SPECIAL ARTICLE

Future perspectives on the treatment of cognitive deficits and negative symptoms in schizophrenia

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Drug discovery based on classic models for cognitive impairment and negative symptoms of schizophrenia have met with only modest success. Because cognitive impairment and negative symptoms may result from disruptions in neurodevelopment, more complex developmental models that integrate environmental and genetic risk factors are needed. In addition, it has become clear that biochemical pathways involved in schizophrenia form complex, interconnected networks. Points at which risk factors converge, such as brain-derived neurotrophic factor (BDNF) and protein kinase B (AKT), and from which processes involved in neuroplasticity diverge, are of particular interest for pharmacologic interventions. This paper reviews elements of neurodevelopmental models for cognitive deficits and negative symptoms of schizophrenia with the aim of identifying potential targets for interventions.

Key words: Schizophrenia, negative symptoms, cognition, neurodevelopment, neuroplasticity, drug development

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The mechanisms responsible for cognitive impairment and negative symptoms in schizophrenia continue to be poorly understood and, as a result, these highly disabling deficits remain relatively refractory to current treatments. Two decades of efforts at drug discovery based on commonly-employed animal models have been largely disappointing, suggesting that new models for these symptom domains are needed. The large literature on previous clinical trials with existing compounds has been reviewed elsewhere (1,2). This paper outlines current etiologic theories for cognitive deficits and negative symptoms, potential animal models, and novel treatment strategies suggested by these models.

Traditional theories of cognitive deficits and negative symptoms in schizophrenia have focused on single neurotransmitters or receptor subtypes and have employed animal models in which the targeted receptor is dysregulated by pharmacological manipulation or genetic engineering. In contrast, emerging theories posit a neurodevelopmental or neurodegenerative diathesis, involving complex interactions between environmental factors and integrated networks of biochemical pathways. The goal of newer models is to identify points of convergence among the many implicated environmental risk factors, genes, and neurochemical pathways that can account for course and symptoms of the illness. This approach assumes that schizophrenia is a single biologically-valid syndrome, although different paths may lead to the development of the illness. If, instead, schizophrenia represents a heterogeneous collection of brain disorders without overlapping etiologies or mechanisms, then multiple models will be necessary to support a personalized approach to treatment.

RISK FACTORS AND NEUROPATHOLOGICAL FINDINGS

Established risk factors for schizophrenia include *in utero* exposure to infection, stress or malnutrition, as well as a large number of common alleles that individually contribute very small incremental risk (3). Many of these risk genes are modulators of brain development, are involved in response to infection or inflammation, or are regulators of synaptic connectivity. Within the category of neurotransmitters, genes involved in glutamatergic, GABAergic and dopaminergic transmission are over-represented (4). In addition to genetic and early environmental risk factors, daily use of cannabis in adolescence also appears to increase risk (5,6).

At the time of onset of symptoms in young adulthood, comparisons with healthy controls have identified elevated serum levels and gene expression of inflammatory markers, increased glucocorticoid response to stress, enhanced oxidative load, and decreased activity of brain-derived neurotrophic factor (BDNF) (7,8). These factors have been associated with loss of gray matter, cognitive deficits and negative symptoms (7,9).

An optimal model for drug discovery should also account for cardinal neuropathological findings in schizophrenia, including gray matter loss (10) and loss of inhibitory interneurons expressing GAD67 (an enzyme required for synthesis of GABA) (11), as well as for dysregulated dopamine release (12) and hypofunction of N-methyl-D-aspartate (NMDA) receptors (13). Intact inhibitory input from GABAergic interneurons is believed to be important for the synchronization of neuronal activity and related cognitive processes (14).

Finally, the study of schizophrenia is complicated by medication effects, which may be both protective and toxic. For example, early treatment of psychosis with antipsychotics has been found to improve functional outcomes (15); however, treatment of nonhuman primates for roughly 18 months (16,17) and rats for 8 weeks (18) with antipsychotics has been shown to result in decreased brain volume with loss of neuropil and cognitive deficits believed to reflect frontal D1 receptor down-regulation (19).

NEUROINFLAMMATION

Exposure to inflammation during early development has emerged as an important component of neurodevelopmental models for schizophrenia. Exposure to acute maternal infection *in utero* is a well-established risk factor for schizophrenia; for example, maternal influenza infection increased risk in offspring 3–8 fold in prospective studies with serologic documentation of infection (20,21). Elevated levels of the inflammatory cytokine, interleukin-8 (IL-8), in second trimester blood samples from pregnant women doubled risk for schizophrenia in offspring (22). While early infection is a far greater contributor to risk than any single susceptibility gene, it has been estimated that 48% of schizophrenia susceptibility genes are directly involved in response to infection (23). Genes comprising the HLA region in particular are strongly implicated (3). Elevated levels of neuroinflammation represented by microglial activation have been demonstrated in post-mortem schizophrenia brain (24,25) and, by positron emission topography (PET) imaging studies, in early and chronic schizophrenia subjects (26–28). A recent meta-analysis clarified that peripheral cytokine elevation is most apparent in medication naïve patients and during periods of relapse (29).

Animal models that simulate maternal viral infection during pregnancy have unique ecological validity, since they duplicate a process known to increase risk for schizophrenia in humans. The injection of polyinosinic:polycytidylic acid (PolyI:C) stimulates maternal release of inflammatory cytokines, mimicking response to viral infection. Offspring exhibit many characteristics similar to the neurodevelopmental abnormalities found in schizophrenia (30). These include increased volume of lateral ventricles, decreased temporal lobe volume, abnormal prepulse inhibition, increased behavioral sensitivity to dopamine agonists and impairments in memory. These deficits are not observed until young adulthood, roughly the age at which humans first exhibit symptoms of schizophrenia (30).

NEUROINFLAMMATION, OXIDATIVE STRESS, AND EXCITOTOXICITY

From a therapeutic perspective, it is important to establish the mechanisms by which early exposure to inflammation may produce neurobehavioral effects suggestive of schizophrenia in adulthood. Equally important is the determination of whether these consequences of early exposure to inflammation are potentially reversible. *In utero* exposure to PolyI:C is associated with decreased density of D1 and D2 receptors in the frontal cortex and of NMDA receptors in the hippocampus (30). In the hippocampus, PolyI:C administration also was shown to lower concentrations of protein kinase B (AKT) and decrease axonal diameter, myelination, and markers of neurogenesis in adolescent offspring (31,32). The changes in AKT, axonal size and myelination returned to normal in adulthood (31), possibly representing a specific period of vulnerability during adolescence. Jukel et al (33) also examined the brains of adolescent offspring exposed to PolyI:C *in utero* and found increased numbers of abnormally activated microglia in the hippocampus and striatum, suggesting that, following exposure to inflammation *in utero*, an active inflammatory state persists later in life at the time of vulnerability for onset of symptoms. The potential reversibility of some of the effects of early neuroinflammation was demonstrated by the administration of clozapine during adolescence (postnatal days 34–47) in PolyI: C-exposed mice, which prevented the development of structural and behavioral changes in adulthood (34).

Neuroinflammation in adulthood may be particularly relevant to cognitive impairment and negative symptoms in schizophrenia, since these deficits have been associated with elevation of C-reactive protein (CRP), a marker for inflammation, in medication-naïve and chronic schizophrenia samples (35–37). Serological evidence of infection with herpes simplex virus has also been associated with impaired cognitive function and gray matter loss in individuals with schizophrenia (38,39).

Inflammatory effects on brain development may be mediated in part by a cytokine-induced increase in oxidative stress and reduction in BDNF release. In both developing and adult brain, administration of the inflammatory cytokine, IL-6, has been shown to increase oxidative stress and inhibit the expression of GABA in inhibitory interneurons (40), consistent with findings in post-mortem schizophrenia brain (11). Maturation of inhibitory circuits continues through adolescence, as reflected in changes in brain oscillations with increased gamma rhythms and improved capacity for executive function (41). Inflammation-associated oxidative stress could disrupt this process in late adolescence, producing cognitive deficits that might be reversible with targeted anti-inflammatory or anti-oxidant therapy early in the course of illness. In chronic schizophrenia patients, elevated markers for oxidative stress have been associated with negative symptoms (42).

An additional consequence of early exposure to neuroinflammation may be a compensatory, protective down-regulation of factors that promote neurotoxicity in the presence of neuroinflammation. For example, the NR2C subunit of the NMDA receptor is down-regulated following exposure to the inflammatory cytokine, IL-6 (43). This down-regulation of the NR2C subunit is associated with a marked reduction in neurotoxicity in response to activation of the receptor by NMDA (43). The expression of the NR2C subunit was found to be selectively decreased post-mortem in the frontal cortex of schizophrenia patients (44). Timing of inflammatory exposure is an important determinant of neurodevelopmental impact; for example, exposure to PolyI:C in adolescence produced elevated expression of NMDA NR2A subunits, along with lowered

seizure threshold and memory deficits in rats; these effects of neuroinflammation in adolescence were reversed by minocycline (45).

BDNF AND AKT

Both inflammation and environmental stress reduce the release of activated BDNF from axons. The effect of environmental stress on BDNF is mediated by cortisol secretion acting on glucocorticoid receptors. BDNF facilitates neuroplasticity by the stimulation of dendritic growth, synapse formation and neurogenesis (46). The BDNF Val66Met genotype is associated with reduced BDNF activity and has been linked to diminished synaptic plasticity in the hippocampus (47). BDNF activity declines with age; this decline has been linked to the reduction in hippocampal volume and cognitive decline in the elderly (48,49). In first episode schizophrenia subjects, BDNF genotype significantly predicted longitudinal change in hippocampal volume (50) and BDNF gene expression predicted cross-sectional volume (7).

BDNF in turn activates (phosphorylates) AKT, a second point of convergence of several risk factors, since AKT activation is also influenced by dopamine D2 receptors, cannabinoid CR1 receptors and metabolic status (51). It has recently been shown that AKT genotype predicts the likelihood that cannabis abusers will develop a psychotic disorder (5). Like BDNF, AKT modulates neurogenesis, neuronal survival, dendritic growth and, in addition, selectively phosphorylates NMDA receptors (NR1 and NR2C subunits) and GABA receptors (A beta2 subunits). While the role of hippocampal neurogenesis in humans remains uncertain, BDNF and AKT may play a role in gray matter volume loss, decreased neuropil, and associated negative symptoms and cognitive deficits. Deficits in neuroplasticity have been found on several cognitive and electrophysiological measures in schizophrenia (52,53).

A NEURODEVELOPMENTAL MODEL

In summary, a complex interplay between environmental factors of inflammation and stress seems to interact with a large number of genes to shift biochemical pathways in the brain from states of neuroplasticity and neurogenesis in the presence of a "benign" environment to a defensive state with reduced neuroplasticity and decreased vulnerability to neurotoxicity under conditions of environmental stress. Dysregulation of this process may underlie the neurodevelopmental origins and expression of several psychiatric conditions, including schizophrenia.

While many parallel and interactive pathways contribute to this regulation of brain equilibrium, the modulation of BDNF by inflammation and by stress-induced elevation of glucocorticoids represents one important point of convergence. Similar to BDNF, AKT functions like a "thermostat", since its level of activity represents a summation of BDNF levels, D2 receptor activation and activity at the cannabinoid receptor. BDNF and AKT both represent a point of convergence of risk factors for schizophrenia and a point of divergence for factors controlling neuroplastic and NMDA/GABAergic regulation that may contribute to phenotypic expression of cognitive and negative symptoms of schizophrenia.

Many schizophrenia genes are involved in pathways involved in these diverse networks, consistent with an "epistatic" combination of multiple genetic factors in determining risk. In addition, the functional state of inflammatory and glucorticoid pathways is influenced by early environmental exposure, thereby contributing an epigenetic component to this model. Given the multiple developmental, genetic and environmental factors interacting in a highly complex and interactive network, the development of therapeutic targets for cognitive impairment and negative symptoms of schizophrenia involves identification of "drugable" factors that can be manipulated to correct pathological imbalances at key developmental stages of the disorder. Non-pharmacologic approaches are also quite promising, such as cognitive behavioral therapy (CBT) to reduce stress, and cognitive remediation, repeated transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) to stimulate neuroplasticity and enhance brain functioning in schizophrenia.

THERAPEUTIC IMPLICATIONS

Studies of offspring exposed to PolyI:C *in utero* predict that neurodevelopmental abnormalities associated with schizophrenia risk factors may be reversible during adolescence or early adulthood. This model might be used to test potential interventions during the prodromal phase of schizophrenia. Whether interventions targeting factors, such as inflammation and oxidative stress, believed to influence neurodevelopment can be effective later in the course of the illness is unknown, but preliminary findings suggest that efficacy tends to be less robust with increasing chronicity.

Anti-inflammatory agents

One example of a therapy based on this neurodevelopmental approach is the use of omega 3 fatty acids (fish oil) in the schizophrenia prodromal phase. Omega 3 fatty acids possess potent anti-inflammatory activity (54). Fish oil is an ideal agent for anti-inflammatory prophylaxis, since it is well tolerated and quite benign. In a placebo-controlled 12-week trial in 81 ultra-high risk (prodromal) subjects, fish oil significantly reduced the rate of conversion to psychosis over a 52 week period (55). A large, multi-center trial is currently in progress to attempt to replicate this finding. Trials of omega 3 fatty acids in chronic

patients have not produced consistent results, however (56).

Several placebo-controlled add-on trials of standard anti-inflammatory agents, including COX-2 inhibitors (57,58) and aspirin (59), have demonstrated efficacy in schizophrenia for positive and negative symptoms, but not for cognitive deficits. A recent meta-analysis of studies of non-steroidal anti-inflammatory agents revealed a moderate therapeutic effect size of 0.4 for total symptom response (60). In general, response to anti-inflammatory agents has been observed most consistently in individuals within the first five years of illness onset (61). In a placebo-controlled study of add-on aspirin treatment, peripheral levels of inflammatory cytokines predicted response of symptoms (59). The use of inflammatory biomarkers to identify patients most likely to benefit and the targeting of early stage patients are two strategies that may improve outcomes in future studies.

Minocycline is also of interest, given that it is well tolerated and has been shown in mice to decrease expression of activated microglia (62) and release of inflammatory cytokines (63). Minocycline significantly improved negative symptoms at 6 months compared to placebo in two studies of early-stage schizophrenia subjects (64,65). Working memory also improved in one of these studies (65).

Anti-oxidants

Strategies to reduce oxidative stress are also promising (66). The best-studied agent is N-acetyl-cysteine (NAC), the glutathione precursor, which is a potent antioxidant and also increases glutamate levels by competing for the cysteine/glutamate transporter (67). In a placebo-controlled trial, NAC significantly improved negative symptoms in chronic schizophrenia patients, producing a moderate effect size that was detected after 6 months but not at 2 months (68). In a 60-day placebo-controlled cross-over study in chronic schizophrenia patients, NAC significantly improved response to mismatch negativity (an evoked potential test of auditory discrimination) (69) and resting-state EEG synchronization (70). Additional studies are needed in early course subjects, ideally with biomarkers for oxidative load. Studies of NAC in early-stage psychosis are currently in progress.

BDNF

Another therapeutic approach suggested by the neurodevelopmental model involves the targeting of BDNF. As described previously, environmental factors such as stress and inflammation that lower BDNF expression and a Met66Val genotype that results in diminished BDNF activity are both associated with loss of brain volume in schizophrenia. Antidepressants appear to act primarily via release of BDNF; this mechanism may account for both antidepressant effects and protection against hippocampal volume loss (71–73). Release of BDNF by antidepressants has been shown to increase neurogenesis and survival of immature neurons in rodent dentate gyrus (74,75). Whereas antidepressants enhance BDNF activity in hippocampus, first generation antipsychotics may decrease BDNF expression (76) and second generation antipsychotics either have no effect (77) or may increase it (78). Effects of selective serotonin reuptake inhibitors (SSRIs) on BDNF have been shown to decrease with age in humans and were diminished in mice with the Val66Met BDNF genotype (79). In chronic patients, antidepressant treatment has been associated with improvement of negative symptoms (80,81). In an open trial, Cornblatt et al (82) found that antidepressant treatment prevented conversion from prodrome to psychosis, whereas treatment with second generation antipsychotics did not. A multi-center placebo-controlled trial (DECIFER) is currently in progress to evaluate the effects of a 12-month trial of an SSRI in first-episode schizophrenia.

Physical exercise and hippocampal-dependent cognitive exercises also enhance neurogenesis in rodent models by stimulating BDNF release (83). A recent controlled study in which schizophrenia subjects exercised on a stationary bicycle found improvement in memory and increased hippocampal volume (84). Cognitive remediation has been reported to elevate peripheral BDNF levels, although this increase did not correlate with cognitive benefit (85).

Folate

Another treatment suggested by the neurodevelopmental model is folate supplementation. Folate deficiency results in elevation of homocysteine, which at high concentrations may be neurotoxic via oxidative stress and activity at NMDA receptors (86,87). Maternal folate deficiency and elevated homocysteine concentrations during pregnancy have been identified as risk factors for schizophrenia (88,89). Risk for schizophrenia is also increased in individuals with a genotype of methylenetetrahydrofolate reductase (MTHFR) associated with reduced availability of activated folate (90), and in offspring of mothers with a similar genotype (91). In chronic patients, MTHFR genotype, in combination with blood folate concentration and other genes related to folate absorption and activation, has been found to predict negative symptoms and cognitive deficits (92–94). In a placebo-controlled pilot trial, MTHFR genotype predicted improvement of negative symptom severity in response to folate supplementation (95). In a large multi-center study, MTHFR and related genes predicted negative symptom response to supplementation with folate and vitamin B12 (96). Cognitive deficits did not improve, however. In a third placebo-controlled study, folate and B12 supplementation improved positive and negative symptoms in schizophrenia subjects with elevated homocysteine levels at baseline (97).

The mechanism by which folate improves symptoms and enhances neuroplasticity is not clear, since it serves multiple roles in brain development and function, including synthesis of neurotransmitters, maintenance of DNA, modulation of prefrontal dopamine concentrations by

methylation of catechol-O-methyl-transferase (COMT), and modulation of gene expression and neurogenesis (98). The potential therapeutic value of folate supplementation in early-phase schizophrenia has not yet been studied.

Other targets

Whereas treatments designed to counter inflammatory response, oxidative stress, glucocorticoid elevation and folate deficiency may be most effective as preventive measures or early in the course of illness, treatment of cognitive impairment and negative symptoms in chronic patients may require a focus on targets that are ultimately impacted by these factors and which are more proximal to symptomatic expression of the illness. Most clearly implicated are dysregulation of dopamine (D1) and glutamate (NMDA) receptors. These factors influence many relevant brain functions, including neuroplasticity, attention, and cortical synchronization. Both D1 receptors and NMDA receptors, along with BDNF, are key elements of neuroplasticity as described by Kandel (99) in his classic studies of the molecular biology of memory. If schizophrenia involves aberrant neurodevelopmental processes that produce defects in connectivity, approaches that facilitate neuroplasticity may be the most effective to improve cognitive efficiency. Non-pharmacologic approaches, such as cognitive remediation and tDCS, may also facilitate neuroplasticity.

As it becomes increasingly clear that neurochemical pathways in the brain are extremely complex and interconnected, many other potential targets may exist that can alter the overall function of these networks in beneficial ways. Prediction of such effects has proven very difficult, however, although network analysis may facilitate this process in the future (100). The reader is referred to other reviews providing descriptions of the rationale and clinical trial results for various additional targets, including GABAergic, cholinergic and serotonergic receptors (1,2).

Dopamine D1 receptors

Dopamine D1 receptor activity in the prefrontal cortex is crucial for attention and working memory. Dopamine levels are determined in part by ventral tegmental dopamine neuronal firing (regulated by D2 and NMDA receptors) and by the rate of dopamine metabolism by COMT. Optimal prefrontal functioning requires precise control of dopamine concentrations – too little or too much may both reduce cognitive functioning.

Several approaches have been suggested to enhance dopaminergic function. In monkeys, Castner et al (19,101) demonstrated that chronic treatment with antipsychotic drugs produced a gradual impairment of cognitive functioning, attributable to a compensatory down-regulation of frontal D1 receptors. Intermittent treatment with a psychostimulant was found to "sensitize" dopamine transmission and improve cognitive functioning (19,101). In individuals with schizophrenia, addition of psychostimulants to antipsychotic medication may enhance frontal D1 receptor activation, while potential psychotomimetic effects of dopamine release are attenuated by D2 blockade. Single dose administration of amphetamine was shown to improve memory in medicated schizophrenia subjects and in healthy controls (102). The COMT inhibitor, tolcapone, has been shown to improve cognitive function in healthy subjects, predicted by COMT genotype (103), and may represent a potential therapeutic approach in schizophrenia. Finally, direct agonists for D1 receptors are under development, but clinical trials have been complicated by problems with tolerability (104).

NMDA receptors

For over two decades, glutamate transmission has been a focus for drug discovery in schizophrenia (105). NMDA receptors in particular have been implicated, since they are involved in many relevant processes: those on ventral tegmental neurons modulate dopamine release, those on inhibitory interneurons modulate brain oscillations, and those on hippocampal and prefrontal neurons modulate neuroplasticity and memory. As has been noted, many of the genes that have been linked to schizophrenia are involved in glutamate signaling. Furthermore, density of certain NMDA receptor subunits has been found to be decreased in the prefrontal cortex of patients with schizophrenia (44). Most impressively, NMDA receptor blockade produces manifestations similar to the psychotic symptoms, negative symptoms and memory deficits characteristic of schizophrenia (106).

In early studies, agonists at the glycine site of the NMDA receptor (glycine, D-serine and D-alanine) and the partial agonist D-cycloserine (DCS), added to first generation antipsychotics, improved negative symptoms and, in some trials, positive symptoms and cognition (107). However, when added to second generation antipsychotics in the CONSIST trial, glycine and DCS produced no effect (108). While the explanation for this failure to replicate results from earlier studies is not clear, it is possible that second generation antipsychotics may enhance glutamate release via 5HT2 antagonism and hence may mask therapeutic effects of glycine site agonists (109). When added to clozapine, DCS worsened negative symptoms, suggesting that clozapine may act, in part, via effects on NMDA receptors (110,111).

Another approach to facilitate activity at the glycine site of the NMDA receptor is the inhibition of glycine reuptake. Sarcosine, an endogenous precursor of glycine which competes with glycine for reuptake, was shown in a preliminary study to improve negative symptoms (112). The selective glycine transporter 1 (GlyT1) inhibitor, RG1678 (bitopertin), produced a modest improvement in negative symptoms in an initial multi-center clinical trial and is currently on registration trials as potentially the first agent to gain Food and Drug Administration approval for negative symptoms.

High doses of D-serine are being investigated; in an unblinded study, high dose D-serine improved cognitive function (113). D-serine concentrations can also be increased by inhibition of D-aminoacid oxidase (DAO); this approach is also currently under study.

D-cycloserine may offer additional therapeutic options as a highly potent agonist at NMDA receptors containing the NR2C subunit (114,115). NMDA receptors containing this subunit have been linked to memory and thalamic oscillations (116,117), although activation by D-cycloserine produces rapid tolerance for memory consolidation (118). Recent work suggests that intermittent (once-weekly) dosing with D-cycloserine may produce persistent improvement of negative symptoms in addition to memory enhancement (119). When combined with CBT in a placebo-controlled cross-over pilot trial, a single dose of D-cycloserine was associated with a large improvement in delusion severity in subjects who received the drug with the first session (120). D-cycloserine has demonstrated efficacy as a facilitator of CBT for anxiety disorders (121) and, by enhancing neuroplasticity and memory, may have a role in facilitating psychosocial interventions in schizophrenia.

CONCLUSIONS

In summary, classical models for drug discovery have been only modestly successful in identifying therapeutic agents for cognitive impairment and negative symptoms of schizophrenia. The evidence from epidemiological and genetic studies suggests that schizophrenia is a complex neurodevelopmental disorder for which modulation of a single neurotransmitter is unlikely to produce full symptomatic response. Analysis of the many environmental and genetic risk factors may identify points of convergence that may contribute to disease expression, such as neuroinflammation, stress, and folate deficiency. These environmental risk factors, in combination with genetic vulnerability, may disrupt normal brain development and produce cognitive deficits and negative symptoms by effects on neuroplasticity, apoptosis and neurogenesis, in part mediated by reduced activity of BDNF and AKT.

Interventions targeting these factors may be effective early in the course of illness, including use of anti-inflammatory agents, anti-oxidants, antidepressants and CBT. In chronic patients, facilitation of neuroplasticity via cognitive remediation, rTMS and tDCS, perhaps combined with agents acting via NMDA and D1 receptors, are also promising approaches for the treatment of cognitive deficits and negative symptoms.

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