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FRONTIER

Role of presynaptic phosphoprotein synapsin II in schizophrenia

Luke Molinaro, Patricia Hui, Mattea Tan, Ram K Mishra

Luke Molinaro, Patricia Hui, Mattea Tan, Ram K Mishra, Department of Psychiatry and Behavioural Neurosciences, McMaster University, Hamilton, Ontario L8N 3Z5, Canada

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Correspondence to: Dr. Ram K Mishra, Department of Psychiatry and Behavioural Neurosciences, McMaster University, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada. mishrar@mcmaster.ca
Telephone: +1-905-5259140-22396
Fax: +1-905-5228804

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Abstract

Synapsin II is a member of the neuronal phosphoprotein family. These phosphoproteins are evolutionarily conserved across many organisms and are important in a variety of synaptic functions, including synaptogenesis and the regulation of neurotransmitter release. A number of genome-wide scans, meta-analyses, and genetic susceptibility studies have implicated the *synapsin II* gene (*3p25*) in the etiology of schizophrenia (SZ) and other psychiatric disorders. Further studies have found a reduction of synapsin II mRNA and protein in the prefrontal cortex in post-mortem samples from schizophrenic patients. Disruptions in the expression of this gene may cause synaptic dysfunction, which can result in neurotransmitter imbalances, likely contributing to the pathogenesis of SZ. SZ is a costly, debilitating psychiatric illness affecting approximately 1.1% of the world's population, amounting to 51 million people today. The disorder is characterized by positive (hallucinations, paranoia), negative (social withdrawal, lack of motivation), and cognitive (memory impairments, attention deficits) symptoms. This review provides a comprehensive summary of the structure, function, and involvement of the synapsin family, specifically synapsin II, in the pathophysiology of SZ and possible target for therapeutic intervention/implications.

Key words: Synapsin II; Schizophrenia; Dopamine; Glutamate; Neuropsychiatry; Antipsychotic drugs

Core tip: The pre-synaptic phosphoprotein, synapsin II, is important in a variety of synaptic functions, including synaptogenesis and regulation of neurotransmitter release. Reduced levels of synapsin II in the prefrontal cortex of humans and animals have been found to confer susceptibility to schizophrenia (SZ). Disruptions in *synapsin II* gene expression, during development and/or adulthood, may cause synaptic dysfunction, resulting in neurotransmitter imbalances that likely contribute to the pathogenesis of SZ. Understanding synapsin II and its role in disease development will help unravel the pathogenic mechanisms of SZ, and may form the basis for use of novel therapeutics in the treatment of SZ.

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SYNAPSIN STRUCTURE

Synapsins were one of the first synaptic vesicle-associated family of proteins identified and characterized[1]. This highly conserved family is the most abundant of neuron-specific phosphoproteins, consisting 9% of the total amount of all vesicle proteins[2-4]. These presynaptic proteins are integral for many functional roles, including: synaptogenesis, synapse function, synapse maintenance and synaptic plasticity[5-7].

Mammalian synapsins are encoded by 3 genes: *synapsin Ⅰ*, *synapsin Ⅱ*, and *synapsin Ⅲ*, which are located on chromosome X, 3 and 22, respectively[8]. Alternative splicing of the aforementioned genes has produced at least 10 different isoforms of synapsin (Figure 1)[5,8-10]. Only one isoform for synapsin Ⅲ is indicated in Figure 1, but multiple synapsin Ⅲ products have been found in the adult brain[11]. Different isoforms of synapsin display differential expression within the body: synapsins Ⅰ and Ⅱ are typically found in mature synapses, while synapsin Ⅲ is often attributed to developing synapses (with lesser overall expression)[1,4,8].

The short N-terminus (approximately 20 residues), as well as the central domains (A and C), of all synapsins are highly conserved. Thus, structural variation among isoforms is often localized to the C-terminus. Of the variable domains found in the synapsin family, 7 have been currently identified[1,8]. Domain A contains a conserved phosphorylation site for protein kinase A (PKA) and Ca^{2+}/calmodulin-dependent protein kinase I (CaM kinase I)[1]. Domain B functions to link the N-terminus to the large central C domain (approximately 300 residues)[1,2]. Functionally, synapsins bind to the lipid surface of vesicles *via* the N-terminus, while the variable, hydrophilic C-terminus often facilitates the stabilization of synapsin on phospholipid bilayers and cytoskeletal elements *via* domain E. Domain E is shared amongst all the "a" isoforms and is thought to have a specific role in the clustering of synaptic vesicles and the maintenance of the reserve pool through interactions with cytoskeletal components[1,4,11-15]. Moreover, domain E may be involved in the forming of synapsin dimers; the "a" isoforms may dimerize to bring weaker targeting isoforms, such as Ib, to synaptic terminals[11,16]. Domains B, D, and F-J are poorly conserved amongst isoforms and are specific to each *synapsin* gene (Figure 1)[1,4,13-15].

Synapsins are functionally mediated through phosphorylation by several protein kinases, including PKA, CaM kinase Ⅱ, mitogen activated protein kinase (MAP kinase Ⅱ), and cyclin-dependent kinase 5 (Cdk5)[11,17-19].

REGULATION OF SYNAPSINS

The promoter region of synapsin Ⅰ and Ⅱ has been found to contain multiple transcription factor binding sites including: inducible zinc-finger transcription factor, early growth response factor (EGR-1), and polyoma enhancer activator 3 (PEA-3). Such control for synapsin Ⅲ has not been well investigated[20]. The *synapsin Ⅱ* gene, in contrast to that of synapsin Ⅰ, also contains a promoter binding site for the transcription factor, activating protein 2-alpha (AP-2α), suggesting the possibility of differential transcriptional regulation of the phosphoproteins depending on the cellular environment. Studies conducted by Skoblenick *et al*[21] showed that the *synapsin Ⅱ* gene promoter is regulated by the AP-2α transcription factor, which is activated by the cyclic AMP (cAMP)-protein kinase pathway. Stimulation of the dopamine (DA)-D1 receptor leads to increased activation of AP-2α *via* cAMP formation, resulting in increased *synapsin Ⅱ* gene expression. Conversely, inhibition of the DA-D2 receptor leads to increased cAMP formation and consequent increase in *synapsin Ⅱ* gene expression. In the absence of AP-2α (induced knockdown by antisense deoxyoligonucleotide, AS, or SiRNA technology), DA-D1 receptor stimulation or antagonism of the DA-D2 receptor were unable to alter synapsin Ⅱ. The knockdown of EGR-1 or PEA-3, on the other hand, had no effect on altering synapsin Ⅱ expression, reinforcing the role of AP-2α in *synapsin Ⅱ* gene regulation (Figure 2)[21]. Furthermore, earlier research conducted by Chong *et al*[22] demonstrated significant reductions in the concentration of synapsin II within the striatum and medial prefrontal cortex (mPFC) following chronic treatment of the DA-D1 receptor antagonist, SCH23390. Inversely, activation of DA-D1 receptors by the agonist, SKF38393, has been shown to cause increased expression of synapsin Ⅱ. Neither haloperidol nor DA-D1 receptor antagonist affected synapsin Ⅰ protein expression in any of these studied brain regions[22,23]. These findings reinforce the notion that DA receptors may specifically regulate synapsin Ⅱ expression through a cAMP-dependent pathway.

Despite the high degree of homology between *synapsin Ⅰ* and *Ⅱ* genes, promoters for both of these genes reveal low homology, suggesting the involvement of differing transcription factors[20]. Not only does synapsin I not contain a promoter region for AP-2α (Figure 2), it also contains two additional EGR-1 binding sites, a neural-restrictive silencer element next to one EGR-1 binding region, and a cAMP-response element next to another (Figure 2)[21-23]. EGR-1 is termed a cellular immediate early gene and *EGR-1* gene expression is highly responsive to neuronal stimulation[20]. Studies have shown that an induction of long-term potentiation causes an increase in EGR-1 mRNA and protein, and subsequent activation of *synapsin I* gene expression three hours later. Given the

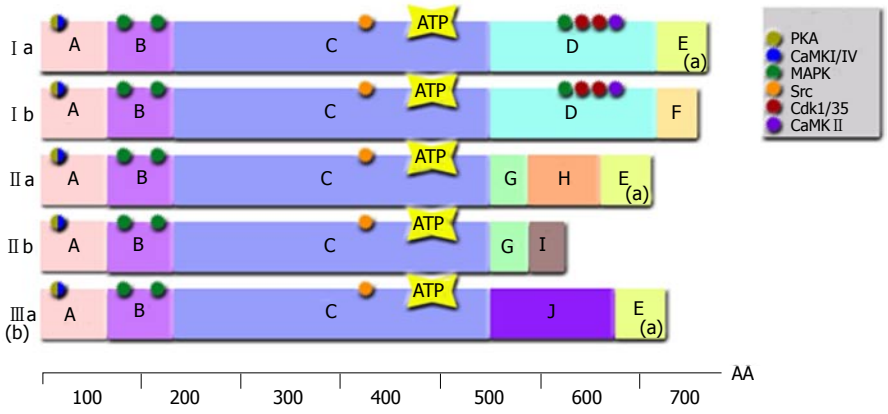

Figure 1 Illustration demonstrating the various mammalian synapsin gene products. Various domains are indicated as well as known phosphorylation sites and their respective kinases (colour coded)[8,11,16]. (a): Domain "E" has been implicated in phospholipid vesicle clustering and dimerization; (b): Only a single version of synapsin III is illustrated.

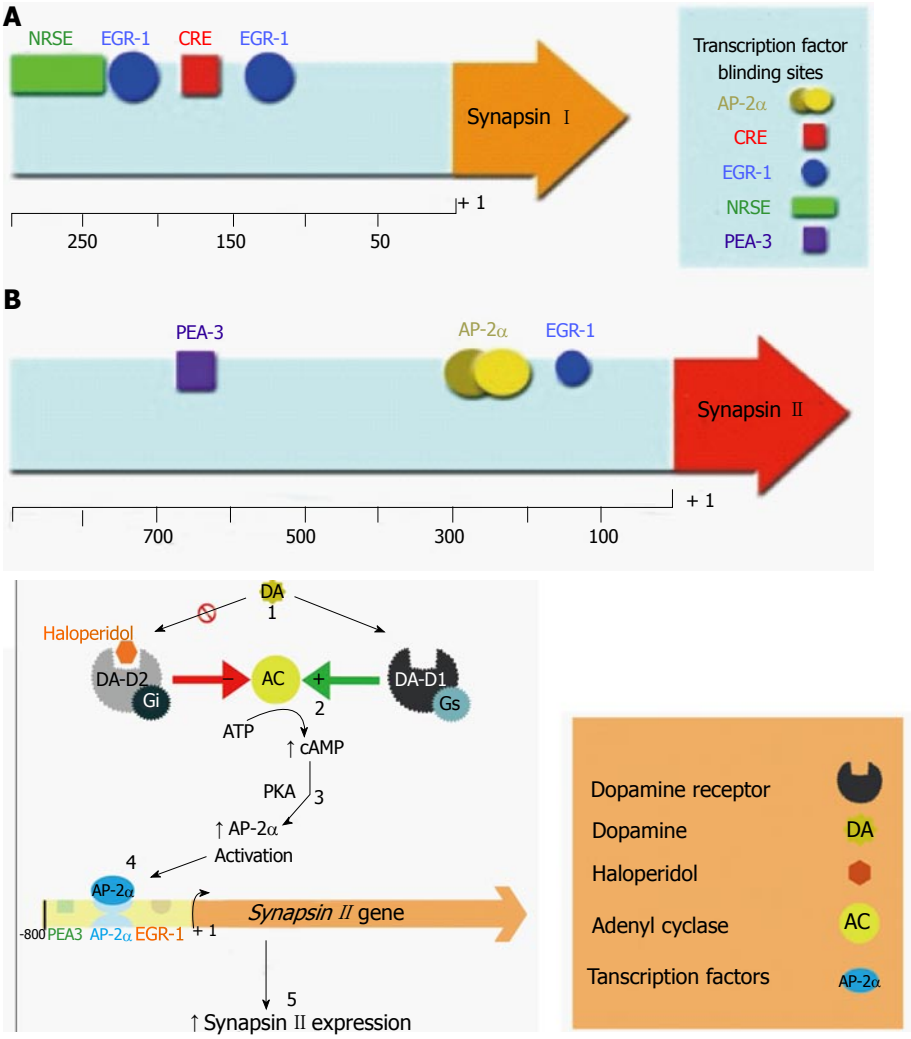

Figure 2 Illustration of the promoter regions of synapsin I and II respectively and proposed mechanism of dopaminergic regulation of synapsin II. A: Illustration of the promoter regions of synapsin I and II respectively. Transcription factor binding sites have been indicated, showing their various positions in the promoter region; B: Proposed mechanism of dopaminergic regulation of synapsin II. Evidence: (1) Immunocytochemstry results indicate that ligand - DA Rc binding results in changes to synapsin protein levels dependant on Rc subtype; (2) Ligand binding causes changes to intercellular cAMP levels; (3) PKA inhibitors (5-24 amide trifluoroacetate salt, Rp-cAMPS) cause changes in synapsin II translation; (4) DA-D1 stimulation may cause AP-2 to bind to synapsin II promoter. Synapsin II expression levels were inhibited when cells were treated with AP-2 ADONs. Subsequent treatment with DA-D1 or -D2 agonists showed to effect on synapsin II expression; and (5) Synapsin 2 expression can be altered *via* upstream alteration at various points. Additional information: (1) EGR-1 levels are not affected by chronic treatment with DA-D1 or DA-D2 antagonists; (2) Antisense deoxyoligonucleotides for AP-2 reduces synapsin II expression levels; and (3) Antisense deoxyoligonucleotides for EGR-1 and PEA3 have no effect on the expression of synapsin II. EGR-1: Early growth response factor-1; PKA: Protein kinase A; cAMP: Cyclic AMP; AP-2α: Activating protein 2-alpha.

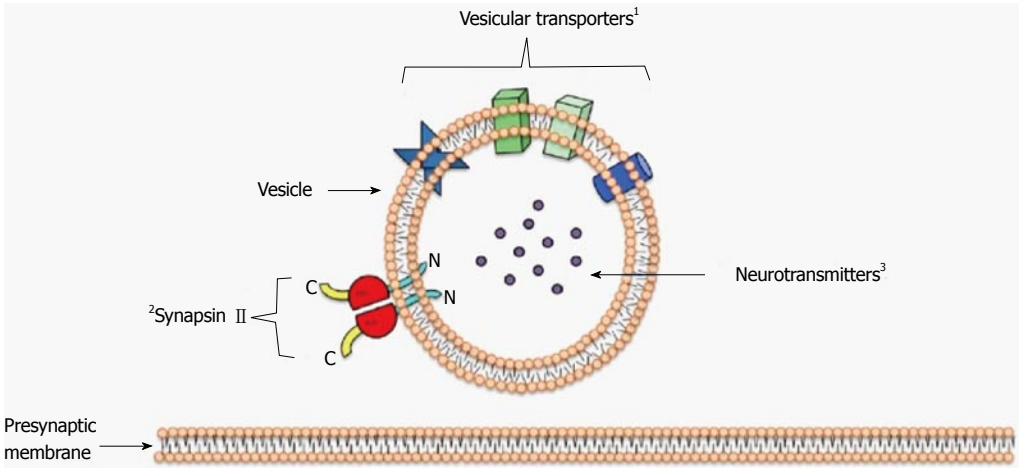

Figure 3 Illustrated depiction of a synaptic vesicle and associated pre-synaptic membrane. This is a simplified depiction containing proteins and neurotransmitters that are most pertinent to the subject matter of this review; others have been omitted for simplicity sake (*ex*. Synapsin I, various transporter proteins, *etc*.). [1]Vesicular transporters (also specific to the type and function of synapse) may include: VGLUT1, VGLUT2, VGAT and VMAT2; [2]Various synapsin isoforms have been implicated in the tethering of synaptic vesicles (depending on the type of neurotransmitter and vesicular transporters associated). Synapsin isoforms include Ia-b, IIa-b, and IIa-e; [3]Neurotransmitters contain within synaptic vesicle, may include: glutamate, GABA, DA, *etc*. VGLUT: Vesicular glutamate transporter; VGAT: Vesicular GABA transporter; VMAT2: Vesicular monoamine transporter 2; GABA: γ-aminobutyric acid.

presence of EGR-1 on the *synapsin Ⅱ* gene, a similar function has been hypothesized for synapsin Ⅱ following the induction of LTP[20].

The PEA-3 promoter is influenced by serum promoters, tumor promoters, and the gene products of several non-nuclear oncogenes including *v-raf*, *vsrc*, *Ha-ras*, and *polyoma middle T-antigen*[20]. These proteins are involved in the signal transduction cascade activating MAP kinase[20]. When activated, MAP kinase translocates into the nucleus and activates the transcription of transcription factors, including PEA-3. Evidence has been provided for extracellular signal molecule activation of synapsin II expression through the MAP kinase pathway and the PEA-3 promoter[20].

In addition to the regulatory mechanisms described above, epigenetic modifications have been proposed to regulate the transcriptional ability of synapsin genes. Studies have found a correlation between H3K4me-3 (an epigenetic indicator of increased expression) rich sites near the promoter regions of both synapsin Ⅰ and Ⅱ, and the increased expression of these genes in the prefrontal cortex (PFC) of mood disorder patients[24]. Current research also suggests that DNA methylation may play a similar role, yet very little evidence exists to suggest it may be responsible for altered synapsin expression and the subsequent pathogenesis of mental illness.

ROLE OF SYNAPSINS IN CELLULAR FUNCTION

Synapsin proteins play a critical role in synaptic function. One role of particular interest is the regulation of synaptic vesicles by synapsins[8]. Dynamic cellular interactions allow synapsins to selectively, and reversibly, bind to synaptic vesicles and interact with actin filaments to tether these vesicles to the cytoskeleton of the reserve pool (Figure 3)[4]. Upon the firing of an action potential, the influx of Ca^{2+} and the subsequent phosphorylation of synapsins, encourage the liberation of vesicles from binding to the cytoskeleton. This transitions the synaptic vesicles from the reserve to the active pools, thereby regulating the availability of synaptic vesicles ready for exocytosis and successive neurotransmitter release[4,25].

Synaptic vesicles contain two classes of obligatory components, namely the vesicular transport proteins and trafficking proteins[1,26]. Vesicular transport proteins are involved in neurotransmitter uptake, and include both the vacuolar-type proton pump, which acidifies the vesicle and generates the electrochemical gradient to fuel the uptake of neurotransmitters through ATPase activity, as well as neurotransmitter transporters, which mediate the uptake of glutamate, γ-aminobutyric acid (GABA), monoamines, and various other neurotransmitters, into the vesicle[1].

Phosphorylation of synapsins can also regulate the availability of synaptic vesicles and alter neurotransmitter release at the synapse. The phosphorylated state of synapsins is increased under the promotion of Ca^{2+}-dependent neurotransmitter release[4]. In contrast, dephosphorylation of synapsins can act as an inhibitory constant preventing the release of synaptic vesicles, of which constraint can be alleviated by phosphorylation with the respective kinases[4,11,14,25].

Synapsins also play a role in short-term synaptic plasticity, axonal outgrowth and synaptogenesis[1,3,26]. Synapsin knockout mice (Ⅰ, Ⅱ, or both) exhibited abnormalities in neurotransmission, reduced synapse numbers, and a lack of vesicle clusters at presynaptic sites[4,14]. Although both synapsins Ⅰ and Ⅱ serve to maintain synaptic vesicle numbers at nerve terminals, they each play distinct roles in the development of cultured hippocampal neurons. Deletion of *synapsin Ⅱ* alone had a greater effect on lammelipodial formation,

neurite formation, and axon differentiation, whereas deletion of synapsin Ⅰ alone more prominently affects the formation of synapses[27]. Transfection of *synapsin Ⅱb* cDNA in a neuroblastoma-glioma cell line resulted in increased nerve terminals and synaptic vesicles within each terminal[4,14]. *Synapsin Ⅱb* cDNA transfection also increased the expression levels of other associated synaptic vesicle proteins within the nerve terminal, thus accelerating the development and maturation of neurons[4,14]. An inhibition of *synapsin Ⅱ* expression by AS in cultured hippocampal neurons, on the other hand, was found to inhibit axon elongation, and interfere with the formation and maintenance of synapses[14,28,29]. A *synapsin Ⅱ* knockout animal was phenotypically more severe than the *synapsin Ⅰ* knockout animal, with a double knockout of *Ⅰ* and *Ⅱ* causing the most drastic changes including a 50% reduction in synaptic vesicle numbers[1,3]. *Synapsin Ⅲ* knockout mice exhibited the least drastic of changes, including a 5% increase in synaptic vesicle density and altered GABA signaling[1].

Given the production of a more detrimental phenotype following *synapsin Ⅱ* knockout, as well as its more diverse regulatory mechanisms, one may suggest the involvement of synapsin *Ⅱ* in the etiology of schizophrenia (SZ).

SZ

Prior to describing the involvement of synapsin Ⅱ in SZ, an understanding of SZ itself is necessary. SZ is characterized by positive (hallucinations, paranoia), negative (social withdrawal, anhedonia), and cognitive (memory impairments, attention deficits) symptoms[30,31]. To date, the exact pathogenesis of the disorder has yet to be elucidated. There are, however, a number of hypotheses that have been suggested. Evidence has shown that neurotransmitters, dopamine, glutamate and GABA, are involved in and play an integral role in the complex etiology of SZ[32-41].

The dopamine hypothesis postulates that hyperdopaminergic activity in the striatum is connected with the positive symptoms of SZ, and hypo-dopaminergic activity in the cortical regions with the negative and cognitive symptoms. Evidence for this has been provided by use of pharmacological agents, such dopamine agonists (*e.g.*, amphetamine), which induce SZ-like symptoms in humans. *In vivo* positron emission tomography (PET) imaging studies utilizing ^{18}F-dihydroxyphenyl-*L*-alanine (^{18}F-DOPA) tracers have demonstrated elevated uptake levels in the substantia nigra and striatum of schizophrenic patients. These results suggest an increase in DA synthesis, in nigral and striatal regions, in SZ[42]. These dopaminergic pharmacological agents are also common inducers of SZ-like behaviour in preclinical animal models. In addition, single photon emission computed tomography (SPECT) and PET studies have shown that patients with SZ show elevated synthesis and release of DA in the basal ganglia[41]. Additionally, under-stimulation of the DA-D1 receptors and low DA activity in the PFC has been suggested to correlate with cognitive impairment and poor performance in tasks involving working memory seen in patients with SZ[43-45]. Therefore, regulation of synapsin Ⅱ by the dopamine receptor is not unexpected.

The glutamate hypothesis originates from the findings that *N*-methy-D-aspartate (NMDA) receptor antagonists, including the drugs ketamine and phencyclidine (PCP), induce symptomatic manifestations indistinguishable from that of SZ. NMDA hypofrontality is therefore implicated in the etiology of SZ[45,46]. Increasing NMDA receptor activity with NMDA agonists like glycine and D-serine can alleviate symptoms in patients with SZ[4,44]. Evidence for both hypoglutamatergic and hyperdopaminergic activity is not exclusive, but rather behaves in a complementary manner. Sustained NMDA hypofunction has been found to induce a reduction in mesocortical dopamine transmission and subsequent increase in subcortical mesolimbic dopamine activity, trends of which are consistent with the DA hypothesis of SZ (Figure 2B and 4B)[44]. Synaptic alterations within the PFC may cause sustained dysfunction of glutamate neurotransmission and cause subsequent secondary abnormalities in DA transmission (subcortical dopamine hyperactivity and cortical DA hypoactivity)[44].

The DA hypothesis associates hyperdopaminergic activity in the striatum to account for positive symptoms, while hypodopaminergic activity in the cortical regions to be responsible for negative and cognitive symptoms[7,8]. The glutamate hypothesis implicates glutamate hypofunctionality in the cortical regions of the brain to account for both negative and neurocognitive symptoms of SZ[14,15]. Both glutamatergic and dopamine projections converge on the dendritic spines of GABAergic medium spiny neurons in the striatum[44]. A dysregulation in GABAergic neurotransmission has been observed with a reduction in GABA-synthesizing enzymes (glutamic acid decarboxylase, GAD) reported in patients with SZ[13,29]. Additionally, a reduction in GABA neuron density has been observed in the PFC and limbic regions of patients with SZ[41].

Interestingly, a synaptic-neurodevelopmental model of SZ has also been proposed by Mirnics *et al*[47] genetic predisposition to defective synaptic protein expression and altered signaling during development, along with possible inadequate adaptation to compensate for deficits during early childhood and/or adolescence, can lead to the manifestation of SZ in the developmental time course[44,47,48]. These abnormalities in presynaptic gene expression and deficits in synaptic functions throughout development may lead to PFC dysfunction and the ensuing cognitive deficits, along with the positive and negative symptoms commonly seen in patients with SZ[44,47].

IMPLICATIONS OF SYNAPSIN Ⅱ IN SZ

The synapsin family of proteins, in addition to other candidate genes, have also been found to be implicated

in the etiology of SZ[49,50]. The *synapsin Ⅱ* gene is located on chromosome 3p25, which was suggested to be a region of vulnerability for SZ[51,52]. Positive associations have been found between SZ development and variants of the *synapsin Ⅱ* gene (single-nucleotide polymorphisms and insertion/deletion polymorphisms) in certain population subsets[25,48,51,53]. Synapsin Ⅱ is known to co-localize with CAPON, which functions as an adapter protein for neuronal nitric oxide synthase 1 (nNOS1). nNOS is responsible for the on-demand production of nitric oxide needed for neurotransmitter release. CAPON has since been identified as a major candidate susceptibility gene for SZ[10,54]. Due to this, a reduction or dysfunction of synapsin Ⅱ may cause reduced nitric oxide localization in proximity of presynaptic targets. Mechanistically, this may act as a factor contributing to the onset of SZ.

Several studies have provided additional data to support a relationship between synaptic dysfunction and the onset of SZ. Research has shown a general reduction in synapsins in post-mortem brain samples of alcoholic, schizophrenic, and bipolar subjects[55-57]. In particular, patients suffering from SZ have shown a significant reduction in synapsin Ⅱ mRNA and protein levels compared to normal control subjects[25,48,58-60]. A more recent study has shown that mRNA expression of the synapsin IIa isoform to be significantly decreased in patients with SZ, relative to healthy patients and bipolar patients. Expression of synapsin IIb mRNA, however, was only significantly reduced in patients with SZ when compared to healthy subjects, and not with patients with bipolar disorder[61]. Treatment with antipsychotic drugs, such as haloperidol and olanzapine, has been found to increase expression levels of synapsin Ⅱ in the human brain[60,61].

Further support for the involvement of synapsin Ⅱ dysfunction in the etiology of SZ can be found in work utilizing pre-clinical animal models. Experiments conducted with gene knockout technology in rodent subjects have revealed behavioural phenotypes similar to those resulting from various accepted pre-clinical animal models of SZ of the disorder. *Synapsin Ⅱ* knockout mice manifest behavioural abnormalities similar to those of animal models of SZ, such as locomotor hyperactivity, social withdrawal, and deficits in sensorimotor gating (prepulse inhibition)[62-64]. Experiments utilizing a knockdown of synapsin Ⅱ in the adult rat mPFC, but not in the cerebellum or hippocampus, resulted in similar behavioural phenotypes including deficits in prepulse inhibition, locomotor hyperactivity, social withdrawal, hypofunction in the PFC (*i.e*., hypofrontality) (not published), deficits in the 8-arm radial maze, and poor performance in the 5-choice serial reaction time task (not published), suggesting the specific role of MPFC syn 2[9,62-64]. These symptoms are all reminiscent of the positive, negative, and cognitive symptom domains of SZ. Furthermore, immunoblotting results demonstrated a reduction in glutamate and GABA signalling, and unaltered DA signaling, within the mPFC resulting from *synapsin Ⅱ* knockdown. Specifically, there were reductions in protein concentration of glutamate vesicular transporters (VGLUT 1, VGLUT 2), vesicular GABA transporter (VGAT)[63]. These findings suggest that synapsin Ⅱ is involved in vesicular loading, and that deficits in synapsin Ⅱ protein expression may result in reduced neurotransmitter uptake and release. In addition, all abnormalities in the measured parameters of the adult rat synapsin Ⅱ model were reversed with administration of the antipsychotic drug (APD), olanzapine[22,63]. Consequently, the study of synapsin Ⅱ and its isoforms is imperative to understanding the pathophysiology of SZ and the mechanisms involved in the therapeutic action of APDs[5].

NEUROCIRCUITRY, ANTIPSYCHOTIC DRUGS AND SYNAPSIN Ⅱ

It has been proposed that a reduction in mesocortical dopaminergic activity results in decreased glutamatergic output from the cortex to the nucleus accumbens and the ventral tegmental area in the brain with SZ[65]. This decrease will then cause subsequent reductions in GABAergic output from the nucleus accumbens to the mesolimbic cells of the ventral tegmental area. Thus, a state of disinhibition is created, whereby dopaminergic output to the nucleus accumbens is elevated. A depiction of this mesolimbic dysfunction is illustrated in Figure 4A.

The potency and efficacy of current APDs to treat symptoms of SZ have been shown to be directly correlated to their occupancy at the DA-D2 receptor, substantiating the role of hyperdopaminergic activity in mechanisms underlying this disorder[35,41,44,66-68].

Typical APDs, such as haloperidol, primarily bind to and antagonize DA-D2 receptors, while atypical APDs, including olanzapine, act on DA-D2 receptors amongst an array of other receptors including the serotonin receptors[34,38,69,70]. Previous research has demonstrated that chronic administration of typical APD, haloperidol, resulted in a significant increase of synapsin II mRNA and protein in the rat striatum, nucleus accumbens (NAc), and to some extent the mPFC[22,23]. Interestingly, these findings vary from those found by Guest *et al*[60], where it was shown that treatment with typical APDs did not significantly increase synapsin Ⅱ levels relative to healthy controls. Conversely, treatment with atypical APDs was shown to significantly increase expression of both isoforms of synapsin Ⅱ in post-mortem tissue samples of the PFC of schizophrenic patients[60]. It can then be suggested that expression of synapsin Ⅱ is differentially regulated by administration of typical or atypical APDs.

The typical APD, haloperidol, can increase cortical synapsin Ⅱ levels, which in turn leads to increased glutamatergic output to the to the NAc. Thus, GABAergic output from the NAc to mesolimbic cell bodies becomes normalized, resulting in downstream normalization

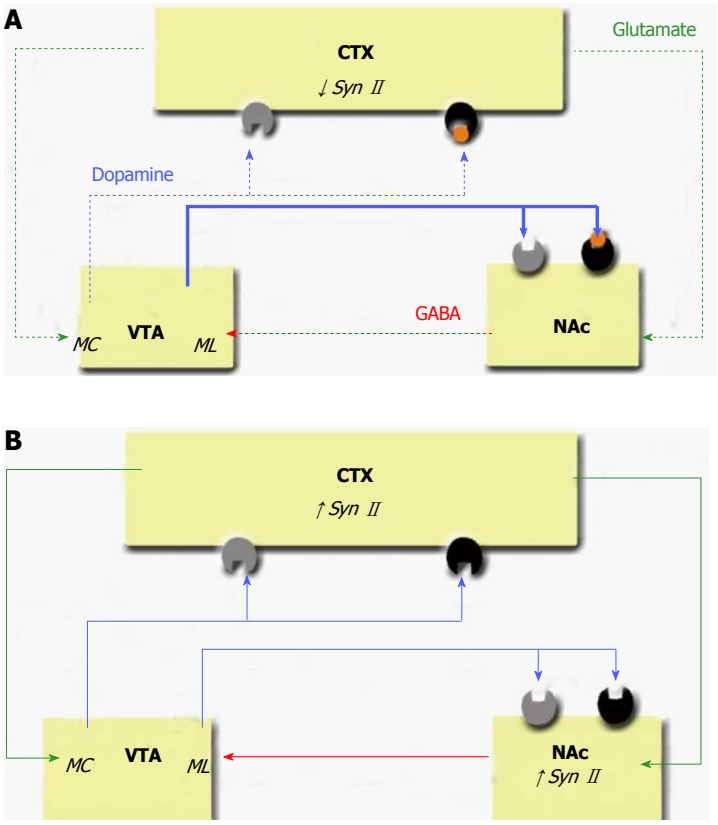

Figure 4 Oversimplified diagram of mesolimbic dysregulation in schizophrenia and the mesolimbic system following Anti-psychotic drug treatment[94,95]. A: Oversimplified diagram of mesolimbic dysregulation in schizophrenia; B: Oversimplified diagram the mesolimbic system following APD treatment. Difference in neurotransmitter output is indicated through the various line colours (green = glutamatergic, red = GABAergic, blue = dopaminergic). Line thickness is reflective of neurotransmitter activity (thicker lines represent increased activity, dotted lines represent reduced activity). The various impacted brain regions are represented within boxes. CTX: Cortex; NAc: Nucleus accumbens; VTA: Ventral tegmental area; APD: Antipsychotic drug.

on the DA levels in the NAc. Haloperidol may also antagonize D2 receptors of NAc cells. This antagonism results in an increase of synapsin Ⅱ in the ventral striatum which also acts to normalize the release of GABA from the NAc to the ventral tegmental area, thus causing further reduction (or stabilization) of dopaminergic activity in the NAc (Figure 4B)[71,72].

In addition to the different pharmacological profiles, typical and atypical APDs differ in the types of adverse side-effects which are induced upon treatment. Chronic treatment with haloperidol and other typical APDs has led to the development of severe extrapyramidal symptoms (EPS), including tardive dyskinesia and other motor impairments[73-75]. Atypical APDs, on the other hand, primarily lead to the development of adverse metabolic effects including, but not limited to, metabolic syndrome and hyperprolactinaemia[76-78].

The development of severe motor impairments following treatment with typical APDs may be a result of drug-induced up-regulation of synapsin Ⅱ in the striatum, a brain region highly involved in motor functioning[23,79]. The blockade of DA-D2 receptors by haloperidol results in a decrease in DA neurotransmission, which is followed by a compensation effect of increased DA synthesis and release in the striatum. Mechanistically, dopaminergic output from the substantia nigra pars compacta (SNc) regulates the GABAergic output from the striatum to the substantia nigra pars reticulata (SNr) and the globus pallidus internal segment (GPi) ("direct" pathway), as well as the output to the globus pallidus external segment (GPe) ("indirect" pathway) (Figure 5A). Both the "direct" and "indirect" pathways control GABAergic output from the SNr/GPi to the thalamus, which in turn regulates the thalamocortical glutamatergic projections and subsequent glutamatergic output from the cortex to the striatum (Figure 5B). Therefore, haloperidol-induced up-regulation of striatal synapsin Ⅱ expression will act to increase striatal GABAergic output along both pathways. Chronic haloperidol use likely increases striatal DA-D2 receptor numbers, while maintaining high synapsin Ⅱ levels in GABAergic output along the direct pathway. This imbalance could further result in exaggerated cortical glutamatergic stimulation thought to produce EPS (Figure 5C)[44,80].

FURTHER IMPLICATIONS OF SYNAPSIN Ⅱ

Synapsin Ⅱ has also been implicated in a number of other mental illnesses, including bipolar disorder (BD) and autism spectrum disorder (ASD). Gene variation studies have suggested that mutations (missense or nonsense) in the *synapsin Ⅱ* gene may be responsible for the development of ASD[81]. A study conducted by Lopez de Lara *et al*[82] found that expression levels of synapsin Ⅱ mRNA were increased in post-mortem PFC samples of BD patients. Additionally, studies have provided evidence for a genetic linkage between synapsin Ⅱ and lithium-responsive bipolar disorder[24,82]. *In vivo* studies measuring effects of lithium, one of the most common treatments for BD, on synapsin Ⅱ levels have proven inconclusive. This is reflected in the results as some patients experience an elevation in synapsin Ⅱ

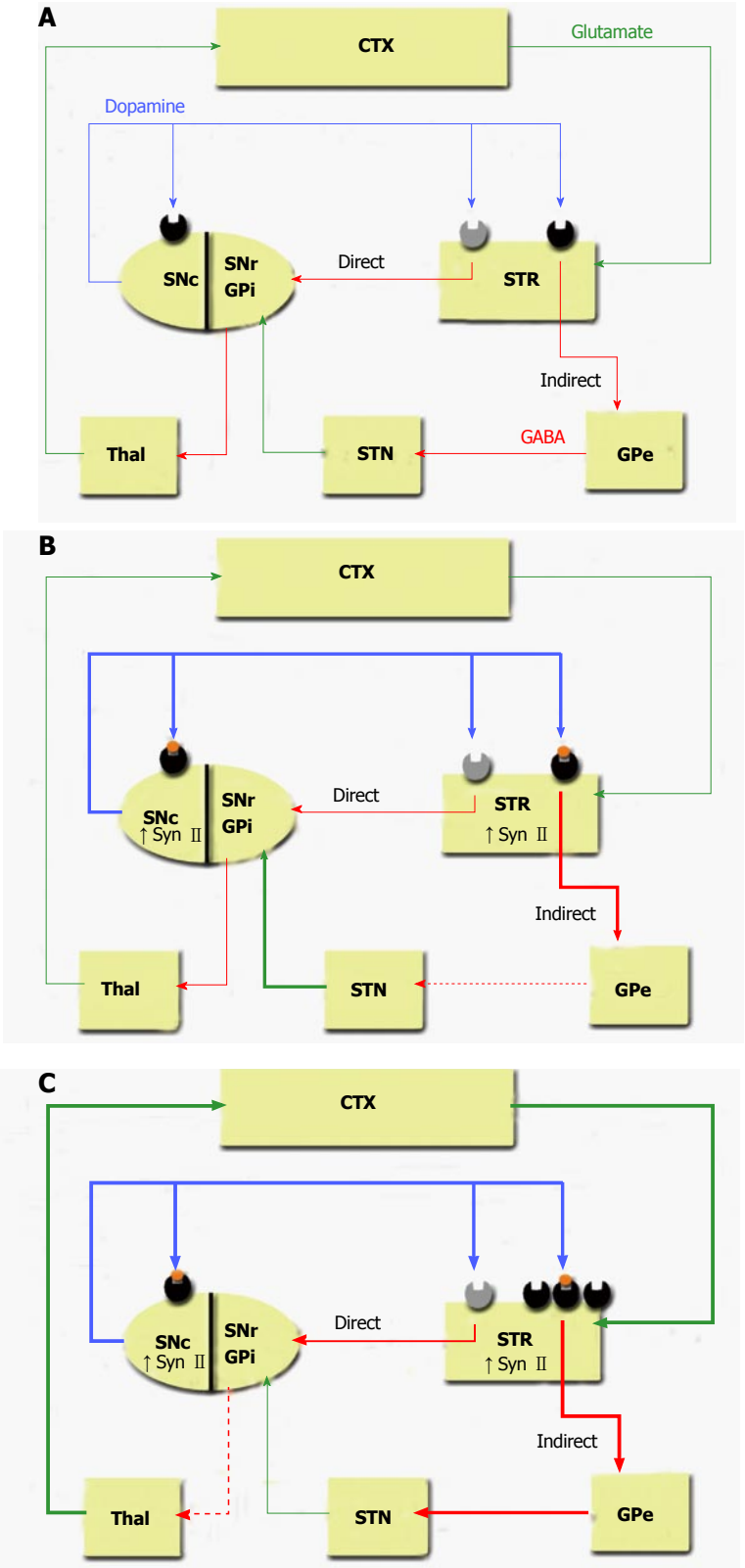

Figure 5 Depiction of basal ganglia interconnectivity. Diagrams showcase both the direct and indirect pathways[94,95]. A: Normal basal ganglia regulation; B: Basal ganglia regulation following sub-chronic haloperidol treatment. Synapsin Ⅱ levels also indicated; C: Basal ganglia regulation following chronic haloperidol treatment and manifestation of EPS. Synapsin levels are also indicated. Difference in neurotransmitter output is indicated through the various line colours (green = glutamatergic, red = GABAergic, blue = dopaminergic). Line thickness is reflective of neurotransmitter activity (thicker lines represent increased activity, dotted lines represent reduced activity). The various impacted brain regions are represented within boxes. Ghose and Tamminga. *Handbook of Contemporary Neuropharmacology* 2007: 251-283. CTX: Cortex; GPe: Globus pallidus external segment; GPi: Globus pallidus internal segment; SNc: Substantia nigra pars compacta; SNr: Substantia nigra pars reticulata; STN: Subthalamic nucleus; STR: Striatum; EPS: Extrapyramidal symptoms.

levels when treated with lithium, while others showcase a decrease in synapsin Ⅱ following lithium treatment[24]. Researchers have suggested that this may be due to the mood stabilizing effects of lithium, and the fact that it functions to normalize variation across different behavioral states[24].

In vitro administration of lithium significantly increased expression levels of the synapsin IIa isoform compared to controls in neuronal cell types. Conversely, lithium treatment did not result in any significant changes to synapsin IIb expression[24,83]. Moreover, synapsin Ⅱ knockout in mice resulted in an epileptic phenotype, stronger at 2-3 mo of age, a period when synapsin Ⅱ levels are highly expressed and synapses

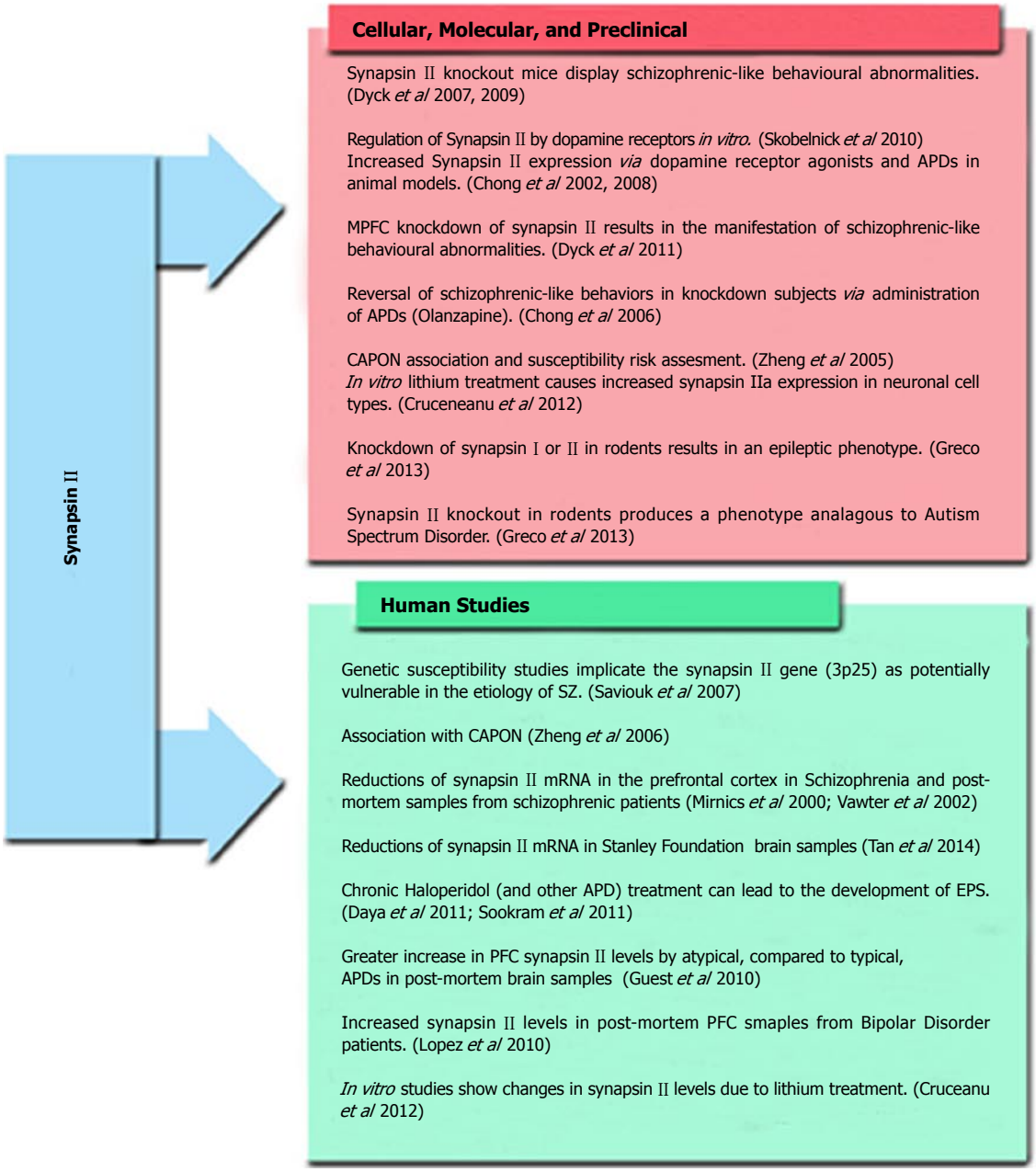

Figure 6 Empirical basis and experimental evidence suggesting the involvement of synapsin II in schizophrenia. Image is a modified version of existing figure[10].

undergo intense maturation and refinement[84]. Similarly, of other synapsin knockout models, mice lacking synapsin Ⅱ demonstrated the most robust phenotype of autism, characterized by reduced social interaction, and decreased interest for environmental stimuli[84].

CURRENT WORK AND FUTURE DIRECTIONS

Taken together, the various behavioral commonalities between SZ with BD and ASD, as well as common risk assessment between the *synapsin Ⅱ* gene and the aforementioned diseases, a potential therapeutic value of synapsin Ⅱ in mental health can be implicated[84,85]. Aside from the information presented above, there are other hypotheses (past or current) which may benefit from studying synapsin Ⅱ. With this in mind, continued work in synapsin Ⅱ is both a current and future task.

One area of current interest and research is the role of synapsin Ⅱ in the neonatal ventral hippocampal (nVH) lesion model of SZ, which is often discussed in support for the neurodevelopmental pathogenesis of SZ[86-92]. In this model, lesions of the hippocampus using ibotenic acid at an early neonatal stage (postnatal day 7) leads to irreversible SZ-like behavioural abnormalities in the adult rat[87-90,92]. In addition, several neurotransmitters, including DA and glutamate, are disrupted in the mPFC at the post-pubertal stage of nVH lesioned pups[88-90]. With these behavioral and biochemical deficits in mind, an implication of synapsin Ⅱ may be considered.

Synapsin Ⅲ may also play a larger role in this model as it is differentially expressed during development and adulthood (decreased expression in adult subjects)[93]. Current work in our lab is set to determine the effects of synapsin Ⅱ dysfunction during development and the resulting behavioral phenotypes in both developing and adult rodents.

Other pre-clinical animal models of SZ are currently of interest with respect to synapsin Ⅱ. Various pharmacological models of SZ present differing symptom profiles making it difficult to accurately study the mechanism behind the etiology of SZ. Currently the phencyclidine model of SZ induces the most robust behavioural phenotypes, with preclinical animal models displaying positive, negative, and cognitive symptoms. Similarly synapsin Ⅱ knockout in adult rats also results in the development of the SZ-like behaviors. Thus, there may exist an association between synapsin Ⅱ expression and PCP induced deficits. Preliminary studies from our lab have found reduced levels of synapsin Ⅱ expression in the in the mPFC of PCP-induced animal subjects (unpublished preliminary studies). These results, in addition to recent work addressing synapsin Ⅱ dysfunction and its various resulting phenotypes (ASD, BD, *etc.*), continued experimentation with regards to synapsin Ⅱ holds merit.

CONCLUSION

Evidence substantiates a crucial role for synapsin Ⅱ in the pathophysiology and therapeutic mechanisms for the treatment of SZ. The empirical basis and experimental findings are summarized in Figure 6. Due to its critical influence on neurotransmitter regulation and synaptic maintenance, a disruption in the expression levels of synapsin Ⅱ in the PFC may lead to a dysregulation in presynaptic function, an imbalance in brain circuitry, and subsequently promote the development of mental illnesses such as SZ, BD, and ASD. The further understanding of synapsin Ⅱ in these synaptic functions remains critical to unraveling the pathogenic mechanisms of SZ, and may facilitate the production of novel and safer therapeutics for treatment of these debilitating disorders.

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