Catching Up on Schizophrenia: Natural History and Neurobiology

Review

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Introduction

Schizophrenia is a brain disorder that is expressed in the form of abnormal mental functions and disturbed behavior. These manifestations characteristically appear in the late second and third decades of life as a heterogeneous constellation of three classes of clinical features. Positive symptoms include delusions (false beliefs), hallucinations (false perceptions), and thought disorganization. Negative symptoms refer to the loss of motivation and emotional vibrancy. Disturbances in basic cognitive functions, such as attention, executive functions, and specific forms of memory (particularly working memory), are also consistently observed in patients and are now thought to be central to the behavioral disturbances and functional disability of schizophrenia. In addition, many patients have concomitant mood symptoms including depression and anxiety that may contribute to the 10% lifetime incidence of suicide in schizophrenia.

Etiology

Vulnerability to schizophrenia is clearly related to genetic factors (Tsuang, 2000). Family, twin, and adoption studies have demonstrated that the morbid risk of schizophrenia in relatives correlates with the degree of shared genes. In contrast to the 1% incidence of schizophrenia in the general population, the incidence of schizophrenia is ~2% in third degree relatives (e.g., first cousins) of an individual with schizophrenia, 2%–6% in second degree relatives (e.g., nieces/nephews), and 6%–17% in first degree relatives (e.g., parents, siblings or children) (Gottesman, 1991). Among twins, the incidence of schizophrenia is ~17% in dizygotic twins of affected individuals, and nearly 50% in monozygotic twins (Gottesman, 1991). Finally, adoption studies have demonstrated that the risk of schizophrenia is related to the presence of the disorder in biological parents but not in the adoptive parents (Gottesman and Shields, 1982).

Regions on a number of chromosomes (e.g., 1, 6, 8, 10, 13, and 22) have been implicated as sites of potential vulnerability genes (Pulver, 2000). For example, 22q11–13 has shown suggestive findings in a number of linkage studies. Interestingly, deletions at this chromosomal region are associated with velo-cardio-facial syndrome (a congenital disorder characterized by cleft palate, car-

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diac malformations, and a distinctive facial appearance), which carries a substantially increased risk of schizophrenia, although the incidence of bipolar disorder in this syndrome is increased as well. Recently, chromosome 1q21–22 was identified as the location of a major vulnerability locus for familial schizophrenia with sufficient power to permit positional cloning of the underlying gene(s) (Brzustowicz et al., 2000).

Environmental factors (including exposure to infectious, autoimmune, toxic, or traumatic insults and stress during gestation or childhood) also may play a role in the pathogenesis of schizophrenia, perhaps via subtle alterations of neurodevelopment (Marcelis et al., 1998). Moreover, maturational processes including apoptosis, synaptic pruning, and myelination, occurring in the postnatal period through adolescence, may unmask the genetic vulnerability to schizophrenia (Lewis, 1997; Jarskog et al., 2000; Raedler et al., 2000). Thus, the etiology of schizophrenia has been conceptualized as involving multiple hits (consisting of genes conferring vulnerability and environmental insults), which are revealed in the context of developmental maturation of brain circuitry. However, unlike other genetic neurodevelopmental disorders (e.g., Down's syndrome or Fragile X syndrome), or severe gestational and birth traumas (e.g., fetal hypoxia or kernicterus), there are no immediate overt manifestations of schizophrenia. Rather, most individuals appear to function normally until they enter the greatest period of risk in late adolescence and early adulthood.

The 1% lifetime incidence of schizophrenia is fairly consistent across cultures, countries, racial groups, and genders (Bromet and Fennig, 1999). There are, however, some notable exceptions that support the involvement of the hypothesized etiologic factors previously described. Studies in both the northern and summer hemispheres have found that persons with schizophrenia show a modest excess of births in the winter and spring months, although similar observations have been made for depressive disorders (Torrey et al., 1997). Individuals with schizophrenia also tend to inhabit lower socioeconomic strata and to be more numerous in urban and selected immigrant populations (Mortensen et al., 1999). In addition, although equal numbers of males and females are affected, some data suggest that males may have more severe manifestations of the disorder, including an earlier age of onset (by 2–4 years), more marked neuropathological abnormalities, poorer response to treatment, and less favorable outcome (Szymanski et al., 1995; Hafner et al., 1998).

Thus, schizophrenia appears to be a polygenic disorder and to be associated with environmental and developmental vulnerability factors. The complexity of these potential interactions clearly complicates research on the underlying disease mechanisms. The clinical syndrome recognized as schizophrenia may be a unitary disease process with a range of severity and clinical manifestations across individuals, perhaps depending upon the degree to which different brain regions or circuits are affected. Alternatively, the clinical heterogeneity could reflect the possibility that what is recognized

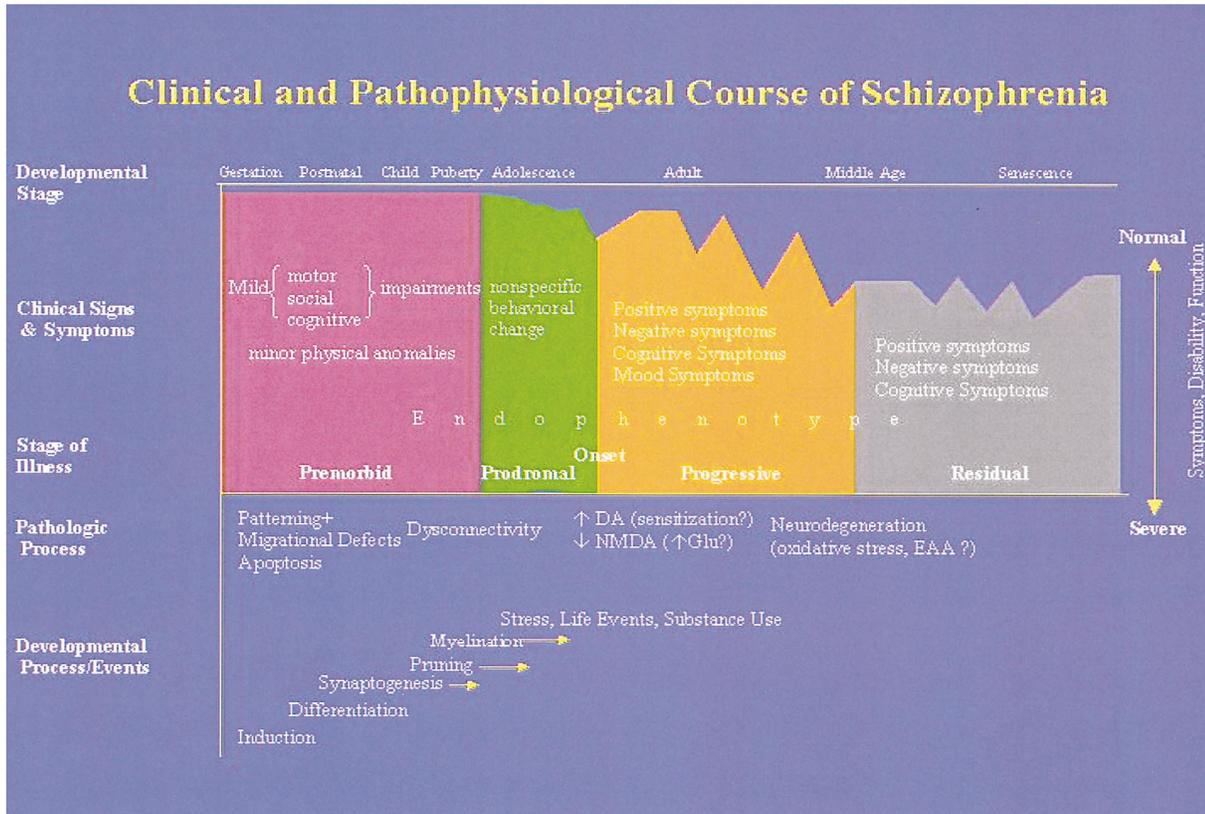## Clinical and Pathophysiological Course of Schizophrenia

Figure 1. Clinical and Pathophysiological Course of Schizophrenia

The diagram attempts to integrate and schematically depict the clinical and pathophysiologcal course of schizophrenia in its various clinical stages. To orient the reader starting from the top row: "Developmental Stage" describes the stage of life during which the various events and phenomena occur; "Clinical Signs and Symptoms" refers to the mental and behavioral manifestations of the illness; "Stage of Illness" describes all premorbid and morbid phases of the illness; "Pathologic Process" refers to the hypothesized pathogenic and pathophysiologic mechanisms that underlie and are causal to the clinical manifestations of the disorder; "Developmental Process and Events" indicates the neurobiological maturational processes and environmental events that may unmask or destabilize the neural circuits made vulnerable by etiologic and pathogenic factors. The following abbreviations are DA, dopamine; NMDA, N-methyl D-aspartate; Glu, glutamate.

as schizophrenia represents a constellation of diseases that share some phenotypic features. Differentiating among these possibilities will require the definitive identification of specific causal factor(s).

Course of Schizophrenia

The time course of schizophrenia follows the fairly stereotyped pattern depicted in Figure 1. High-risk and longitudinal birth cohort studies have identified mild deficits in social, motor, and cognitive functions during childhood and adolescence that may represent premorbid features of the illness (Jones, 1997). For example, subtle motor abnormalities during infancy (Walker and Lewine, 1990) and deficits in social functioning, organizational ability, and intellectual functioning at ages 16–17 have both been reported to be associated with the later appearance of schizophrenia (Davidson et al., 1999). In addition, a number of minor physical anomalies, such as variations in limb length and angle and finger-print patterns, are present in a subgroup of patients and can also be detected in populations with increased genetic risk. All of these features, however, are mild in severity and have low predictive validity as individual markers.

Prodromal symptoms and behaviors (i.e., those that herald the approaching onset of the illness) may include attenuated positive symptoms (e.g., illusions, ideas of reference, magical thinking, superstitiousness), mood symptoms (e.g., anxiety, dysphoria, irritability), cognitive symptoms (e.g., distractibility, concentration difficulties), social withdrawal, or obsessive behaviors to name a few (McGlashan, 1996; Yung and McGorry, 1996). Because many of these prodromal phenomena extensively overlap with the range of mental experiences and behaviors of persons in the ages of risk who do not subsequently develop schizophrenia, they cannot be considered diagnostic. In the vast majority of cases, these prodromal manifestations, and subsequently positive and negative symptoms by which the diagnosis is made, develop gradually over a period of weeks, months or even years beginning some time in the mid second through the third decade of life. The environmental events that typically occur during this developmental epoch (e.g., entering college, the military or the workforce, exposure to drug abuse) may act as stressors on vulnerable neural circuits that exceed their adaptive capacity, thereby producing the behavioral symptoms that signal the onset of the illness (Lieberman et al.,

1997). In contrast, schizophrenia rarely has its onset before puberty or after age 40.

The evidence that schizophrenia is a genetically mediated, neurodevelopmental disorder bred the belief that affected individuals were "doomed from the womb" and thus had a pessimistic prognosis. In contrast, recent studies have shown that, if treated properly early in the course of their illness, most patients experience a substantial reduction and even remission of psychotic symptoms following an initial episode, although associated negative and cognitive symptoms can persist (Lieberman et al., 1993; Sheitman et al., 1997; Robinson et al., 1999a). However, following recovery, the majority of patients eventually discontinue medication and then subsequently experience a relapse of psychotic symptoms. In the context of subsequent psychotic episodes, they may not respond to treatment as well as in prior episodes and fail to achieve symptom remission (Lieberman et al., 1996; Robinson et al., 1999b). Through this process of repeated exacerbations and relative remissions, most patients sustain the clinical deterioration that is the hallmark of schizophrenia and that leads to an end-stage of the illness in which severely affected patients exhibit persistent symptoms and profound functional disability (Figure 1). Interestingly, this pattern of clinical deterioration is most pronounced in the early stages of the illness (first 5–10 years) and then reaches a plateau (although the most severe variants may continue to decline into senescence [Harvey et al., 1999]).

Pathogenesis and Pathophysiology

A major challenge in schizophrenia research has been to understand how a genetically mediated, neurodevelopmental disorder is not expressed clinically until 1.5–3 decades postnatally, but then proceeds to progressively disable its victims. It is hypothesized that the interaction of a genetic diathesis and early neurodevelopmental insults result in defective connectivity between a number of brain regions, including the midbrain, nucleus accumbens, thalamus, temporo-limbic, and prefrontal cortices (Selemon and Goldman-Rakic, 1999). This defective neural circuitry is then vulnerable to dysfunction when unmasked by the developmental processes and events of adolescence (myelination, synaptic pruning, and hormonal effects of puberty on CNS) and exposure to stressors as the individual moves through the age of risk (Lieberman et al., 1997; Raedler et al., 2000) (Figure 1).

These factors have prompted speculation about which neurochemical systems might mediate the progressive changes seen during the early phases of schizophrenia (Lieberman, 1999). Such speculation has centered on the dopamine and glutamate systems (Figure 2). An overactivity of dopamine neurotransmission in the mesencephalic projections to the limbic striatum has long been suspected in schizophrenia. However, the evidence supporting the involvement of dopamine had, until recently, been predominantly indirect. This included the positive correlation between the clinical potency and D_2 binding affinity of antipsychotic drugs, on one hand, and the ability of indirect dopamine agonists to induce psychosis in healthy volunteers and provoke psychotic symptoms at very low doses in patients

with schizophrenia, on the other (Carlsson 1988). Although both postmortem and PET studies had found increased levels of D_2 receptors in the brains of schizophrenia patients, antipsychotic drug treatment as the cause could not be ruled out (Wong et al., 1986; Farde et al., 1990). More recently, direct evidence of dopamine hyperactivity has emerged from both preclinical and clinical studies, implicating dysfunctions in presynaptic storage, release, reuptake, and metabolic mechanisms in dopamine meso-limbic systems (Giros et al., 1996; Laruelle et al., 1996; Breier et al., 1997). These studies suggest that abnormalities in dopamine storage, vesicular transport, release, or reuptake by the presynaptic neuron may be the proximal cause of psychotic symptoms (Laruelle et al., 1999) and may contribute to the risk for schizophrenia (Egan et al., 2000). It has been further hypothesized that disturbances in the presynaptic regulation of dopamine could lead to enduring consequences through the induction of sensitization and/or oxidative stress (Lieberman et al., 1997; Laruelle, 2000). In contrast, the functional activity of dopamine may be decreased in the neocortex in schizophrenia (Davis et al., 1991; Okuba et al., 1997; Akil et al., 1999).

Glutamate has also been implicated in schizophrenia by studies of behavioral effects of NMDA receptor antagonists (e.g., PCP, MK-801, ketamine) and in the context of the NMDA receptor hypofunction hypothesis (Javitt and Zukin, 1991; Olney and Farber, 1995; Jentsch and Roth, 1999). Acute administration produces psychotic symptoms and cognitive dysfunction in healthy subjects (Krystal et al., 1994) and exacerbates psychotic, negative, and cognitive symptoms in patients with schizophrenia (Lahti et al., 1995). NMDA receptor hypofunction induced by the administration of NMDA antagonists results in decreased corticofugal inhibition of subcortical dopamine neurons and consequent increased mesolimbic dopamine release (Breier et al., 1998; Kegeles et al., 2000), while chronic administration produces decreased release, or hypoactivity, of dopamine in the prefrontal cortex (Jentsch and Roth, 1999). It has also been suggested that hypofunctioning NMDA receptors can cause an excess compensatory release of glutamate that can overactivate other glutamate receptor subtypes that are not being antagonized and are functionally active (Moghaddam and Adams, 1998; Duncan et al., 2000). Finally, NMDA receptor hypofunction may also produce disturbances in neuroplasticity of neurons by altering synaptic connectivity.

Structural Pathology

Structural brain abnormalities have also been extensively documented in individuals with schizophrenia (McCarley et al., 1999). These include enlargement of the lateral and third ventricles and reduced volume of the cortical gray matter and related structures. The latter changes do not appear to represent a uniform abnormality, but rather to effect preferentially certain association cortices including those located in the superior temporal gyrus, the dorsal prefrontal cortex (PFC), and limbic areas such as the hippocampal formation and anterior cingulate cortex (Goldstein et al., 1999; McCarley et al., 1999) (Figure 2). Many of these structural abnormalities are evident in first-episode, never-medicated subjects
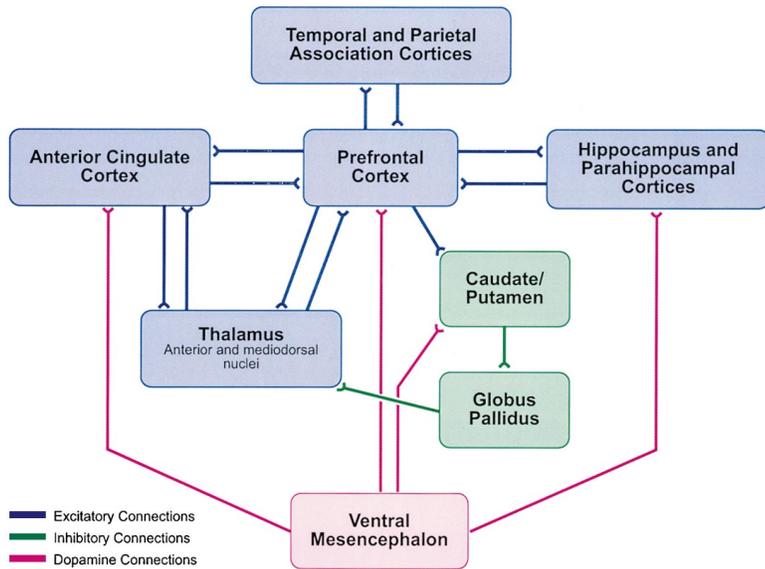
Figure 2. Affected Brain Regions in Schizophrenia

Schematic diagram summarizing some of the brain regions that have most consistently been implicated in the pathophysiology of schizophrenia. The nature of the pathophysiological changes appears to differ across regions with a reduction in neuronal number reported in some nuclei of the thalamus, decreases in markers of synaptic connectivity in the prefrontal cortex and hippocampal formation, and evidence of either a functional excess or deficit of dopamine neurotransmission in the striatum and prefrontal cortex, respectively.

with schizophrenia, and may be present prior to the clinical onset of illness, suggesting that they reflect the primary disease process and are not a secondary consequence of the illness or of its treatment. In addition, longitudinal neuroimaging studies have shown apparent neuropathological progression in the form of gray matter volume decreases and fluid compartment increases (in lateral and third ventricles and subarachnoid space) over the course of the illness (Davis et al., 1998; Gur et al., 1998a; Rapoport et al., 1999). The fact that postmortem studies have not found evidence of gliosis is consistent with an emphasis on the hypothesized role of neurodevelopmental factors in the pathogenesis and pathophysiology of schizophrenia (Harrison, 1999). However, recent evidence also suggests the possible involvement of apoptotic mechanisms (Jarskog et al., 2000).

Circuitry-Based Pathological Changes
Understanding the pathophysiological significance of these structural brain abnormalities requires knowledge of which specific neural elements are affected and how the disturbances in different brain regions may be related. To date, these questions have been most extensively explored for the neural circuitry of the hippocampal formation and the dorsal PFC.

Multiple imaging and postmortem studies over the past 2 decades have documented a slight bilateral reduction in the volume of the hippocampal formation (Harrison, 1999; McCarley et al., 1999), an observation supported by more recent in vivo proton spectroscopy findings of reduced hippocampal N-acetyl aspartate, a putative marker of neuronal pathology, in both unmedicated adult and childhood onset subjects with schizophrenia (Bertolino et al., 1998). In addition, positron emission tomography studies have provided evidence of hippocampal dysfunction during episodic memory retrieval in subjects with schizophrenia (Heckers et al., 1998). Initial reports of hippocampal neuron disarray or misplaced neurons in the superficial layers of the adjacent entorhinal cortex have been widely cited, but these observations have not been replicated in most

subsequent studies (Harrison, 1999). Reduced hippocampal volume also does not appear to be attributable to decreased neuronal number, but several independent studies have found reductions in neuronal cell body size in various subregions of the hippocampus proper (Benes et al., 1991; Arnold et al., 1995; Zaidel et al., 1997). In addition, there are consistent reports of reductions in the gene products for synaptophysin and related presynaptic markers and in dendritic markers, such as microtubule-associated protein, in certain subdivisions of the hippocampus (see Weinberger, 1999, for review). Although these findings are limited in a number of respects, they have given rise to testable models postulating that genes involved in the formation and maintenance of hippocampal circuitry play a role in disease vulnerability (Weinberger, 1999).

In general, the magnitude and consistency of gray matter reduction in the PFC is not as robust as in the hippocampal formation. However, multiple studies of the PFC have been motivated by the observation that subjects with schizophrenia consistently perform poorly on certain cognitive tasks, such as those requiring working memory, that are subserved by circuitry involving the dorsal PFC (Goldman-Rakic, 1994). In addition, these subjects fail to show normal activation of the dorsal lateral PFC (e.g., Brodmann area 46) when attempting to perform the Wisconsin Card Sort Task, N-back tasks, or other tasks that require working memory (Weinberger et al., 1986; Taylor, 1996). Since the long-term prognosis for individuals with schizophrenia appears to be best predicted, not by the severity of positive symptoms, but by the degree of cognitive impairment (Green, 1996; Weinberger and Gallhofer, 1997), understanding the nature of PFC brain abnormalities may be particularly important for improving clinical outcome.

Many, but not all, postmortem studies have reported a 5%–10% reduction in cortical thickness, with a corresponding increase in cell packing density, but no change in total neuron number, in the dorsal PFC of subjects with schizophrenia (Selemon and Goldman-Rakic, 1999). Although the size of some PFC neuronal populations,

particularly pyramidal neurons in deep layer 3, is smaller in schizophrenic subjects (Rajkowska et al., 1998), these findings are also likely to reflect a decrease in the number of axon terminals, distal dendrites, and dendritic spines that represent the principal components of cortical synapses. Consistent with this interpretation, levels of synaptophysin, a presynaptic terminal protein, have been found to be decreased in the PFC of subjects with schizophrenia in multiple studies (Perrone-Bizzozero et al., 1996; Glantz and Lewis, 1997; Karson et al., 1999; Honer et al., 1999). Furthermore, as in the hippocampus, levels of N-acetyl aspartate, a marker of axonal and/or neuronal integrity, are reduced in the PFC of subjects with schizophrenia (Bertolino et al., 2000).

The reason for this reduction in synaptic connectivity in the PFC is not fully known. One contributing factor may be fewer projections from the thalamus. Indeed, enlargement of the third ventricle (whose lateral boundaries are formed by the thalamus) appears to reflect a reduction in size of the thalamus (Andreasen et al., 1994; Buchsbaum et al., 1996; Frazier et al., 1996; Gur et al., 1998b). Moreover, thalamic volume has been correlated with prefrontal white matter volume in subjects with schizophrenia, suggesting that a reduction in thalamic volume is associated with fewer axonal projections to the PFC (Portas et al., 1998). Consistent with these observations, several postmortem studies have revealed a 30% reduction in the total number of neurons in both the mediodorsal thalamic nucleus (MD), the principal source of thalamic projections to the PFC, and in the anterior nuclei, which project to the PFC and anterior cingulate cortex, but not in at least some other thalamic nuclei (Pakkenberg, 1990; Popken et al., 2000; Young et al., 2000). However, the small sample sizes and limited assessment of potential confounds in these studies indicate that additional investigations in this area are required.

Despite these limitations, the potential importance of these findings is strengthened by the convergence of other lines of evidence that support the hypothesis that schizophrenia is associated with abnormalities in thalamo-prefrontal connectivity (Figure 3). For example, a putative marker of MD axon terminals appear to be reduced in the PFC of subjects with schizophrenia (Lewis, 2000). In addition, basilar dendritic spines on PFC deep layer 3 pyramidal neurons, a principal synaptic target of the excitatory projections from the MD, have been reported to be decreased by ∼25% in subjects with schizophrenia (Garey et al., 1998; Glantz and Lewis, 2000). In contrast, pyramidal neurons in at least some other cortical layers or regions of the same subjects, and in individuals with major depressive disorder, appear to lack or to exhibit less marked changes in spine density. Since the elimination of presynaptic axon terminals typically leads to resorption of the postsynaptic dendritic spine, these observations are consistent with a reduced number of afferents from the MD in schizophrenia.

In the primate visual system, monocular deprivation, which leads to reduced cortical inputs from the thalamus, has been associated with a decline in markers of activity in cortical γ-aminobutyric acid (GABA) neurons (Hendry and Jones, 1988), including the expression of the mRNA for glutamic acid decarboxylase (GAD_{67}), the synthesizing enzyme for GABA. If these findings in the visual system hold for MD-PFC connectivity, then a similar reduction in GAD_{67} mRNA expression would be expected in the PFC of subjects with schizophrenia. Consistent with this prediction, GAD_{67} mRNA and protein levels have been reported to be reduced in the PFC of subjects with schizophrenia (Akbarian et al., 1995; Costa et al., 2000; Volk et al., 2000). Furthermore, it appears that a subset of GABA neurons (∼25%) is primarily affected. For example, the density of GABA transporter-immunoreactive axon cartridges (the distinctive, vertically arrayed axon terminals of GABAergic chandelier neurons, which synapse exclusively on the axon initial segment of pyramidal neurons), is selectively decreased in the dorsal PFC of subjects with schizophrenia (but not in individuals with other psychiatric disorders) with the reduction most evident in the middle cortical layers (Pierri et al., 1999).

Thus, correlative evidence across a range of observations suggests that schizophrenia is associated with impaired MD-PFC connectivity. Given the dependence of working memory tasks on the integrity of this circuitry, it would not be surprising if such an impairment could account for working memory dysfunction in schizophrenia. The relationship of this impairment to the positive and negative symptoms of schizophrenia is less obvious. Nor is it clear that MD-PFC connections are the primary site of pathogenesis. For example, experimental studies in rodents suggest that dysfunction of the PFC may appear postpubertally following perinatal lesions of the hippocampus (Weinberger and Lipska, 1995). Finally, the apparent deficits in PFC function are also likely to reflect disturbances in both intrinsic and cortico-cortical connections (Goldman-Rakic and Selemon, 1997; Mirnics et al., 2000).

Treatment of Schizophrenia

Much remains to be learned about the etiology and pathophysiology of schizophrenia, but the efficacy of treatments for this disorder has been clearly demonstrated (see Table 1). Although all available treatments have limitations in their effectiveness and are associated with adverse side effects, it is an established fact that antipsychotic medications can alleviate the psychotic symptoms of the disorder and prevent their recurrence (Kane, 1996). Moreover, in doing so, antipsychotic drug treatment, strategically used, appears to reduce the degree of clinical deterioration that occurs from progression of the illness. This has led to the hypothesis that the early identification and treatment of schizophrenia (before or soon after symptom onset) may reduce, or even prevent, the cumulative morbidity of the illness (McGlashan, 1996). Although pharmacotherapy provides the foundation for the treatment of schziophrenia, various psychosocial therapies can be useful adjuncts to drug treatment (Kane, 1996).

Until recently, most pharmacological treatments for schizophrenia were based on synaptic modulation of dopamine neuronal systems mainly by antagonism of postsynaptic D_2 receptors. With the advent of the so-called atypical antipsychotic drugs, this focus has now broadened to include other neurotransmitters such as serotonin, norepinephrine, acetylcholine, histamine, and glutamate, as well as various neuropeptides and neu-
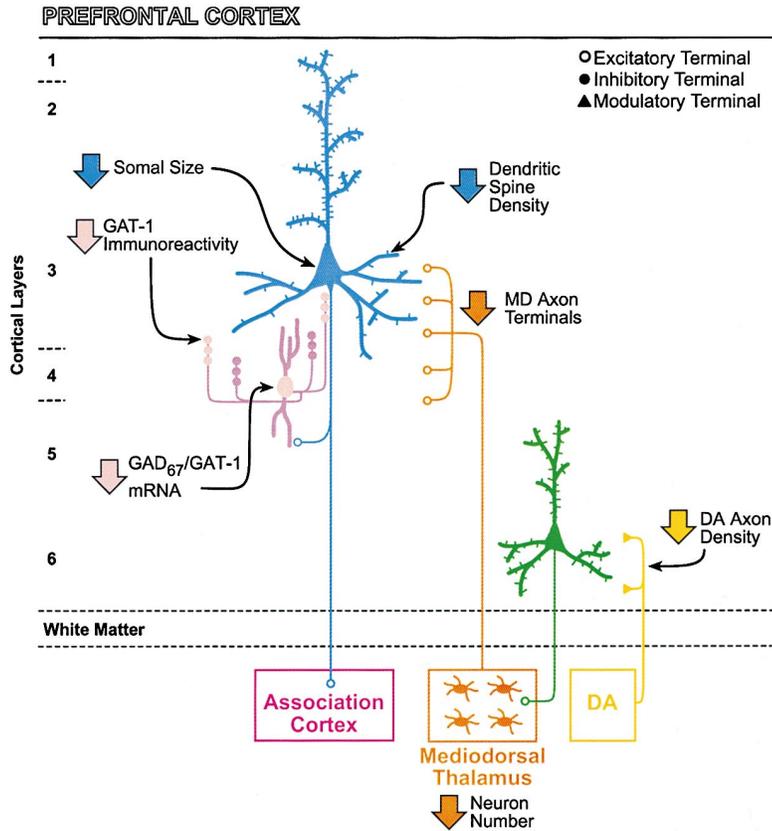
PREFRONTAL CORTEX

Figure 3. Cortical Circuitry in Schizophrenia

Schematic diagram summarizing disturbances in the connectivity between the mediodorsal (MD) thalamic nucleus and the dorsal prefrontal cortex (PFC) in schizophrenia. Postmortem studies have reported that subjects with schizophrenia have (1) decreased number of neurons in the mediodorsal thalamic nucleus; (2) diminished density of parvalbumin-positive varicosities, a putative marker of thalamic axon terminals, selectively in deep layers 3–4, the termination zone of MD projections to the PFC; (3) preferential reduction in spine density on the basilar dendrites of deep layer 3 pyramidal neurons, a principal synaptic target of the excitatory projections from the MD; (4) reduced expression of the mRNA for glutamic acid decarboxylase (GAD_{67}), the synthesizing enzyme for GABA, in a subset of PFC GABA neurons; (5) decreased density of GABA transporter (GAT-1)-immunoreactive axon cartridges, the distinctive, vertically arrayed axon terminals of GABAergic chandelier neurons, which synapse exclusively on the axon initial segment of pyramidal neurons; and (6) decreased dopamine innervation of layer 6, the principal location of pyramidal neurons that provide corticothalamic feedback projections (see Lewis, 2000, for additional details and references).

rosteroids (Kinon and Lieberman, 1996). These compounds have either low ratios of affinities for the D_2 and $5-HT_{2a}$ receptors (called $D_2/5-HT_2$ antagonists [e.g., risperidone]) or possess affinities for some combination of multiple neuroreceptors and reuptake sites including $D_{1,2,3,4}$, $5-HT_{1a,b, 2a,c, 3, 6, 7}$, $NE\alpha_{1, 2}$, $MACH_{1, 4}$, $H_{1,2}$, DAT, NET, ST (called multi-neuroreceptor antagonists [e.g., clozapine]). At present, all effective treatments appear to possess some threshold level of D_2 receptor antagonism, though selective nondopamine antagonists have attempted to challenge this concept (Kapur et al., 2000). At the same time, there is clearly no pharmacologic "magic bullet" for the different pathologic dimensions of schizophrenia. This is reflected by the common practice of using multiple drugs in combination when treating patients with schizophrenia. Whereas, the psychotic symptoms appear to be mediated primarily by dopamine overactivity in mesolimbic circuits and negative symptoms by dopamine underactivity in prefrontal cortical neurons (thus can be exacerbated by classical antipsychotics with high D_2 affinity), the cognitive impairment appears to also involve disturbances in glutamate activity. Interestingly, the second generation or atypical antipsychotic drugs, which are thought to have a broader range of therapeutic effects including reducing cognitive impairment, have been found to block the cellular and behavioral effects of NMDA antagonists, despite the fact that they lack affinities for any of the ionotropic or metabotropic glutamate receptors (Mohn et al., 1999; Duncan et al., 2000). It is therefore assumed that atypical antipsychotic drugs must be acting more directly through dopamine receptors (S. Miyamoto et al., submitted) or other neuroreceptors (e.g., 5-HT, noradrenergic, etc. [Duncan et al., 2000]) in modifying glutamate mediated function and behavior.

Schizophrenia researchers have historically used pharmacology in a bootstrap approach to simultaneously develop treatments and pathophysiological disease models (as previously described). This productive process of cross-fertilization continues as we see experimental treatments and drug development strategies derive from the results of the emerging neuroscience of schizophrenia (Miyamoto et al., 2001).

Future Directions
These research findings provide new opportunities and new challenges to understanding and treating schizophrenia. Certainly, a major challenge is to determine the genetic susceptibilities and pathogenetic mechanisms that can produce the complex clinical phenotype of schizophrenia. The identification of pathways of dysfunction, such as thalamo-prefrontal circuitry or the connections linking other cortical, subcortical, and cerebellar regions implicated in schizophrenia, permits studies of the relationships among the various alterations in a circuit and the elucidation of a putative endophenotype. For example, does a given abnormality represent a primary brain disturbance due to a causal factor of the disorder, or does it reflect a downstream pathologic consequence of the primary brain disturbance or an adaptive response that attempts to normalize the function of the circuit?

Answers to these types of questions may create new opportunities for research at the intersection between

Table 1. Treatment of Schizophrenia

Interventions	Advantages	Disadvantages
Pharmacological		
Antipsychotic Drugs (APDS)		
CLASSICAL: High-affinity D_2 antagonists	Reduces and prevents recurrence of psychotic symptoms.	Limited efficacy against negative and cognitive symptoms. High rates of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD).
ATYPICAL: Mixed neuroreceptor antagonists; low-affinity D_2 high affinity $5HT_{2A}$ (e.g., clozapine, risperidone, olanzapine, quetiapine, ziprasidone)	Reduces and prevents psychotic symptoms; broader efficacy against negative mood and cognitive symptoms; may prevent illness progression. Less EPS and TD.	Various side effects including blood dyscrasias, weight gain, increased glucose, and triglycerides; more expensive.
Adjunctive Treatements of APDS		
Benzodiazepines	Control agitation.	Limited potency and duration of action.

Mood stabilizers
    Anticonvulsants
    Lithium
	Augment antipsychotic effects; control mood symptoms and hostility.	Few studies; limited efficacy.

Antidepressants	Reduce depressive and negative symptoms.	Limited efficacy against negative symptoms.
Anticholinergics	Reduce EPS.	Side effects (dry mouth, constipation, memory impairment).
Dopamine agonists	Reduce negative symptoms.	Possible exacerbation of psychotic symptoms.
Experimental Treatments		
Dopamine partial agonists (e.g., aripripazole)	May reduce psychotic and negative symptoms; few side effects.	Few clinically available compounds; few studies.
5-HT agents (e.g., M100907, ritanserin)	May improve negative symptoms; few side effects.	No proof of concept as monotherapeutic agent. Weak effect as adjunct; few clinically available compounds.
Cholinergic agonists (muscarinic/nicotinic)	?	No proof of concept.
Glutamatergic agents		
Allosteric modulators (e.g., glycine, serine, D-cycloserine)	Reduce negative symptoms; may improve cognition, prevent illness progression.	Weak to moderate effect; few studies and clinically available compounds.
Glycine uptake inhibitors	?	No proof of concept.
Glutamate release-inhibiting drugs (e.g., LY-293558)	?	No proof of concept.
AMPA/kainate receptor agonists (e.g., CX516)	May improve congnition.	Very few studies.
Protein kinase C inhibitors (e.g., tamoxifen)	?	No proof of concept.
Steroidal agents (e.g., estrogen, dihydroepiandrosterone)	May reduce negative symptoms; improve cognition; prevent illness progression.	Few studies.
Phsopholipid compounds (e.g., 3-omega fatty	May improve cognition; prevent illness progression.	No proof of concept.
Psychosocial		
Psychoeducation	Increases awareness and insight of patient family.	Few studies; must be combined with drug R_x.
Psychotherapies	May be useful adjunct.	Limited to problem-oriented and supportive therapies; must be combined with drug R_x.
Assertive community treatment	Improves R_x compliance.	Underutilized more labor intensive.
Cognitive behavioral therapy	May reduce positive symptoms.	Few studies; must be combined with drug R_x.

systems level investigations and genetic approaches. Current views hold that schizophrenia is probably a consequence of multiple interacting genes; individually, these genes may have relatively little independent influence, and they may not all be involved in every individual who meets diagnostic criteria for the illness. Thus, assessment of the patterns of altered gene expression in the affected brain circuits of subjects with schizophrenia (using cDNA microarray technology or related techniques), and comparison of the chromosomal locations of these genes with regions implicated in schizophrenia through linkage studies (Pulver, 2000), may provide convergent approaches to the identification of specific vulnerability genes. For example, a recent study of gene expression profiling in the dorsal PFC of subjects with schizophrenia revealed that, of over 250 gene groups, the group of genes encoding proteins involved in the regulation of presynaptic function were most consis-

tently altered (Mirnics et al., 2000). Although the subjects with schizophrenia appeared to share a common abnormality in the control of synaptic transmission, the specific combinations of genes involved in presynaptic function that showed reduced expression differed among them. Interestingly, a number of the chromosomal loci that have been implicated in schizophrenia contain genes encoding proteins related to presynaptic function (Mirnics et al., 2000).

Recent research suggests that the heterogeneous phenotype of schizophrenia may be the result of multiple pathophysiological processes occurring at different stages of the illness (Lieberman, 1999). These can be further characterized using multiple investigative approaches including in vivo neuroimaging, genetics, molecular neuropathology, and the development of animal models. Although animal models can only approximate the complex clinical phenotype of schizophrenia, they are essential to understand the molecular and cellular mechanisms that underlie the pathogenesis and pathophysiology of schizophrenia and can be used to test predictions from direct investigations of the illness. For example, conditional knockouts can be used to assess the consequences, at different stages of development, of the deficient expression of genes observed in subjects with schizophrenia. Therapeutic strategies based on this knowledge offer the promise of more effective interventions (including secondary and tertiary prevention), reduced morbidity, and better outcomes for patients.

Thus, it should be apparent that although great progress has been made in catching up on schizophrenia, much remains to be done.

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