disruption in any of these pathways may contribute to the pathophysiology of schizophrenia. The muscarinic signaling pathway also plays a significant role in the hippocampus, where cholinergic neurons interact with CA1 pyramidal neurons through the neurotransmitter acetylcholine. In the midbrain, dopaminergic neurons communicate with medium spiny neurons in the nucleus accumbens, primarily through the release of dopamine. These interactions highlight the complex neurochemical landscape that underlies schizophrenia and its associated cognitive deficits. Created with BioRender.com. GABA: Gamma aminobutyric acid.

excessive dopamine activity in certain brain regions, such as the mesolimbic pathway, is linked to the development of positive symptoms (**Figure 4**, see the section Dopaminergic Pathway, Midbrain and Nucleus Accumbens). AP drugs, which primarily target dopamine D2 receptors, effectively reduce these symptoms, providing clinical support for this hypothesis (Howes and Kapur, 2009; Boyd and Mailman, 2012). In contrast, positron emission tomography studies have reported unchanged or decreased dopamine levels in TRS (Demjaha et al., 2017; Jauhar et al., 2019; Takeuchi et al., 2019). Additionally, patients unresponsive to clozapine exhibit decreased dopamine synthesis in the striatum (Kim et al., 2017). These findings suggest that the mechanisms underlying TRS are distinct from those in treatment-responsive patients and may also vary within the spectrum of treatment-resistant cases. Moreover, while dopamine dysregulation evidently plays a role in the symptoms of SCZ for many patients, the inability of AP dopamine blockers to manage symptoms in some cases suggests that other neurotransmitters are likely involved in the development of TRS (Schwartz et al., 2012; Brisch et al., 2014). Early detection and appropriate intervention in TRS hold promise in improving outcomes. Therefore, identification of individuals who might be TRS, or not responsive to antipsychotics that target dopamine pathways in particular, is an important clinical strategy in precision psychiatry.

Glutamatergic pathways

Negative and cognitive symptoms of SCZ are thought to be associated with dysfunctional glutamatergic neurotransmission (Stogios et al., 2021; Mecca et al., 2022). Glutamate, the primary excitatory neurotransmitter in the brain, plays a crucial role in synaptic plasticity and cognitive processes. Disturbances in glutamate signaling, particularly in the NMDA receptor system, have been implicated in the pathogenesis of these symptoms (Pal, 2021). The glutamate hypothesis has been proposed to elucidate the role of alternative neurotransmitter systems in the neurobiology of SCZ. It suggests that dopaminergic hyperactivity is a downstream effect of disruptions in glutamate and gamma aminobutyric acid (GABA) signaling (Howes et al., 2015). NMDA receptor (NMDAR) hypofunction on GABAergic interneurons serves as the initial perturbation, and its dysfunction results in a diminished inhibitory control exerted by GABAergic interneurons on glutamatergic pyramidal neurons in cortical and hippocampal regions (Nakazawa and Sapkota, 2020). Consequently, there is a disinhibition of these glutamatergic neurons, particularly those projecting to the basal ganglia, leading to their hyperactivation and excessive glutamatergic signaling, which in turn modulate the dopaminergic transmission in the mesolimbic pathway (Lodge and Grace, 2007; Lodge et al., 2009; Schwartz et al., 2012). Evidence supporting this hypothesis comes from pharmacological studies involving phencyclidine, a known NMDA receptor antagonist. Clinical observations demonstrate that individuals with SCZ experience an intensification of positive symptoms when administered phencyclidine. Furthermore, when healthy subjects were prescribed phencyclidine, they exhibited symptoms that closely resembled the positive symptoms characteristic of SCZ (Fujigaki et al., 2019). These findings lend credence to the proposed role of NMDA receptor dysfunction in the pathophysiology of SCZ (**Figure 4**, see the section Glutamatergic Pathway, Prefrontal Cortex).

Neuroimaging studies have revealed elevated glutamate levels in the anterior cingulate cortex of TRS patients compared to both healthy controls and treatment-responsive patients, suggesting that disruptions in glutamatergic signaling may play a role in TRS (Demjaha et al., 2014, 2017;

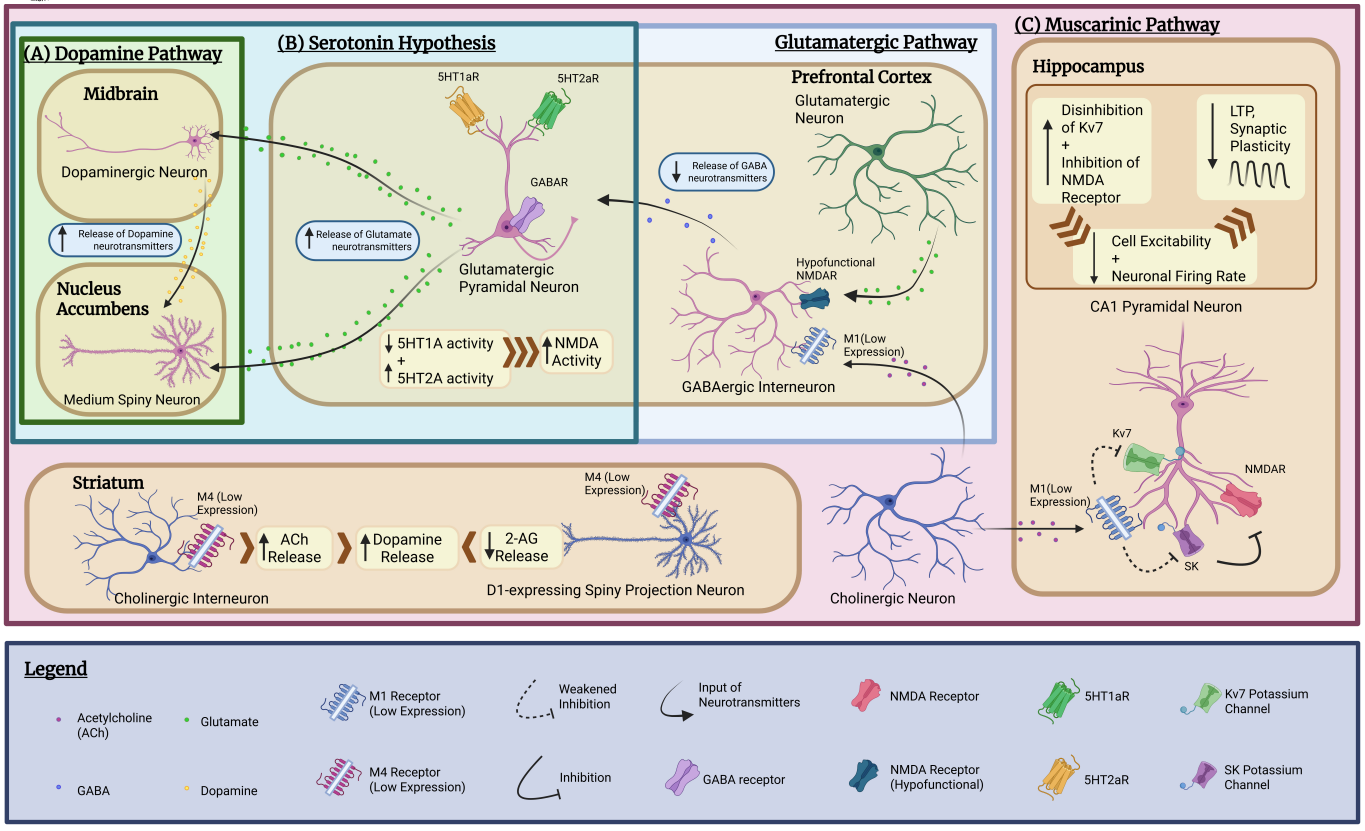

Figure 4 | **Proposed pathological pathways of schizophrenia.**
(A) Dopamine hypothesis begins in the midbrain, where the dopaminergic neurons produce and release much more dopamine than usual, which can affect the mesolimbic pathway as it excites the medium spiny neurons in the nucleus accumbens that governs the reward system in the brain. Glutamate hypothesis suggests that in the prefrontal cortex, hypofunction of the NMDA receptor at the GABAergic interneurons results in fewer GABA inhibitory signals to the glutamatergic pyramidal neurons. This, in turn, causes the glutamatergic neuron to release more excitatory glutamate neurotransmitters to the midbrain and nucleus accumbens. (B) Serotonin hypothesis is less well defined, but it has been shown that imbalances in 5HT receptors, particularly subtypes 1 and 2, are associated with increased dopamine levels in the striatum. (C) Muscarinic hypothesis is based on the evidence that muscarinic receptors, particularly M1R (blue), have lowered expression in the brain, particularly the cortical and hippocampal regions. In the hippocampus, M1R is suggested to inhibit Kv7 to depolarise the CA1 pyramidal neuron, as well as increase NMDA receptor activity by inhibiting the SK potassium ion channel. The overall effect is the increased excitability of the CA1 pyramidal neurons while promoting long-term potentiation and synaptic plasticity. In schizophrenic patients, the reduced level of M1R in the hippocampus would result in the fall in long-term potentiation and synaptic plasticity in the hippocampus, which is associated with a decrease in learning and cognitive function. Reduced level of M1R in the cortical region is also shown to reduce long-term depression of glutamate signaling by the pyramidal neurons and is associated with an increase in dopamine levels in the striatum. On cholinergic interneurons, M4R (red) regulates dopamine release by inhibiting excessive release of acetylcholine, thereby preventing excessive nAChR-dependent release of dopamine in dopaminergic neurons. In D1-spiny projection neurons, it is shown that M4R activation stimulates the release of 2-AG, which inhibits dopamine release via a cannabinoid receptor-dependent pathway. Decreased levels of M4R result in the disinhibition of dopamine release, resulting in increased levels of dopamine in the striatum. Created with BioRender.com. 2-AG: 2-Arachidonoylglycerol; GABA: gamma aminobutyric acid; LTP: long-term potentiation; NMDA: N-methyl-D-aspartate; NMDAR: N-methyl-D-aspartate receptor.

Mouchlianitis et al., 2016). Studies of clozapine on the glutamatergic system serve to provide indirect evidence for the neurotransmitter role in clozapine-responsive TRS (Tanahashi et al., 2012). In a rat model, it has been shown that clozapine exhibits a strong affinity for DRD4 receptors. Blockade of DRD4 receptors in this model resulted in an upregulation of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, thereby enhancing glutamatergic transmission (Yuen et al., 2010; Veerman et al., 2014). Similarly, clozapine enhances the release of L-glutamate and D-serine and has the potential to upregulate NMDA receptors as a result (Tanahashi et al., 2012). It is also proposed that clozapine can compensate for the hypofunctional state of NMDA receptors in some TRS patients (Veerman et al., 2014). In a study that investigated the levels of D- and L-serine in patients with TRS before and after clozapine treatment, it was found that patients with TRS had significantly lower D-serine levels compared to healthy controls prior to receiving clozapine treatment. However, this difference in D-serine levels between patients with TRS and healthy controls became non-significant after the administration of clozapine treatment (Yamamori et al., 2014). Likewise, the study also revealed that the D-/L-serine ratio was notably lower in patients with TRS prior to receiving clozapine treatment. However, after the administration of clozapine, the D-/L-serine ratio in patients with TRS was not significantly different from that of healthy controls. This finding further strengthens the hypothesis that the mechanism of action of clozapine may involve the regulation of a dysfunctional glutamatergic pathway in individuals with TRS (Yamamori et al., 2014).

Serotonin and GABAergic pathways

Other neurotransmitter systems, such as serotonin and GABA, are also believed to be involved in the pathophysiology of SCZ and may contribute to negative and cognitive symptoms. Most studies have focused on serotonin as one of the biomarkers for cognition. It is also known as 5-HT (5-hydroxytryptamine), acts as a neurotransmitter that regulates many consequential physiological processes such as sleep, motor activities, and higher brain functions, including cognition and emotional behaviors (Ciranna, 2006). Preclinical and clinical studies have shown that the 5-HTergic system activity is related to cognitive performance in many psychiatric disorders including SCZ (Lin et al., 2014). Moreover, altered serotoninergic and GABAergic neurotransmission at the prefrontal cortex may disrupt neural circuitry and synaptic function (Dean, 2001; Boyer et al., 2007), leading to impairments in emotional regulation, attention, and information processing (**Figure 4B**).

There is abundant evidence showing that the 5-HT system plays a major role in regulating the activity of dopamine in the brain, and vice versa (Akhondzadeh, 2001; Brisch et al., 2014). 5-HT1A and 5-HT2A receptors are given more attention as they are attributed to the development and progression of SCZ. These two receptors are often

found together on the same cell, even though they are known to trigger opposing responses. During the early stages of abnormalities in the SCZ brain, it is often found that there is an imbalance of 5-HT1A (higher) and 5-HT2A (lower) receptors (Ngan et al., 2000; Hurlemann et al., 2008). This downregulation of 5HT2A could be a form of compensatory mechanism for hyperactive downstream signaling in which 5-HT2A receptors are known to regulate the ERK pathway which is proposed to upregulate NMDAR function on prefrontal cortex pyramidal neurons (Yuen et al., 2008). This could explain how serotonin is linked to psychosis and why 5-HT2A antagonists are often used as atypical antipsychotic drugs (**Figure 4**, see see the section Serotonin Hypothesis). Moreover, irregular ratios in receptor density are closely linked to the severity of positive and negative symptoms, which are commonly evaluated using the Scale for the Assessment of Negative Symptoms and the Scale for the Assessment of Positive Symptoms.

Similarly, GABAergic dysfunction has been implicated in cognitive impairments in TRS patients in particular (Miyazawa et al., 2022). In the study, exome sequencing conducted on 14 TRS patients identified four single nucleotide polymorphisms with GAD1 and GABBR2 showing nominal-level significance when compared against healthy controls, suggesting that the GABA system is compromised in SCZ or TRS (Miyazawa et al., 2022). Other supportive studies conducted previously concurrently reported the decreased levels of GAD67 mRNA in SCZ patients, further supporting the importance of the GABAergic system (Raux et al., 2007; Vorstman et al., 2009). Furthermore, the GABA system is a target for clozapine where the drug is thought to directly bind to GABAB receptor (Gammon et al., 2021). A recent study conducted on 98 treatment-responsive and resistant SCZ patients also revealed the overall group differences in the GABA levels of the midcingulate cortex using proton magnetic resonance spectroscopy (Ueno et al., 2022). Heightened levels of GABA are reported in resistant SCZ patients with more longitudinal studies required to determine if GABA levels could be a potential biomarker for clozapine resistance prediction (Ueno et al., 2022).

Muscarinic pathways

Muscarinic receptors are a class of receptors that respond to the neurotransmitter acetylcholine. These receptors play a significant role in various physiological processes, including cognition, memory, attention, and sensory perception. The cholinergic hypothesis of SCZ proposes that dysfunction in the muscarinic receptor system may contribute to the cognitive impairments observed in the disorder.

Studies have shown that there were alterations in muscarinic receptor density and function in individuals with SCZ, particularly in brain regions involved in cognitive processes. Specifically, decreased levels of muscarinic receptors, particularly the M1 subtype, have been reported in the prefrontal cortex and hippocampus of individuals with SCZ (Dean et al., 2023). These brain regions are critical for working memory, attention, and executive functions that are commonly impaired in SCZ.

Studies in rodent models provided insight into how the M1 receptor (M1R) contributes to the pathology of SCZ. In particular, M1R localized in the hippocampal region is critical in the learning and memory processes by modulating synaptic plasticity (Dickinson et al., 2009; Bradley et al., 2010; Buchanan et al., 2010; Dasari and Gulledge, 2011) and promoting long-term potentiation (Adams et al., 2004; Langmead et al., 2008; Buchanan et al., 2010; Dasari and Gulledge, 2011; Mitsushima et al., 2013). It is suggested that activation of M1R leads to increased CA1 pyramidal neuron excitability via two ways; the inhibition of voltage-dependent Kv7 potassium channel that generates M currents, which are antagonistic to neuronal depolarization (Hoshi, 2020), and the inhibition of SK potassium channels, which negatively regulates potentiation of NMDARs (Buchanan et al., 2010). Low M1R expression in schizophrenic patients would therefore have lower CA1 pyramidal neuronal excitability, and hence reduced long-term potentiation and synaptic plasticity in the hippocampal region, affecting cognition (**Figure 4**, see the section Muscarinic Pathway, Hippocampus). Reduced expression of M1R on GABAergic interneurons in the cortical region also leads to fewer release of GABA neurotransmitters onto the glutamatergic pyramidal neurons, resulting in increased excitability and subsequently in increased release of glutamate neurotransmitters onto the dopaminergic neurons in the midbrain (Paul et al., 2022; **Figure 4**, see the section Glutamatergic Pathway, Prefrontal Cortex). A complete knockout of M1R in mice also revealed that M1R plays a role in activating the mitogen-activated protein kinase (MAPK) pathway, which has a large impact on synaptic plasticity and cognitive ability (Hamilton and Nathanson, 2001; Adams and Sweatt, 2002). M1R deficient mice were also found to be associated with a two-fold increase in dopamine levels in the striatum (Gerber et al., 2001).

M4R, mainly localized in the striatum of the brain, is also found to be linked to the pathophysiology of SCZ. M4R expressed on both cholinergic interneurons and D1-spiny projection neurons were reported to play a role in regulating dopamine release (Shin et al., 2015). On cholinergic interneurons, M4R is expressed as an autoreceptor, and is suggested to regulate dopamine release by inhibiting excessive release of ACh, thereby preventing excessive nAChR-dependent release of dopamine in dopaminergic neurons (Shin et al., 2015). In D1-spiny projection neurons, it is shown that M4R activation stimulates the release of 2-arachidonoylglycerol (2-AG), which inhibits dopamine release via a cannabinoid receptor-dependent pathway (Foster et al., 2016). Decreased levels of M4R result in the disinhibition of dopamine release, resulting in increased levels of dopamine in the striatum (**Figure 4**, see the section Muscarinic Pathway, Striatum).

Animal studies using M4 loss of function ($CHRM4^{-/-}$) mice support the receptor-critical roles in regulating both dopaminergic and cholinergic activity in the sub-cortical regions (Gomeza et al., 1999; Tzavara et al., 2004). Mice lacking the CHRM4 gene have notably higher baseline levels of dopamine in the nucleus accumbens. When exposed to d-amphetamine and phencyclidine, these mice experience a more pronounced increase in dopamine release compared to normal mice (Tzavara et al., 2004). Moreover, there was a slight yet noteworthy rise in baseline locomotor activity, recognized as a behavior in mice linked to heightened dopaminergic function in the $CHRM4^{-/-}$ mouse (Gomeza et al., 1999). These data substantiate the idea that the lack of CHRM4 leads to heightened dopaminergic activity in the central nervous system, which is also suggested to be implicated in the development of psychotic symptoms in individuals with SCZ (Dean et al., 2023). Hence, there exists a biological foundation for the proposition that selectively activating CHRM4 could serve as a mechanism to alleviate the psychotic symptoms of SCZ. This hypothesis has gained support from a recent trial indicating that the CHRM4 positive allosteric modulator, emraclidine, diminishes the severity of both acute psychotic and acute negative symptoms in individuals with SCZ. This provides evidence that targeting CHRM4 with emraclidine may be a promising approach for managing symptoms of SCZ (Krystal et al., 2022).

Moreover, findings using the $CHRM4^{-/-}$ mouse have also underscored the robust interactions of CHRM4 and the glutamatergic systems. This is evident as these mice exhibited heightened sensitivity to the disruption of pre-pulse inhibition following NMDAR blockade by phencyclidine (Felder et al., 2001). These data hold significance as abnormal control of pre-pulse inhibition has been proposed as a potential biomarker for the diagnosis of SCZ (Mena et al., 2016).

Additionally, manipulating the muscarinic receptor system through pharmacological interventions has shown potential for improving positive and negative symptoms, as well as cognitive impairments in SCZ. Lately, two successful Phase 3 (EMERGENT-2 and EMERGENT-3) trials of drugs targeting M1 and M4 receptors without dopamine D2 blockage to treat SCZ have been reported (Kaul et al., 2024b). Since the mechanisms by which muscarinic receptor dysfunction contributes to SCZ and the specific role of each muscarinic receptor subtype are still not fully understood, these promising data of novel drug inventions targeting muscarinic receptors for the treatment of SCZ reemphasizes the need to review the roles of these receptors in the disorder pathology (Dean et al., 2023). Overall, while alterations in muscarinic receptors and cholinergic neurotransmission have been implicated in the cognitive impairments seen in SCZ, more research is required to better understand the underlying mechanisms and develop targeted therapeutic approaches to address these deficits.

Genes Implicated in Schizophrenia Identified by Recent Genome-Wide Association Study and Their Associated Molecular Pathways

Genes involved in synaptic transmission

A recent study utilized MAGMA (de Leeuw et al., 2015) and DNENRICH (Fromer et al., 2014) to conduct gene ontology (GO) enrichment analyses in both the Psychiatric Genomics Consortium

GWAS and the Schizophrenia Exome Sequencing Meta-Analysis studies to test whether specific molecular and biological pathways were enriched among the associated genes (Nakamura and Takata, 2023). The study aims to uncover how the results from these two studies converged and identified enriched pathways, particularly in terms of molecular functions. Their result suggests that there is a convergence of molecular and biological pathways affected by both common single nucleotide polymorphisms and rare deleterious variants (Nakamura and Takata, 2023). Specifically, four GO terms related to voltage-gated channels and synaptic transmission were found to be significantly enriched in both the Psychiatric Genomics Consortium GWAS and the Schizophrenia Exome Sequencing Meta-Analysis studies, even after applying the Bonferroni correction. These findings indicate a possible involvement of these pathways in the genetic basis of the SCZ (Nakamura and Takata, 2023). Additionally, when the 32 GO terms with Bonferroni-corrected $P<0.05$ in either dataset were visualized as networks by connecting them based on the similarity of the contained genes, it was observed that there was a formation of three clusters, each related to channel or transporter activities; neuronal components (synapse, axon, and dendrite); chromatin or histone organization (Nakamura and Takata, 2023).

Several studies collectively provide evidence suggesting the involvement of voltage-gated calcium channels (VGCC) subunits in the pathogenesis of SCZ. Through linkage analyses, GWAS and candidate gene association studies, genes identified include *CACNA1C* (Schizophrenia Psychiatric Genome-Wide Association Study (GWAS) Consortium, 2011; Ripke et al., 2013; He et al., 2014; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014), *CACNB2* (Wang et al., 2010; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013), *CACNG5* (Curtis et al., 2011; Guan et al., 2016) and *CACNA11* (Irish Schizophrenia Genomics Consortium and the Wellcome Trust Case Control Consortium 2, 2012; Andrade et al., 2016), encoding various subunits of the VGCC. The results suggest a potential involvement of VGCCs in the development of SCZ, although the exact molecular mechanism underlying this association is not yet understood.

Recent evidence also recasts the spotlight on the involvement of abnormalities in synaptic transmission and synaptic plasticity in SCZ (Stephan et al., 2009). The largest GWAS to date reported by Trubetskoy and coworkers identified a significant number of loci associated with synaptic genes in SCZ patients (Trubetskoy et al., 2022). Four of these genes (*GRIN2A*, *SP4, STAG1*, and *FAM120A*) were also listed amongst the 10 exome-wide significant Schizophrenia Exome Sequencing Meta-Analysis genes (Singh et al., 2022). Noteworthy, *GRIN2A*, which encodes the NMDAR subunit GluN2A, mediates excitatory synaptic transmission together with α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and kainate receptors. These receptors can be regulated by various neurotransmitter systems (Traynelis et al., 2010). NMDARs are remarkable because they serve a dual function as regulators of both synaptic communication and long-term changes in synaptic strength, such as long-term potentiation and depression (long-term potentiation and long-term depression) of AMPAR-mediated synaptic signaling (Rebola et al., 2010; Hunt and Castillo, 2012). SCZ patients are known to demonstrate impaired NMDAR functions, along with an exacerbation of symptoms when exposed to NMDAR antagonists based on clinical studies (Law and Deakin, 2001; Weickert et al., 2013). In a validation study examining *GRIN2A* and *AKAP11*, it was found that *Grin2a* and *Akap11* mutant mice display patterns of brain activity that closely resemble the abnormal features observed in individuals with SCZ (Herzog et al., 2023). This suggests that the absence of these genes causes significant alterations in brain function, further supporting the characterization of these two genes as genetic models of SCZ (Herzog et al., 2023). *SP4*, on the other hand, is a transcription factor that regulates the expression of multiple target genes involved in neural development, synaptic function, and glutamate signaling (Priya et al., 2013). Mice with reduced expression of *SP4* exhibited multiple potential markers for SCZ and other psychiatric disorders (Zhou et al., 2010).

Additional analyses of the 106 prioritized genes using the SynGO database further shortlisted 48 genes with known synaptic localization or function, including genes encoding receptors and ion channels (voltage-gated calcium and chloride channels (*CACNA1C* and *CLCN3*), metabotropic receptors (glutamate (*GRM1*) and GABA (*GABBR2*)), and the afore-mentioned ligand-gated NMDAR subunit (*GRIN2A*) (Trubetskoy et al., 2022). *SNAP91* (Synaptosomal-associated protein 91) is a gene involved in endocytosis, a process that regulates the retrieval of neurotransmitter receptors from the cell surface back into the presynaptic terminal. *DLGAP2, LRRC4B, GPM6A, PAK6*, and *PTPRD* are genes associated with synaptic organization and differentiation (Trubetskoy et al., 2022). These genes may play a role in the formation and maintenance of connections between neurons, and in the development of neuronal networks.

Other identified genes associated with synaptic function, *MAPK3, DCC, CLCN3*, and *DLGAP2*, were also prioritized in the study (Trubetskoy et al., 2022). They are thought to regulate the release and reception of neurotransmitters, which are crucial for neuronal communication. These findings suggest that abnormalities in endocytosis, synaptic organization, differentiation, and chemical transmission may contribute to the underlying molecular mechanisms of SCZ. Their findings further support other GWAS studies that propose abnormalities in the postsynaptic region of synapses playing a role in the SCZ pathogenesis. However, GWAS findings comprising the TRS subgroup that links to VGCC and synaptic biology are currently lacking.

Genes involved in immune and inflammatory pathways

SCZ is influenced by a range of genetic and environmental factors that elevate the risk of developing the disorder. Recent research suggests that these factors may converge through their effects on immune processes. Evidence indicates that immune processes are critical in shaping brain development, as studies of SCZ patients have reported heightened immune function and increased chemokine responses (Frydecka et al., 2018; Kroken et al., 2018). Moreover, anti-inflammatory therapeutics targeting immune function have shown some efficacy in symptom remission (Sommer et al., 2014). Importantly, there is a correlation between subclinical inflammation and cognitive deficits in SCZ (Misiak et al., 2018), which usually determine illness prognosis.

Microglia, which are phagocytes within the central nervous system, have several roles including coordinating innate immunity in the brain. They have established functions in promptly responding to inflammatory stimuli by actively monitoring the central nervous system parenchyma (Liu et al., 2019), and contribute to the removal of debris and apoptotic cells through the process of phagocytosis (Ayata et al., 2018; Galloway et al., 2019). These highly complex cells also contribute to the integrity of neuronal circuitry by engaging in various processes such as synapse manipulation, elimination, maintenance, and plasticity (Hammond et al., 2018; Bohlen et al., 2019). Notably, there is increasing evidence to support microglial dysfunction in SCZ (Hercher et al., 2014; Bloomfield et al., 2016; Trepanier et al., 2016; De Picker et al., 2017; Sellgren et al., 2019; Uranova et al., 2020).

The major histocompatibility complex locus, situated on chromosome 6, exhibits the strongest association with SCZ (Stefansson et al., 2009; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). Within this region, a couple of genes have known roles in innate immunity. Complement 4A (*C4A*), located in the major histocompatibility complex locus, confers a strong association with SCZ. Increased levels of this protein directly correlated with SCZ risk (Sekar et al., 2016). In addition to their well-known role in immune defense, complement proteins also play a significant role in various stages of brain development, including neurogenesis, cellular migration, and synaptic development (Veerhuis et al., 2011; Lee et al., 2019). Over recent years, research has linked complement proteins to the process of microglia-mediated pruning of synapses, implying the direct link between *C4* and SCZ pathology (Schafer et al., 2012; Hong et al., 2016). The molecular mechanism driving heightened expression of *C4A* to synaptic loss remains obscure, but mouse models overexpressing the neuroimmune gene have resulted in the localization of postsynaptic protein PSD-95 to microglial lysosomes. This process in turn leads to upregulated microglia-dependent synaptic engulfment (Comer et al., 2020). This excessive pruning leads to a reduction in synapse density, particularly during critical developmental periods such as adolescence (Germann et al., 2021; Zhuo et al., 2023). Studies using patient-derived neuronal cultures have also shown that microglia exhibit increased synapse elimination associated with these genetic variants (Sellgren et al., 2019; Yilmaz et al., 2021; Zhuo et al., 2023). The complement system's activation is pivotal in mediating microglial engulfment of synapses, with evidence suggesting that this process is altered in individuals with SCZ (Soteros and Sia, 2022).

Moreover, in schizophrenic patients, microglia are often found in a hyperactivated state, releasing pro-inflammatory cytokines (e.g., interleukin-6 and tumor necrosis factor-α) and reactive oxygen species that can be neurotoxic and contribute to cognitive decline (Zhuo et al., 2023; Koskuvi et al., 2024). This chronic neuroinflammatory state is thought to exacerbate synaptic loss by promoting excessive synaptic pruning (Hartmann et al., 2024).

In another study assessing C4 serum levels and AP medications response in a cohort of twenty-five SCZ patients with first-episode psychosis before prescription and followed by a 1-year post-treatment assessment, non-responders show significantly elevated baseline C4 levels compared to responders (Mondelli et al., 2020), suggesting the possibility of monitoring C4 baseline levels as a clinical tool for predicting medical outcome. However, the study focused on a limited number of genes, so the correlation between other immune markers and psychosis progression remains unclear. Nonetheless, *CSMD1*, a key regulator of *C4*, as well as genetic variants located in both *CSMD1* and *CSMD2* genes, are reported to be implicated in SCZ (Havik et al., 2011) and their dysfunction has been thought to be associated with cognitive decline (Athanasiu et al., 2017).

More recently, a study conducted on SCZ using datasets from Gene Expression Omnibus and single-sample gene set enrichment analysis reported immunoregulatory genes with co-expression of gene modules determined through weighted gene correlation network analysis (Wu et al., 2024). The study aims to define the relationship between immunoregulatory reactions in SCZ development. Analysis of enriched bioprocesses related to immune genes with differential expression reveal key biological processes such as interferon-beta, IgG binding, and response to interferon-gamma, based on GO and Kyoto Encyclopedia of Genes and Genomes (Wu et al., 2024). A total of 112 genes exhibited significant variations in their expression levels between the two categories of immune genes, high immunity and low immunity subgroups consisting of 81 SCZ patients (Wu et al., 2024). *PLSCR1, FCGR1B, MT2A, IFITM1, GBP1, BST2, IFITM3, GBP2, CD44, FCER1G, HLA-DRA, FCGR2A, IFI16*, and *FCGR3B* are closely associated with interferon-beta response, IgG binding, and interferon-gamma response. The analysis of the protein-protein interaction network further identified eight hub genes implicated in immune infiltration in SCZ. These genes include *IFITM1, GBP1, BST2, IFITM3, GBP2, CD44, FCER1G, HLA-DRA, FCGR2A, IFI16*, and *FCGR3B*.

The mentioned study focused on the involvement of immune response abnormalities in the development of SCZ. Within the context of this study, two central genes, namely *IFITM1* and *IFITM3*, were identified as hub genes with potential relevance to the disease. The interferon-inducible transmembrane (IFITM/Fragilis) family of genes is responsible for the production of small proteins that are predominantly located in the plasma and endolysosomal membranes (Bailey et al., 2014; Zhao et al., 2018; Liao et al., 2019). IFITM proteins function as viral restriction factors, inhibiting viral entry and replication within host cells. Higher expression of these proteins can result in a complex cascade of immune activation observed in SCZ (Severance and Yolken, 2016; Ermakov et al., 2022).

Studies have consistently shown that mRNA levels of IFITM1 and IFITM3 are significantly increased in the prefrontal cortex and hippocampus of individuals with SCZ compared to healthy controls (Hwang et al., 2013). For instance, studies reported a marked increase in IFITM expression correlating with higher levels of pro-inflammatory cytokines such as interleukin-6 and interferon-β, which are known to induce IFITM expression (Hwang et al., 2013; Volk et al., 2015; Sanders et al., 2017). In addition, another study found that IFITM expression was significantly increased in a "high inflammation" SCZ subgroup compared to both a "low inflammation" SCZ subgroup and a "low inflammation" control subgroup (Cai et al., 2020). This suggests that IFITM expression may be particularly elevated in SCZ individuals who have a more pronounced inflammatory profile (Cai et al., 2020). Their upregulation may reflect a heightened immune response to perceived threats, which could lead to chronic inflammation. This persistent inflammatory state can disrupt normal neuronal function and contribute to the neurodevelopmental aspects of SCZ pathology (Horváth and Mirnics, 2014).

Additionally, prior research studies have demonstrated intricate and region-specific changes in the prefrontal cortex of SCZ patients concerning the increased transcript levels of interleukin-6 and interferon-β which induce IFITM expression, and lower levels of Schnurri-2, an inhibitor of IFITM expression (Fillman et al., 2013; Siegel et al., 2014; Volk et al., 2015). Taken together, these findings collectively support the disorders reported in SCZ patients' brains.

Genes involved in lipid oxidation and transport

Characterization and understanding of the complexity of TRS have been attempted using proteogenomic approaches (Wei et al., 2023). The team leveraged on TRS-related proteome-wide association studies conducted on GWAS from CLOZUK and the Psychiatric Genomics Consortium which consists of a database including TRS participants (*n*=10,501) and non-TRS participants (*n*=20,325). With comparison to the reference datasets from human brain proteome from ROS/MAP, they identified a total of 41 differentially expressed proteins and two statistically significant proteins, CPT2 and APOL2 (Wei et al., 2023). By extending the analysis from gene-based to pathway-based, 14 gene ontology terms were identified leading to a single candidate pathway, lipid oxidation and inflammation, and mitochondria function which may play an essential role in TRS. A previous study supported the findings by reporting increased lipid peroxidation in TRS patients compared to the AP responsive group, suggesting that alterations in the lipid content of synaptic membranes may be responsible for neuronal dysfunction (Medina-Hernandez et al., 2007).

CPT2, carnitine palmitoyl transferase 2, localized in the inner mitochondrial membrane, has functions of the transportation of long-chain fatty acids into the mitochondria matrix for oxidation. The role of lipid regulation in TRS has also been supported by several studies. Clozapine has been shown to modulate the AMPK-ACC-CPT1 pathway, the central lipid metabolism pathway, and affects the lipid levels in the rat frontal cortex (Kim et al., 2012). Moreover, SCZ patients were also reported to have alterations in lipid compositions in their frontal cortex (White et al., 2020). β-Oxidation, contributes to TRS, as indicated by increased levels of β-oxidation enzymes upon deletion of CTP2 in the nervous system (Kaul et al., 2024a). Genetic disorders affecting mitochondrial fatty β-oxidation have been associated with neurological disorders (Virmani et al., 2015; Merritt et al., 2018). Since CPT is expressed mainly in the brain regions, this could suggest that dysfunction in CTP2 may directly impact the central nervous system (Xie et al., 2016).

On the other hand, APOL2, primarily localized in the endoplasmic reticulum, is involved in cholesterol biosynthesis and trafficking and plays a role in inflammatory processes (Galindo-Moreno et al., 2014). Elevated APOL2 expression has been observed in SCZ patients, while polymorphism of this gene has been associated with risk in the disorder (Takahashi et al., 2008). APOL2 is expressed mainly in the brain (Luo et al., 2020), but more studies are required to further elucidate its precise function in the brain.

In a more recent GWAS study coupled with quantitative proteomic and metabolomic assay, and genotyping, comprising general SCZ patients without stratification of their drug responses, 20 differentially expressed proteins were identified (Kopylov et al., 2023). These include ALS, A1AG1, PEDF, VTDB, CERU, APOB, APOH, FASN, and GPX3. It was notable that almost half of the list consists of new hits for SCZ. Integration of multi omics layers with quantitative analysis for mapping molecular mechanisms relating to SCZ, lipid transport, and oxidative stress were two main events implicated in SCZ pathophysiology (Kopylov et al., 2023).

Lipid peroxidation which involves oxidative degradation of lipids mostly mediated by oxidative stress is one of the potential contributing factors leading to the pathophysiology of the disease. Increased levels of these lipid peroxide products such as malondialdehyde have been observed in SCZ patients (Guidara et al., 2020). These products can cause damage to cellular structure, including membranes and cellular organelles contributing to neuronal damage and inflammation, processes that are shown to be associated with the onset and progression of SCZ. Arachidonic acid, one of the well-known inflammatory lipid eicosanoids derived from polyunsaturated fatty acid, seems to be contributing to altered neuronal membrane dynamics, structure, fluidity, and permeability (Khan et al., 2002; Ayala et al., 2014). Specific behavioral symptoms of SCZ are shown to be associated with the impact of arachidonic acid alterations on the neurochemistry of deaminase, glutamate release, and the levels of endocannabinoids anandamide and 2-arachidonoylglycerol in circulation (Arvindakshan et al., 2003).

Emerging Therapeutics for Schizophrenia and Treatment-Resistant Schizophrenia

The recent development of treatments for SCZ has moved away from targeting dopamine D2 receptors. A search on Cortellis (https://clarivate.com) for drugs targeting SCZ with drug pipeline target-based actions other than dopaminergic pathway modulators in Phase 2 development and higher generates a total of 33 records as of October 2024. Of these, 8 records are under pre-registration phase or in Phase 3 clinical trials. **Additional Table 1** shows the list of companies with drugs in Phase 2 or higher in development for active indications in SCZ. Regrettably, the transition from promising preclinical data and occasionally hopeful early clinical results into successful Phase 3 trials and subsequent new drug approvals for addressing SCZ symptom domains has been overwhelmingly lacking. Alpha-7 nicotinic acetylcholine receptor agonists such as encenicline did not demonstrate a statistically significant difference in the placebo at week 26 of analysis in Phase 3 trials (Brannan, 2019). Likewise, enhancement of glutamate signaling via glycine transporter type 1 inhibitor, d-amino acid oxidase inhibitor, and metabotropic glutamate mGluR2 and mGluR3 receptors agonists had failed to meet primary endpoint efficacy in Phase 2 and 3 trials (Adams et al., 2014; Bugarski-Kirola et al., 2016; Murthy et al., 2024). In a Phase 2 trial of another inhibitor of glycine transporter type 1, iclepertin was found to be well tolerated and showed significant improvements in cognition leading to Phase 3 trials (Rosenbrock et al., 2023). Disappointingly, Boehringer Ingelheim announced in January 2025 that the topline results from the Phase 3 CONNEX trials did not meet the primary endpoints for cognitive impairments in schizophrenia for iclepertin (Source: Boehringer Ingelheim Press Release). Some encouraging results of glutamate modulation in the treatment of SCZ come from the use of evenamide as an add-on treatment to AP in TRS patients, showing significant improvement in the PANSS total score at 6 weeks. Evenamide, developed by Newron Pharmaceuticals, is a selective inhibitor of voltage-gated sodium channels that normalizes excessive glutamate release believed to occur due to the hypofunction of NMDAR (Anand et al., 2023). It remains to be seen if evenamides demonstrate similar efficacy in Phase 3 trials.

Muscarinic acetylcholine receptor subtypes M1 and M4 are implicated in the pathology of SCZ. Targeting these receptors presents a promising opportunity for developing novel therapeutic strategies to treat the symptoms of SCZ, particularly those not effectively addressed by current AP. These findings are supported by preclinical and clinical research, as well as by molecular neuroimaging studies that have further elucidated the roles of muscarinic receptors in the molecular pathology of SCZ (Foster et al., 2021; Yohn et al., 2022; Dean et al., 2023). M4 muscarinic receptor in the brain reduces the release of acetylcholine from interneurons, leading to decreased dopamine transmission and heightened glutamatergic neurotransmission (Kantrowitz et al., 2023). Cobenfy, previously known as KarXT (xanomeline-trospium) originally developed by Karuna Therapeutics is a first-in-class M1/M4 muscarinic receptor agonist with the peripherally restricted muscarinic receptor antagonist trospium chloride, has demonstrated efficacy and an improved safety profile as compared to traditional AP (Correll et al., 2022). Cobenfy has recently been approved by the Food, Drug and Administration based on two pivotal phase 3 trials that met the primary end-point with about a 21-point reduction in PANSS score (Kingwell, 2024). Data from EMERGENT-3 trial showed a statistically significant and clinically meaningful reduction of 8.4 points in the PANSS total score among participants who received KarXT for 5 weeks (–20.6 points) compared to those who received a placebo (–12.2 points) (Kaul et al., 2024a). Data from EMERGENT-2 trial demonstrated favorable reduction of PANSS total score from baseline to week 5 among participants who received KarXT (–21·2 points) *versus* placebo (–11·6 points) (Kaul et al., 2024b). In both trials, common adverse events experienced by KarXT include constipation, dyspepsia, vomiting, and nausea. There were no significant differences in adverse event-related discontinuation rates between KarXT and placebo, and the measures of extrapyramidal symptoms, including weight gain, were comparable across both treatment groups (Kaul et al., 2024b). A second muscarinic agent CVL-231 (Emraclidine) developed by Cerevel Therapeutics and acquired by AbbVie functions as a positive allosteric modulator that selectively targets the M4 muscarinic receptor. It exhibited a favorable side-effect profile in Phase 1b trial and advanced to Phase 2 developments (Krystal et al., 2022; Kantrowitz et al., 2023). However, recent Phase 2 clinical trial results from EMPOWER-1 and EMPOWER-2 did not meet their primary endpoint for Emraclidine (source: AbbVie News Center). These disappointing findings suggest that selective M4 receptor agonism alone may be insufficient for meaningful clinical improvement, whereas the combined activation of M1 and M4 receptors (as seen with KarXT) may be more effective. Moving forward, we hypothesize those muscarinic receptor-targeted therapies for schizophrenia will likely require a polypharmacological approach, as single-receptor modulation appears unlikely to yield optimal outcomes.

Other than muscarinic receptor agonism, Trace amine-associated receptor 1 has emerged as another therapeutic target for SCZ (Dedic et al., 2021). The mechanism of action of TAAR1 in SCZ involves modulating dopaminergic neurotransmission. By targeting TAAR1, the aim is to effectively treat the various symptoms of SCZ, including positive and negative symptoms, as well as cognitive impairments, with fewer overall side effects than current AP medications (Nair et al., 2022; Siafis et al., 2024). TAAR1 agonism promotes heterodimerization of the TAAR1 receptor with pre- and postsynaptic D2 receptors leading to the internalization of receptors and subsequently reducing presynaptic dopamine synthesis (Kantrowitz et al., 2023). Unfortunately, in Phase 3 trials - Developing Innovative Approaches for Mental Disorders (DIAMOND) 1 and DIAMOND 2, multicenter, randomized, double-blind, parallel-group, fixed-dose clinical studies, administering Ulotaront, a dual TAAR1 and 5-HT1AR agonist developed by Sumitomo Pharma (Sumitomo News Room), once daily to adults with SCZ was shown not to be superior to placebo (Zilberg et al., 2024). Recent insights from a comprehensive systematic review and meta-analysis of human and non-human data on TAAR1 agonism for psychosis suggest that TAAR1 agonists may be considered less effective than currently available dopamine D2 receptor antagonists for treating SCZ, as they are suggested to have potentially smaller positive effects compared to other AP (Siafis et al., 2024).

Recently, there has also been significant industry effort in developing PDE10A inhibitors for SCZ (Menniti et al., 2021). This focus is due to the importance of striatal dopamine signaling in SCZ, where phosphodiesterases (PDE), including PDE10A, play a role in modulating dopamine receptor-associated second messenger machinery, which is closely linked to drug-induced gene regulation in the striatum. PDE10A inhibitors work by blocking the activity of the phosphodiesterase 10A enzyme, responsible for breaking down signaling molecules such as 3 cyclic adenosine 3′,5′-monophosphate (cAMP) and cyclic guanosine 3′,5′-monophosphate (cGMP). By inhibiting PDE10A, these inhibitors increase the levels of cAMP and cGMP, affecting cellular communication and signaling in specific neurons, such as the medium spiny neurons in the striatum (Bonate et al., 2022). The increased cyclic nucleotide levels in these neurons may impact dopamine-mediated signaling and contribute to the modulation of striatal function related to action selection and behavioral control (Amin et al., 2021; Menniti et al., 2021). PDE10A inhibition has been shown to produce AP-like effects in preclinical rat models of SCZ and has also demonstrated cognitive enhancement, particularly in domains such as recognition memory, attention, impulsivity, working memory, and executive function (Shiraishi et al., 2016; Arakawa and Maehara, 2020; Harada et al., 2020). Supporting PDE10A inhibition in improving PANSS scores in acute SCZ, a randomized, double-blind, placebo- and active-controlled Phase 2a trial evaluated the PDE10A inhibitor MK-8189 developed by Merck & Co., Inc., Rahway, NJ, USA. The study demonstrated a trend towards improvement in PANSS total score after 4 weeks compared to placebo (difference = –4.7 points, P = 0.074), although it was not superior to risperidone (difference compared to placebo = –7.3 points, P = 0.033). Nevertheless, MK-8189 showed lower discontinuation rates due to adverse events and significant weight loss in obese subjects compared to risperidone (Mukai et al., 2024). However, results from clinical trials of other PDE10A inhibitors have been mixed. In a randomized, parallel-group, placebo-controlled Phase 2 study by Takeda that evaluated the phosphodiesterase 10A inhibitor TAK-063 compared to placebo in adults with acutely exacerbated symptoms of SCZ, the study did not meet the primary endpoint, as the least-squares mean difference in change from baseline in PANSS total score at week 6 between TAK-063 and placebo was not statistically significant (Macek et al., 2019). Similarly, results from another Phase 2 study by Pfizer to evaluate the efficacy of PF-02545920 compared to placebo in treating acute exacerbation of SCZ, showed that at day 28, neither dose of PF-02545920 was significantly different from placebo on the primary endpoint of change from baseline in total PANSS score (Walling et al., 2019). Understanding the specific reasons

for the lack of efficacy of some of the PDE10A inhibitors could provide valuable insights for future drug development in the treatment of psychosis and SCZ.

Outlook and Conclusion

Current limitations in SCZ research exist across multiple domains. Emphasis on single neurotransmitter systems, such as dopamine, fails to capture the complex interplay between dopaminergic, glutamatergic, serotonergic, and GABAergic pathways. Clinically, overlapping symptom presentations, particularly in early-onset cases and with predominantly negative symptoms, contribute to diagnostic ambiguity and potential misdiagnosis. Mechanistically, a lack of comprehensive understanding remains, particularly in immune dysfunction, lipid metabolism abnormalities, and genetic risk partitioning, which hinder the development of targeted treatments. These limitations highlight the need for more comprehensive, integrated, and multidisciplinary approaches that address the complexity and heterogeneity of SCZ.

Although AP remain the cornerstone of treatment, their limited efficacy and associated adverse effects underscore the urgent need for novel therapeutics that target mechanisms beyond the traditional dopamine D2 receptor (Remington et al., 2015b). Promising emerging strategies, such as targeting muscarinic acetylcholine receptor subtypes M1 and M4, as well as the development of PDE10A inhibitors, constitute ongoing research efforts to address these challenges.

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Additional file:

Additional Table 1: *A list of companies with Phase 2 or higher development with active indications for treatment of schizophrenia.*

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