Schizophrenia: Treatment Targets Beyond Monoamine Systems

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Abstract

We develop the proposal in this review that schizophrenia is a syndrome made up of component symptom complexes, each with distinctive clinical correlates, pathophysiology, and selective treatments. Psychosis is the necessary component of the syndrome; it has a young-adult onset and is sensitive to current antipsychotic drugs. Cognitive dysfunction often precedes psychosis onset, does not present an episodic course, and is poorly responsive to antipsychotic drugs. Treatments for cognition are being developed largely on the basis of animal pharmacology. Drugs for component symptom complexes will theoretically be coadministered to independent symptomatic end points. Animal models, some with genetic characteristics, can be more easily and directly developed to match an individual component than to match an illness definition as broad as schizophrenia.

1. INTRODUCTION

Schizophrenia is a chronic incapacitating syndrome that affects 1% of the population. It begins during young-adult years, but cognitive disturbances are often evident earlier (1, 2). Profound psychosocial disability occurs, with only 15% of probands employed, 20% married, and 5% recovered during lifetime (3). It is estimated to be the seventh most costly illness because of the high frequency of hospitalizations, need for psychosocial services, and lost productivity (4, 5). There is no diagnostic test for schizophrenia, no blood test, and no radiological diagnosis; clinicians lack biological markers to define onset and follow illness progression; and treatments are symptomatic and pathophysiology remains unknown (6). It is easy to recognize that medical need is high and increased understanding is imperative.

Many illness categories are defined by a unitary molecular pathophysiology. However, this is not the case with schizophrenia, which is a diagnosis defined by behavioral presentation and illness course. In addition, although it is an illness that has been described for millennia, pharmacological treatments have been available only in the past half century (7). The past decade has seen the development of the idea that these illness categories may be constructed incorrectly and that it would be more informative for research and for novel treatment development to start from symptom domains or component symptom complexes (8).

2. SCHIZOPHRENIA REVISITED: COMPONENT SYMPTOM COMPLEXES

Partly in response to the intransigence of discovery in schizophrenia, schizophrenia is being reconceptualized to clarify research and to advance treatment goals. Schizophrenia has long been conceptualized as a single illness with complex or mixed manifestations—requiring unitary models of illness and treatment targets. A new model proposes that the syndrome is a complex of individual component symptom complexes (8) in which multiple components are composed of similar symptoms that hypothetically have a common pharmacology, course, pathophysiology, and—by analogy—treatment. The evidence for these components derives from clinical population-based studies, where factor analysis is used to discover which symptoms display common characteristics (especially of disease course and pharmacology); the studies consistently find multiple characteristic clusters of symptoms in the illness (2, 9). The typical component symptom complexes reported are psychosis (e.g., hallucinations, delusions, and thought disorder), cognitive dysfunction (e.g., reductions in attention, memory, and executive function), negative symptoms (e.g., anhedonia, asociality, and alogia), and depressed mood (**Figure 1**).

Psychosis is the target of our current antipsychotic compounds, whose pharmacology involves dopamine and other monoamine antagonism. Antipsychotic drugs (APDs) treat psychosis in schizophrenia rather well, albeit with considerable side effect burden and residual symptomatology (10–12). However, even in individuals with schizophrenia who are nearly psychosis-free, troublesome elements of cognitive dysfunction exist—symptoms that serve to broadly impair ultimate psychosocial recovery in the illness. Cognitive dysfunction is selective, manifesting most impairment in attention, executive function, and working and declarative memory, leaving other areas of cognition relatively unimpaired. Considerable research attention has been directed toward the correct articulation and effective treatment of cognitive dysfunction in the illness (13–15). Affective disturbances in schizophrenia are treated with the same medications used in primary affective illnesses. Antidepressants and mood stabilizers are used in schizophrenia with limited research support, but the common use of these drugs indicates that they provide benefit regarding the symptoms of depression and mood instability (16). This new formulation of schizophrenia

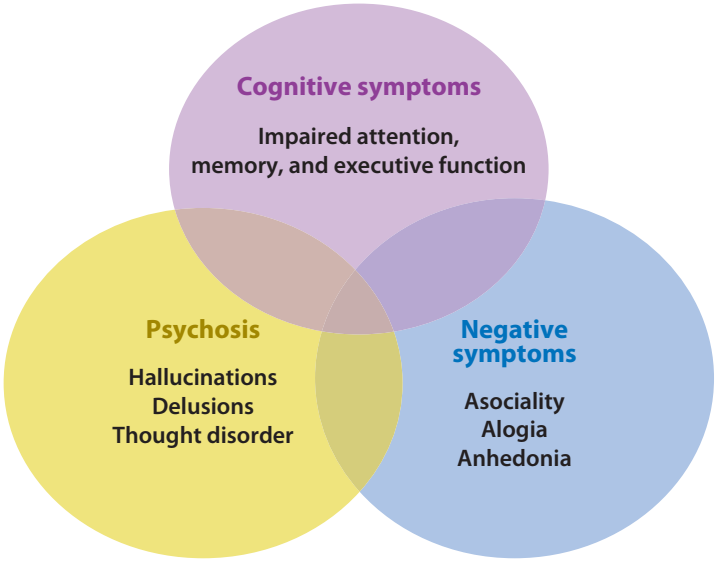

Figure 1

Component symptom complexes in schizophrenia. Schizophrenia has been viewed as a single illness with mixed manifestations. A new model proposes that schizophrenia is best conceptualized as a clinical syndrome, a complex of individual component symptom complexes with distinct course, pathophysiology, pharmacology, and treatment response.

includes the assumption that distinct components can have independent animal models, molecular mechanisms, and pharmacological treatments. The two most common component symptom complexes, each nearly ubiquitous in schizophrenia and the two we consider here, are psychosis and cognitive dysfunction.

2.1. Psychosis

Psychosis defines schizophrenia (17). Its hallmark feature is reality distortion, with hallucinations and delusions; thought disorder represents a more serious deterioration in the structure of language and communication as manifested in psychosis. Psychotic symptoms are particularly impairing because they are accompanied by "lack of insight," meaning that patients do not have a way of regarding them as not truly real (**Table 1**) (3). Psychosis has several distinct definitions in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition Text Revision* (*DSM-IV-TR*) (17). The most restrictive definition is "delusions and prominent hallucinations, with the hallucinations occurring in the absence of insight into their pathological nature." The broader definition includes "other positive symptoms of schizophrenia (disorganized thought process, and grossly disorganized or catatonic behavior)" in addition to delusions and hallucinations (17, p. 29). This broader description of psychosis is what is commonly used in making clinical diagnoses. Observers rarely see psychotic symptoms in any form in their full manifestation anymore because antipsychotic treatments are so ubiquitous. However, the historical reports (18) and first-person accounts (19, 20) of psychotic illness provide a reminder of the impact of this symptom domain on function.

In schizophrenia, psychosis begins in late adolescence and early adulthood. The course of psychosis is chronic, can be continuous or episodic in nature, and rarely shows full recovery. After

Table 1 Frequency of psychotic symptoms in schizophrenia

Lack of insight	97%
Auditory hallucinations	74%
Verbal hallucinations	70%
Ideas of reference	70%
Suspiciousness	65%
Flatness of affect	65%
Voices speaking	65%
Paranoid state	64%
Thought alienation	52%
Thoughts spoken aloud	50%

Data from Reference 3.

florid onset, psychotic symptoms often become less severe with time, notably after 50 years of age (21). If untreated, psychosis often results in unmanageable behaviors, whereas APD treatments reliably reduce psychosis. Residual psychotic symptoms in treated populations do not predict poor psychosocial outcome (22, 23). On the basis of course severity and pharmacology, psychosis is considered to be a symptom domain independent from cognition.

2.2. Cognitive Dysfunction

Cognitive disabilities in selected domains are present in schizophrenia, with deficits most pronounced in the areas of memory and attention (24). Cognitive dysfunction has a disease course that is distinct from psychosis, often beginning before psychosis onset and persisting evenly (without episodes) throughout the illness (25). Cognitive defects are similar in acute and chronic schizophrenia (26–30), similar in adult- and adolescent-onset patients (31, 32), and similar in type (although not in degree) in family members (33–35) and in high-risk, not-yet-ill persons (36). Moreover, cognitive deficits show only small to moderate correlations with clinical state (37) and are not thought to change with APD treatment (38). The nature of this dysfunction has been extensively examined (24, 39–44) and is thought to be basic to the illness (45). Although a generalized compromise in cognition in the illness is widely acknowledged, certain domains of function stand out as particularly affected, including visual and verbal declarative memory, working memory, and processing speed (30, 41, 43, 46–49). The degree to which these distinct cognitive domains are independent has been argued (50–52) and is an issue important for therapeutics (44). Because the nonpsychotic cognition symptoms of schizophrenia are powerful determinants of poor psychosocial function, the development of specific treatments for this component complex is urgent (53). Cognitive impairments are considered to be the most disabling and persistent features of the illness (54) and appear to be the best predictor of long-term outcome in patients with schizophrenia (21, 53).

3. COMPONENT SYMPTOM COMPLEXES: PHARMACOLOGICAL TREATMENTS

Whereas previously, treatment development in schizophrenia was directed at the entire illness, now treatments can be directed to component symptom complexes, the manifestations of the illness that run together over the disease course and share pharmacological characteristics. It has

taken some time and study to recognize that the entire symptom manifestations of the illness (e.g., especially cognitive dysfunction and negative symptoms) do not have the same lifetime course as psychosis nor do they share its specific pharmacology. Although we do not have a firm molecular understanding of schizophrenia or its component symptom complexes, a framework of more limited and rational treatments is being hypothesized and can be tested.

3.1. Psychosis

There was no effective pharmacological treatment for psychosis until the 1950s, when Delay and Deniker serendipitously discovered the antipsychotic activity of chlorpromazine (reviewed in Reference 7). Since the 1950s, two generations of APDs have been developed, both successful (**Table 2**). The first generation is best represented by haloperidol, a potent dopamine receptor antagonist (55). The second generation, best represented by clozapine (which is itself an old antipsychotic drug), shows mixed dopamine and other monoamine antagonism. Considerable knowledge about the acute and chronic actions of these drugs exists (11, 12, 56, 57), including recent naturalistic studies of their antipsychotic actions in large patient populations (58, 59). Essentially, with the exception of clozapine, all APDs are potent antipsychotics with equivalent primary actions but with distinctive side effect profiles. The first-generation APDs demonstrate notable extrapyramidal symptoms including dystonia, akathisia, dyskinesia, and Parkinsonian symptoms. Second-generation APDs have a lower risk of extrapyramidal symptoms, but they are associated with adverse metabolic effects including weight gain and metabolic syndrome. Clozapine alone shows superior antipsychotic action but is accompanied by a high side effect burden (60, 61). In many respects, drug development for schizophrenia has not substantially or conceptually progressed since the emergence of the first antipsychotic in the 1950s. Drug discovery models in schizophrenia have focused almost exclusively on probes that are capable of blocking D_2 receptors.

Treatment of schizophrenia with antipsychotics rarely, if ever, produces a cure or entirely reverses symptoms of the illness. Only 5–10% of persons with schizophrenia go on to achieve a full recovery with or without these medications. Approximately 30% show a good but partial response, and another 30% show an inadequate but partial response. The remaining 20–25% of schizophrenic persons are resistant to treatment with any current APD (2, 62). These treatment-resistant individuals suffer continuously without relief and use a disproportionate amount of health care services. Thus their treatment is a priority. We have recently seen a gradual shift in focus to embrace "recovery," rather than reduction in or remission of psychotic symptoms, as a treatment target. However, there is lack of consensus on the definition of recovery in schizophrenia; descriptions vary from leading a life in complete absence of disease, which entails cure (or recovery

Table 2 Current antipsychotics

First generation	*Second generation*
Chlorpromazine	Clozapine
Thioridazine	Risperidone
Haloperidol	Olanzapine
Perphenazine	Quetiapine
Thiothixene	Ziprasidone
Fluphenazine	Aripiprazole
Flupentixol	Iloperidone
Etc.	Asenapine

"from" the illness), to leading a meaningful and productive life despite the illness (or recovery "in" the illness). However, descriptions generally imply significant improvement in psychosocial functioning, including living independently in the community, developing social relationships, working competitively, and finding adequate housing and financial support. From this perspective, treatment needs are broader than dopamine and monoamine antagonism can provide.

There exist distinctive but effective antipsychotics that have a high affinity to dopamine and serotonin receptors but show agonist instead of antagonist action (63). The group of agonists that is therapeutically relevant is the low-intrinsic-activity dopamine agonists, of which aripiprazole is the first-in-class antipsychotic. Aripiprazole has a high affinity for the D_2 dopamine receptor but generates low intrinsic activity at the DA receptor, such that it delivers a minimal amount of agonist action, in fact a lower agonist action than the natural neurotransmitter dopamine. Hence the drug reduces dopamine-mediated neurotransmission at the synapse. Moreover, aripiprazole may reduce dopaminergic activity through its actions at the presynaptic D_2 receptor to reduce dopamine synthesis and release (61). Additional effective antipsychotics that exhibit this action are still being pursued, in part, with the hope that the dopamine agonist action might enhance cognitive function and psychosocial "recovery."

In addition, two novel drugs, each with positive proof-of-concept studies, represent other potential mechanisms of antipsychotic action. One drug with a novel muscarinic agonist action is represented by xanomeline. Xanomeline has been shown to improve PANSS (positive and negative symptoms scale) ratings in patient volunteers with acute psychosis, including positive psychotic symptoms as well as cognitive deficits (64). Moreover, previous studies with physostigmine also showed an antipsychotic action (65, 66). The potential antipsychotic action of muscarinic agonists needs further study and should not be overlooked.

The other novel mechanism that has shown clear antipsychotic activity is the $mGluR_{2/3}$ agonist represented by LY-2140023. This $mGluR_{2/3}$ agonist demonstrated significant antipsychotic activity in a three-arm, placebo-controlled Phase II trial where olanzapine served as an active control. Treatment with LY-2140023 was safe and well tolerated, and it led to significant improvements in both positive and negative symptoms compared with placebo ($P < 0.001$ at week 4) and comparable to olanzapine. This result suggests that $mGluR_{2/3}$ receptor agonists have antipsychotic properties and may provide a novel alternative for the treatment of schizophrenia (67, 68).

Looking across these distinctive drug groups for a common mechanism of antipsychotic action prompts one possible formulation that these drugs, including dopamine and serotonin, act on neural systems in the brain and modulate the activity of these long-tract neuronal pathways that link the cortical with the subcortical gray matter areas (69, 70). Thus these drugs can be said to affect whole systems of neural activity putatively involved in behavioral symptoms.

3.2. Cognition

Although APDs have been effective in reducing psychosis, the long-term outcomes of schizophrenia (community functioning and quality of life) remain poor. In 1996, Green (71) reported that residual cognitive deficits, such as poor memory and attention, predict poor functional outcome; this pivotal meta-analysis focused research attention on the development of treatments for poor cognition in schizophrenia. The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project, led by experts from academia, industry, and government, developed from the awareness that cognition was significantly undertreated in schizophrenia and that a focus on this symptom domain could result in therapeutic advances (**Figure 2**). The MATRICS group identified seven separable cognitive dimensions that are altered in schizophrenia: speed of processing, sustained attention, working memory, verbal learning, visual learning, executive

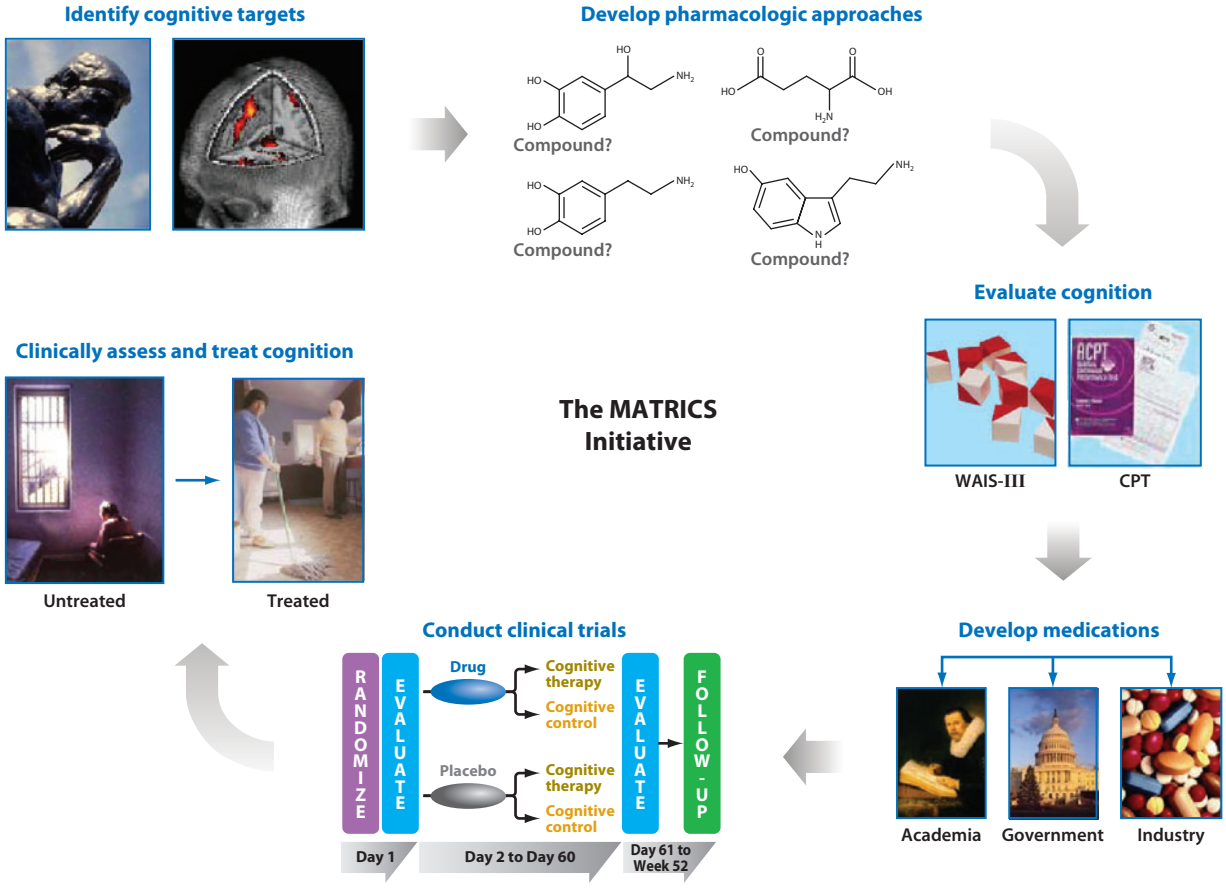

Figure 2

The Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) project. This initiative was sponsored by the National Institute of Mental Health and brought together experts from academia, government, and industry. It identified seven distinct cognitive dimensions that are impaired in schizophrenia and proposed several putative molecular targets.

function, and social cognition (44, 72) (**Table 3**). It also designated putative molecular targets for remediating cognitive function in schizophrenia, including receptors for acetylcholine, dopamine, and glutamate.

Many research compounds representative of these specified molecular targets have undergone initial testing for treating poor cognition in schizophrenia (**Table 4**). Because the rationale for

Table 3 Areas of neurocognitive dysfunction in schizophrenia

Verbal learning and memory
Speed of processing (verbal fluency)
Working memory
Reasoning and problem solving
Attention and vigilance
Visual learning and memory
Social learning

Table 4 Potential treatments for cognition in schizophrenia

Type of treatment	Examples
Nicotinic partial agonist	DMXB-A; varenicline; TC-5619; S-24795
Muscarinic agonist	ACP-104; xanomeline
Glutamate enhancer	Org-24448; LY-2140023
GABA-A partial agonist	NGD 97-1; MK-0777
GABA-B antagonist	CGP-35348
Serotonin-(1A;6) antagonist	SB-742457; Lu AE58054
Histamine agonist	BF2-649
Phosphodiesterase inhibitor	ITI-002

these molecular targets was developed largely from animal studies, the supportive rationale for therapeutic response is theoretical, and no treatments have been demonstrated to be effective. Nonetheless, because the medical need is high and the rationale is clear, considerable investigation is continuing. The drugs are being tested as cotreatments against placebo, along with the ongoing administration of a stable APD regimen. We review here the pharmacologic strategies considered most likely to enhance cognition.

3.2.1. Cholinergic targets for cognition. The target judged most favorably for improving cognition is agonism of central cholinergic function at the nicotinic or muscarinic receptor; allosteric and orthosteric compounds are being tested. The highest densities of nicotinic receptors are located in the medial temporal lobe, an area that is known to be important in schizophrenia pathology and that shows reductions in the expression of the α7-nicotinic receptor in the illness (73). In particular, the central role of the hippocampal α7-nicotinic receptor in attention and sensory gating and the reported impairment of this receptor in schizophrenia are bases for strategies that augment α7-nicotinic receptors in schizophrenia. Several α7-nicotinic cholinergic receptor agonists have been identified and evaluated for cognition treatment. DMXB-A derives from a naturally occurring alkaloid and is a partial agonist at human α7-nicotinic receptors. An initial single-dose proof-of-concept study in patients with schizophrenia reported that DMXB-A had a positive effect on cognition (74). However, a subsequent Phase II trial showed no significant differences in the MATRICS battery of cognitive measures between DMXB-A and placebo (75), suggesting the possibilities that either (*a*) the strategy does not work or (*b*) there are critical unrecognized design issues with evaluating cognitive enhancement.

Muscarinic cholinergic receptors have also been implicated in schizophrenia. Postmortem studies have reported reductions in M_1 and M_4 muscarinic receptor density or binding in several brain regions including frontal cortex, striatum, and hippocampus (76–79), and single-photon emission computed tomography (SPECT) studies have shown decreases in muscarinic receptor binding in schizophrenia in prefrontal cortex (78, 80). Xanomeline is a potent nonselective agonist of muscarinic M_1/M_4 receptors. In a Phase III study in 20 patients with schizophrenia, xanomeline resulted in significant improvement in cognitive measures, especially verbal learning and working memory; however, xanomeline was associated with gastrointestinal side effects (presumed to be mediated by peripheral M_3 muscarinic receptors) such as nausea and vomiting (81). Over the past years, progress has been made in developing M_1-selective agonists that are less likely to cause muscarinic side effects. *N*-desmethylclozapine (NDMC) is an active metabolite of clozapine and has some pharmacological properties similar to its parent compound, with the notable exception of M_1/M_4 muscarinic agonist activity instead of the M_1/M_4 antagonist activity of clozapine

(82, 83). This distinct pharmacological property suggests that NDMC may have improved action on cognitive dysfunction in schizophrenia along with superior clozapine-like antipsychotic action. In a Phase II placebo-controlled trial in 24 patients with schizophrenia or schizoaffective disorder, ACP-104 was well tolerated and showed evidence of potential antipsychotic effect (84); however, effects of ACP-104 on cognition in schizophrenia have not been studied.

3.2.2. D_1 dopaminergic targets for cognition. In nonhuman primate models of working memory, Goldman-Rakic et al. (85) demonstrated the importance of D_1 dopamine (DA) signaling in working-memory performance, a critical domain of dysfunction in schizophrenia. Convergent lines of evidence have suggested that DA signaling may be deficient at the D_1 receptor in patients with schizophrenia (86–90). In addition, animal studies show that D_1 but not D_2 antagonists disrupt working memory, whereas D_1 agonists promote cognition (85). These studies provide the rationale suggesting that augmentation of D_1 signaling in schizophrenia could improve cognition, especially working memory. Dihydrexidine (DAR-0100) is a potent D_1 DA receptor agonist that was studied in a Phase I, single-dose, placebo-controlled, subcutaneous infusion in 20 patients with schizophrenia and 4 people with Parkinson's disease. DAR-0100 was well tolerated (91). Gadolinium-contrast magnetic resonance perfusion scanning showed that DAR-0100 induced significant increases in prefrontal perfusion compared with placebo (92). Because of pharmacokinetic characteristics, DAR-0100 is difficult to pursue even as a probe drug. However, atomoxetine, a drug that blocks noradrenergic and dopamine reuptake in the prefrontal cortex and thereby increases both norepinephrine (NE) and DA there, does not improve cognition in schizophrenia (93, 94). This result weakens but does not firmly rule out the rationale for this D_1 dopaminergic approach.

3.2.3. Glutamatergic targets for cognition. Drugs that enhance glutamatergic function and plasticity in brain especially at the NMDA receptor (NMDAR) can claim a strong theoretical rationale for improving cognition. Augmentation of NMDA signaling can, under certain experimental circumstances, improve cognition in animals. Conversely, ketamine, an NMDAR antagonist, adversely affects cognition in normal and schizophrenic persons (95–97). Postmortem and genetic studies have identified molecular changes in schizophrenia arguably associated with its pathophysiology that are consistent with reduced transmission at the NMDAR (98, 99). Given the complexity of the glutamatergic synapse, drugs can exert agonist activity at the NMDAR itself, at its coagonist site (glycine), through NMDAR or AMPAR (AMPA receptor) trafficking, or through downstream signaling systems associated with the NMDAR. Drug candidates for cognitive enhancement acting as agonists at the NMDAR include glycine, D-serine, D-alanine, sarcosine, and D-cycloserine. Yet a meta-analysis (100) of 26 placebo-controlled studies suggested that these compounds are only modestly effective in treating cognitive deficits in schizophrenia (effect size = 0.28). D-cycloserine was reported to be least efficacious. Nonetheless, glycine reuptake (GlyT) blockers are thought to enhance glutamatergic transmission through increasing levels of the coagonist glycine at the NMDAR. A GlyT blocker RG1678 is being evaluated for cognition and negative symptoms in schizophrenia (101).

Metabotropic glutamate receptors potentiate presynaptic glutamate release—and thereby postsynaptic NMDA neurotransmission—and are colocalized with NMDA receptors in human cortex. They are also being investigated for cognitive enhancement in schizophrenia. A Phase III trial with $mGluR_{2/3}$ agonist LY-2140023 did not examine its cognitive effects but showed an antipsychotic action (68). Another $mGluR_{2/3}$ agonist, LY-354740, has been demonstrated as effective in animal models for psychotic symptoms of schizophrenia but not in models of cognitive impairment (102).

3.2.4. Other neurotransmitter targets. Selective deficits in GABA receptor (GABAR) subunits within subpopulations of GABAergic neurons in the prefrontal cortex have led to the strategy of augmenting GABA neurotransmission at the α subunit of the GABAR in prefrontal cortex (103). In addition, substantial evidence suggests that serotonin 5-HT_{1A}-receptor and possibly 5-HT_2-, 5-HT_4-, and 5-HT_6-receptor active drugs may have cognitively enhancing effects. GABA and serotonin strategies are being tested with pharmacologic probes.

The medical need for discovery in schizophrenia is vast. Novel agents are sorely needed, even in the face of undiscovered disease mechanisms. The field has developed component symptom complex targets, targets believed to be pharmacologically independent; they can be separately modeled in animals. Once candidates are developed, their efficacy will need to be demonstrated not only in improving neuropsychological performance but also in improving psychosocial function. It is the hope that efficacy in treating cognitive dysfunction in the illness will partially mitigate the overwhelming disease burden of schizophrenia.

4. ANIMAL MODELS FOR COMPONENT SYMPTOM COMPLEXES

Efforts to develop more effective, hypothesis-driven treatments for schizophrenia critically depend on a better understanding of the etiology and pathophysiology of the disorder. Animal models have been pivotal in providing knowledge of the neurobiological mechanisms of human brain disorders. Although several animal models of schizophrenia are in use, finding a model that replicates the breadth of the symptoms observed in the disease has proven difficult. A shift in the drug discovery process from considering schizophrenia as a unitary disorder to considering it as a disorder of component symptom complexes suggests that animal preparations be refocused around component models of psychosis, cognitive dysfunction, and negative symptoms. This approach will ease the burden of discovery by providing phenotypes that are more accessible in animals and for which the neurobiology promises more direct and novel treatments.

Ideal models of schizophrenia should have good face, construct, and predictive validities. Face validity implies that behaviors of the animal model are similar to the human symptoms. Construct validity entails that neurobiological features of the illness are demonstrable in the model. Finally, predictive validity signifies that treatment modalities, which have proven to be effective in the illness, reverse symptoms. The more valid the model turns out to be, the greater its significance and utility (104). Component symptom complex animal models have the potential to be increasingly refined in their focus and outcome measures and thus be candidates for greater face, construct, and predictive validities.

4.1. Putative Psychosis Component Symptom Complex Model: Medial Temporal Lobe

Studies of the hippocampus in schizophrenia suggest that this region of the brain demonstrates reproducible and specific pathological features: (*a*) a consistent, albeit small, reduction in hippocampal volume; (*b*) an increase in hippocampal perfusion (blood flow) at baseline; (*c*) an activation deficit during declarative memory tasks, especially tasks that depend on relational memory; and (*d*) a reduction in dentate gyrus (DG) excitatory signaling efferents from DG granule cells within the mossy fiber pathway (105). A number of these in vivo alterations correlate with symptoms of the illness (106, 107) and thus are functionally relevant. Meanwhile (as discussed above), the conceptualization of schizophrenia is evolving away from categorical distinctions and toward a dimensional component formulation (8), which encourages a model that separates psychosis and cognitive pathology. The genetic etiologies of schizophrenia are multiple and complex (108–113),

and the neurochemical pathways implicated in symptom formation have become more varied (74, 114–117) yet no more certain; perhaps both are specific to components. At the same time, cognitive neuroscience is providing a rich foundational literature from which to understand the functional neurobiology of schizophrenia using learning and memory models. We have proposed a model for the psychosis component in schizophrenia, guided by models of learning and memory (105).

This model is based on evidence of a significant, but localized, reduction in glutamatergic transmission in DG and in its efferent pathways (99, 118–123), an idea consistent with subfield-specific, hypoglutamatergic function in schizophrenia (124–126). We suggest that DG, because it is situated at the proximal end of the trisynaptic pathway, may generate two co-occurring outcomes consequent to a reduction in its excitatory efferent activity. First, it may alter the plasticity characteristics of its target region, CA3, lowering the threshold in that subfield for long-term potentiation (LTP). Second, it may reduce the functional contribution of the DG → CA3 pathway to hippocampal memory computations, diminishing DG-mediated pattern separation (mediated largely in DG) and promoting CA3-mediated pattern completion (mediated largely in CA3). The processes that mediate both of these outcomes, LTP and memory function, have been previously studied in human, animal, and tissue systems. Thus markers of both are understood and can be tested in living humans, in postmortem brain tissue, and in simplified animal models, focusing on LTP in CA3 tissue, reduced glutamate transmission in DG, and reduced pattern-separation memory function in vivo in persons with schizophrenia or psychosis.

This psychosis model suggests that psychosis as a component symptom complex derives from hyperassociational function within CA3, a pathology that is initiated by reduced DG → CA3 mossy fiber innervations and that is driven and intensified by the direct EC → CA3 innervation and especially by the active recurrent collateral system in CA3. One could safely speculate that the genetic mutations in schizophrenia risk genes contribute to this risk—namely disrupted-in-schizophrenia 1 (*DISC1*) single-nucleotide polymorphisms (SNPs) and neuregulin 1 (*NRG1*) Icelandic haplotype, both of which are known to affect synaptic plasticity in hippocampus. We speculate that an extensively overactive CA3 associational drive will generate mistaken associations and false ideas, which then get laid down in memory with psychotic content.

One interesting aspect of this proposal is the possibility and early evidence that D_2 dopamine antagonists could affect and inhibit LTP in hippocampus as one of the mechanisms of their antipsychotic actions. However, of greater importance for novel drug development is the implication that drugs that act to decrease the induction of LTP in CA3, especially while increasing glutamatergic transmission in DG, might directly and through a novel mechanism antagonize psychotic states and reduce psychotic symptoms. Developing an animal preparation based on this component symptom complex model would be straightforward, by downregulating glutamate transmission at the NMDAR in DG and stimulating neuronal activity nonspecifically in hippocampus with amphetamine or phencyclidine (PCP). If the psychosis model proposed here can be verified in both human tissue and the animal model by demonstrating increased LTP markers in CA3 that are associated with reduced mossy fiber activity, it would provide a component animal model for psychosis pathophysiology.

4.2. Putative Cognitive Dysfunction Component Symptom Complex Model: Prefrontal Cortex

Animal models of cognition are particularly accessible because they have been used extensively to gain an understanding of the diverse types and mechanisms of cognition and to establish treatments for impaired cognition in dementia. Because the MATRICS teams have specified the types of

cognition that are particularly affected in schizophrenia (**Table 3**), the component targets are clear. Moreover, animal behaviors that mimic these human cognition functions have been defined, for the most part, and the brain regions involved in their mediation can also be specified. Working memory, which is known to be impaired in schizophrenia, is mediated largely in the dorsolateral aspects of the prefrontal cortex. Pat Goldman-Rakic has termed this area the "scratch-pad of the brain" (127). That the prefrontal cortex is known to be dysfunctional in schizophrenia is consistent with this working memory dysfunction. Therefore, clinical scientists have focused on this aspect of cognition in developing models of the illness.

Working memory function utilizes prefrontal cortical regions to generate a short-term memory system that allows the holding and processing of mnemonic information. Studies have suggested that patients with schizophrenia suffer from working memory impairments (128) that are independent of psychotic symptoms (128, 129). Working memory in normal individuals depends on the coordinated firing of subsets of dorsolateral prefrontal cortex (DLPFC) pyramidal neurons. The synchronized activity of cortical pyramidal cells is in turn regulated by a subset of DLPFC GABA interneurons that express the calcium-binding protein parvalbumin, including chandelier cells. Studies in patients with schizophrenia have reported reductions in GAD67 mRNA, an enzyme that synthesizes GABA, in parvalbumin-positive GABA interneurons. These reductions in GAD67 mRNA result in (*a*) reduced GABA synthesis and release in a specific population of interneurons and (*b*) decreased signaling from parvalbumin-positive GABA cells to pyramidal neurons. Lewis et al. (131) have suggested a model proposing that impairments in working memory in schizophrenia are mediated through reduction in GABA-mediated inhibitory modulation due to a decline in GABA-synthesizing enzymes and GABA synthesis in certain interneuron populations in the cortex (130–132). On the basis of this model, the authors further proposed that nonsedating, subtype-selective, positive allosteric modulators of GABA-A receptors may have a therapeutic effect on working memory deficits in schizophrenia (103, 133, 134). MK-0777—a selective GABA-A positive allosteric modulator—was tested and found to improve working memory and other measures of prefrontal function in a 4-week placebo-controlled proof-of-concept trial in patients with chronic schizophrenia (103), although an additional trial has been less encouraging. This suggests that restoring normal inhibition of pyramidal cell activity in cortex and restoring coordination in the activity among neuronal populations will reestablish normal prefrontal cortex function in schizophrenia, particularly working memory and executive function.

4.3. Considering Genetic Models in Component Symptom Complexes

Twin, adoption, and family studies suggest that genetic factors play a prominent role in the pathogenesis of schizophrenia; up to 80% of the risk for illness onset may arise from genetic factors (135–137). Moreover, considerable additional evidence suggests that schizophrenia results from an interaction between genes, possibly multiple genes working together, and environmental factors (1). Although more than 30 risk genes have been identified and more than 1,000 have been predicted (109–111), the identification of genes for schizophrenia has proven difficult (9, 13, 14). Two strategies are being pursued to identify pivotal risk genes: One has relied on associating genes with a unitary diagnosis of schizophrenia, i.e., the entire phenotype; the other tests the idea that genes will associate more strongly with intermediate phenotypes or endophenotypes (104, 138). Endophenotypes are measurable hereditary traits that reflect brain behaviors, which may be a more direct reflection of brain function than disease complexes. Endophenotypes cosegregate with the illness, are state independent, and are found in nonaffected family members at a higher rate than in the general population (139). Individual endophenotypes could purportedly more directly associate with genes than the more complex phenotype of schizophrenia. A group of endophenotypes

have been proposed in schizophrenia and are also being tested more broadly in psychosis as a component (140–143).

A proposal that draws directly from the theme we have developed in this review is the idea that different risk genes for schizophrenia will associate primarily with distinct component symptom complexes. In this scenario, some risk genes would associate with psychosis, others would associate with cognitive dysfunction, and still others would associate with negative symptoms. Indeed, evidence for this formulation has recently been proposed by Kaymaz & van Os (144), who suggest that the cognitive dysfunction and negative symptoms components carry a prominent genetic burden, whereas the psychosis component could be generated primarily by environmental risk factors. Evidence for the segregation of risk genes to the component symptom complexes can be generated from animal model studies in addition to epidemiological approaches.

The ability to induce specific genetic mutations by deleting or inserting individual genes has provided a means to investigate putative roles of genes in schizophrenia models. Informative animal models have been developed on the basis of genetically modified animal preparations that bear schizophrenia susceptibility genes (145, 146). These genetic preparations can display schizophrenia-like behaviors and thus have considerable construct validity, generating hope that focused genetic models will provide superior disease models. In addition, genetic preparations are likely to be increasingly used for testing new drugs. Whether the predictive validity of the genetic models will prove to be superior to pharmacologic models and pave the way toward novel drugs remains an open question.

Among several genes that have been implicated in risk of schizophrenia, *DISC1* and *NRG1* have emerged as leading candidates on the basis of genetic and clinical association studies (147, 148). *DISC1* is a protein-coding gene disrupted by a balanced translocation between chromosomes 1 and 11; it was found to segregate with mental illness including schizophrenia, major depression, and bipolar disorder in a large Scottish family and several populations worldwide (149–157). *DISC1* codes for a protein abundant in the hippocampus and cortex, key brain regions in the pathogenesis of schizophrenia. Although the exact functions of *DISC1* remain unclear, it may play an important role in neuronal growth and migration (158). Various *DISC1* mutation models display schizophrenia-like symptoms, including impairments in working memory, spatial memory, and prepulse latent inhibition as well as enlarged lateral ventricles (34–37, 150, 151, 159, 160). In addition, *DISC1* variations are associated with decreased gray matter density in the prefrontal cortex and hippocampus and with impaired cognitive function in individuals with and without schizophrenia (40, 160). Evidence suggests that antipsychotic treatment increases *DISC1* expression in several brain regions (40).

NRG1 was first proposed as a potential susceptibility gene for schizophrenia in an Icelandic study, and subsequent studies have supported this association (145, 161–163). *NRG1* plays a key role in several neural processes, including synapse formation and plasticity, neuronal migration, axonal myelination, and oligodendrocyte development (164, 165). Variations in *NRG1* expression are associated with decreased numbers of oligodendrocytes and structural changes in myelin sheaths in patients with schizophrenia, and a carrier status of an *NRG1* risk allele predicts development of psychosis in normal individuals with a strong family history of schizophrenia (166, 167). Neuroimaging studies suggest that the number of *NRG1* risk alleles carried in healthy individuals correlates with diminished verbal fluency and reduced activations in anterior cingulate, inferior frontal, and middle temporal cortex (168). In addition, *NRG1* mice mutants exhibit deficits in prepulse inhibition, impairments in working memory and social interaction, and behavioral abnormalities that are reversed by antipsychotic medication (145, 161, 169, 170).

In summary, we suggest that genetic association studies will be successful with the component symptom complexes but not with the broad illness definition of schizophrenia. Therefore,

applying these genetic animal model preparations to the study of specific illness components will be straightforward.

5. CONCLUSION

We have developed the thesis that schizophrenia is composed of domains or component symptom complexes that have important implications for understanding schizophrenia mechanisms as well as for developing novel treatments and accessible animal models. We have reviewed psychosis and cognitive dysfunction, the two nearly ubiquitous component complexes in schizophrenia, and proposed novel treatment approaches and parallel component disease models. We hypothesize that this new conceptual approach will allow the development of paradigm-shifting discoveries in this field that will change our understanding and management of schizophrenia.

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