

Schizophrenia: New Pathological Insights and Therapies

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Abstract

The neurodevelopmental hypothesis of schizophrenia posits an interaction between multiple susceptibility genes and one or more environmental insults in early life, resulting in altered brain development and the emergence of psychosis in early adulthood. Based on this framework, it has been argued that most neuropathological deficits observed in post mortem and neuroimaging studies of schizophrenia represent one or more lesions that originated in early life and remained static thereafter. However, recent longitudinal neuroimaging studies demonstrate a progressive component to the neuropathology of new-onset schizophrenia. This opens the possibility that the functional decline seen in many patients following the onset of illness may be halted or slowed. This review provides an update on developments in research on the neuropathology of schizophrenia and discusses recent advances in antipsychotic treatment and the potential impact on long-term outcomes.

DLPFC:
dorsolateral
prefrontal cortex

ACC: anterior
cingulate cortex

INTRODUCTION

Schizophrenia is widely considered a neurodevelopmental disorder that stems from interactions among genetic and environmental factors. Although the contribution of any single gene appears to be quite small, the combined influence of multiple susceptibility genes contributes substantially to the risk of developing schizophrenia (1). Epidemiological studies have also identified a number of environmental factors that confer additional risk, including early life exposure to infection, trauma, and hypoxia (2). Despite the influence of multiple genetic and environmental factors on brain development, however, the clinical symptoms of psychosis typically remain dormant until adolescence or early adulthood. It has been postulated that the delayed onset of symptoms may be due to maturational processes such as puberty, cortical synaptic pruning, and myelination, which “unmask” preexisting deficits (3). Whereas the neurodevelopmental hypothesis posits a static lesion based on the presence of fixed deficits established in early development, recent studies indicate that new-onset schizophrenia is often characterized by a period of clinical and functional decline accompanied by progressive neurostructural changes, which suggests that a limited neuroprogressive process may also be involved (3).

Converging evidence from neuroimaging, neurocognitive, gene array, and post mortem neuropathological studies indicate that the pathophysiology of schizophrenia involves disrupted synaptic connectivity that affects both inhibitory and excitatory circuits. These findings are consistent with emerging evidence of cortical hypofrontality that has prompted revisions to the traditional dopamine hypothesis, i.e., that schizophrenia stems from subcortical hyperdopaminergia. The most recent neurochemical hypothesis implicates a primary cortical hypoglutamatergia that enhances subcortical hyperdopaminergia and cortical hypodopaminergia (4). This hypothesis provides a more nuanced and uni-

fying explanation for the clinical presentation of schizophrenia. It accounts for positive symptoms (e.g., delusions, hallucinations), negative symptoms (e.g., apathy), and cognitive symptoms (e.g., disorganization), and it provides the basis for novel treatment approaches that extend beyond dopamine subtype-2 (D₂) receptor antagonism.

This brief review is necessarily selective. Recent advances in the neuropathology and genetics of schizophrenia are discussed in the context of prevailing etiopathogenic hypotheses. We also review recent developments in pharmacotherapy, including FDA-approved and novel experimental approaches that demonstrate promise.

NEUROPATHOLOGY

Neuronal and Glial Density

Unlike many classic neurodegenerative disorders, schizophrenia is not characterized by large-scale neuronal loss. One of the few studies to have examined total cortical neuronal number found no difference between schizophrenics and controls (5). In dorsolateral prefrontal cortex (DLPFC), several studies found increased neuronal density in schizophrenia due to slight reductions in cortical neuropil, but overall neuronal numbers were not changed (for review, see Reference 6). Other studies identified reductions in the densities of neuronal subpopulations, including interneurons in layer II of DLPC and in layers II–VI of anterior cingulate cortex (ACC) (7, 8). Several studies (9, 10), though not all (11), found that in contrast to cortical areas, neuronal density in mediodorsal thalamus was reduced. In hippocampus, most studies have not demonstrated an overall loss of neurons (12); however, several studies have identified reductions in GABAergic (gamma-aminobutyric acid) interneuron subpopulations (13).

Also in contrast to classic neurodegenerative disorders, schizophrenia is characterized by an absence of glial proliferation (14), and

recent data even suggest that cortical glial density is decreased (15). The absence of gliosis strongly suggests the absence of a classic neurodegenerative process, providing general support for schizophrenia as a disorder of neurodevelopment. However, the absence of gliosis does not rule out a more limited degenerative process.

Synapses and Dendrites

Many lines of evidence suggest that schizophrenia is a disorder of synaptic connectivity and involves a reduction in cortical neuropil (6). This is supported by evidence of reduced density of dendritic spines and dendritic length in DLPFC in schizophrenia (16). Furthermore, reduced expression in DLPFC of Cdc42 and Duo, two members of the RhoGTPase family involved in regulating spine dynamics, could contribute to the underlying mechanism of altered spine density (17). Reduced neuropil is also consistent with decreased levels of the presynaptic marker synaptophysin in DLPFC (18). Synaptic pathology is similarly suggested in hippocampus, where investigators have found reduced levels of synaptophysin (19) and the dendritic spine marker spinophilin (20). Altered synaptic connectivity in schizophrenia is also supported by a gene array study showing reductions of multiple genes that code for synaptic gene products in DLPFC (21). Finally, reductions in pyramidal neuronal size in DLPFC have been reported (22). This may not be surprising, since the extent of dendritic and axonal arborization contributes to somal size (23).

GABAergic Deficits

Deficits in GABAergic interneurons in DLPFC are among the best-replicated neuropathological findings in schizophrenia. Because of the importance of GABAergic inhibition in critical circuits of normal brain function—including working memory—

deficits in GABAergic neurons are likely to make important contributions to cognitive and other clinical dimensions of schizophrenia (24). For example, glutamic acid decarboxylase (GAD)—the GABA-synthesizing enzyme—is substantially reduced in DLPFC (25). Similarly, GABA_A receptor binding is increased in ACC and DLPFC (26), representing a potential compensatory up-regulation in response to lower GABA levels (27). Furthermore, studies have found fewer GABA membrane transporter (GAT-1) cartridges in the GABAergic chandelier neurons of DLPFC (28). GAT-1 cartridges reflect the vertical arrangement of axon terminals of chandelier cells that synapse at the axon initial segment of layer 3 pyramidal neurons in DLPFC and are thought to modulate excitatory output from pyramidal neurons.

Investigators have also examined parvalbumin (PV) expression, a calcium-binding protein present in subpopulations of interneurons. Several studies found that PV-immunoreactive (IR) neurons were reduced in DLPFC in schizophrenia (29) whereas another study found no difference (30). Reduced PV-IR varicosities have also been reported in layer III of DLPFC (31), but although PV mRNA was also reduced, this reduction was per neuron rather than an overall reduction of PV mRNA-containing neurons (32). In summary, although total interneuron numbers do not seem to be altered, deficits in GABAergic neuron subpopulations are evident in schizophrenia.

Evidence of Progressive Neuropathological Changes

Cross-sectional structural neuroimaging studies have demonstrated consistent brain abnormalities in schizophrenia. These include enlarged lateral and third ventricles and reduced cortical gray matter volume in whole cortex and in cortical subregions, especially prefrontal and temporal areas (for review, see Reference 33). Evidence for modest but significant volume reduction in hippocampus

GABA:

gamma-amino butyric acid

GAD: glutamic acid decarboxylase

GAT-1: GABA membrane transporter

PV-IR:

parvalbumin-immunoreactive

has also been established (34). The finding of reduced cortical gray matter even in the first episode of psychosis (35) suggests that the loss of gray matter at least in part predates the onset of clinical symptomatology. Because cross-sectional studies cannot demonstrate whether these changes incorporate a progressive component, recent studies have applied longitudinal neuroimaging strategies.

Interestingly, progressive loss of gray matter has been identified in several cortical and subcortical regions in prodromal patients who later developed psychosis (36). In childhood-onset schizophrenia, excess cortical gray matter loss compared to normal controls was observed in frontal, temporal, and parietal cortices (37, 38). Likewise, in new-onset schizophrenia, progressive volume loss has been reported globally and in multiple cortical subregions (39, 40). These data suggest that the onset of schizophrenia is associated with a progressive loss of cortical gray matter and provide *in vivo* support for the hypothesis that there may be active loss of neuropil and synaptic elements in the early stages of psychosis (41).

One challenge in understanding the basis of the progressive neurostructural changes relates to the potential confounding effects of antipsychotic treatment. A recent two-year longitudinal study of first-episode schizophrenia found that only patients randomized to haloperidol experienced significant cortical gray matter loss, whereas patients who received olanzapine had no gray matter loss (42). Although this study could not distinguish underlying pathophysiology from medication effects, it is clear that antipsychotic medications can influence longitudinal neuroimaging data. A recent post mortem analysis of monkeys treated chronically with haloperidol, olanzapine, or placebo supports the conclusion that antipsychotics may contribute to gray matter loss (43). A longitudinal neuroimaging study of antipsychotic- and placebo-treated monkeys would help disentangle the relative contributions of medications and pathophysiology.

Genetic Associations

A recent meta-analysis of twin studies demonstrated that the genetic contribution to the etiology of schizophrenia is upward of 80% (44). A handful of genes are now beginning to emerge as likely to be implicated in schizophrenia, including *neuregulin-1 (NRG-1)*, *Disrupted-in-schizophrenia-1 (DISC1)*, *Regulator of G-protein signaling 4 (RGS-4)*, *Catechol-O-methyl-transferase (COMT)*, and *Dysbindin (DTNBP1)* (45). These associations have been verified in multiple cohorts, and each also has at least reasonable biological plausibility (for review, see Reference 1). For example, one elegant study (46) showed that *DISC1* is involved in critical aspects of normal microtubular dynamics and that loss of normal *DISC1* function recapitulates several aspects of the neuropathology of schizophrenia, including stunted neurite outgrowth and subtle migration abnormalities. It is important to note that individual genes, rather than being causative, appear to confer risk of developing the disorder. The current iteration of the neurodevelopmental hypothesis suggests that the etiology of schizophrenia involves a complex interplay among risk genes and protective genes in the setting of particular environmental factors during early development. These environmental factors modify the genetic risk, and gene-environment interactions ultimately determine whether a given individual will develop psychosis (1). As larger populations are examined and more sophisticated experimental approaches are undertaken, some of the current list of promising genes may not stand the test of replication, and new genes of risk are likely to be identified.

ANTIPSYCHOTIC TREATMENTS

Typical Antipsychotic Drugs and Their Limitations

The era of pharmacological treatment for schizophrenia began with the discovery of the antipsychotic properties of chlorpromazine

in 1952, and since then other typical (first-generation) antipsychotic drugs (APDs) such as haloperidol and perphenazine have been developed. All were based on the hypothesis that schizophrenia reflected a disorder of striatal hyperdopaminergia, with the D₂ receptor most strongly associated with antipsychotic response (47). Although typical APDs are often effective for treating positive psychotic symptoms, up to two thirds of patients remain symptomatic and are labeled either treatment-refractory or partially responsive (48). In addition, typical APDs have little impact on negative symptoms or cognitive impairments, which are closely associated with functional outcome in schizophrenia (49). D₂ antagonists also produce a variety of side effects, including acute extrapyramidal side effects (EPS) and hyperprolactinemia as well as tardive dyskinesia associated with long-term exposure (50). These side effects may reduce medication compliance, which in turn leads to psychotic relapse and rehospitalization.

Pharmacological Basis of Atypical Antipsychotics

The reintroduction of clozapine in 1990 represented a breakthrough in the pharmacotherapy of schizophrenia. Clozapine was found superior to typical APDs in treatment-resistant schizophrenia (51), although its potential has never been fully realized because of the elevated risk of agranulocytosis. Other atypical (second-generation) antipsychotic drugs, including risperidone, olanzapine, quetiapine, and ziprasidone, have since been introduced in efforts to match the therapeutic benefits of clozapine without the associated risk of blood dyscrasias. Although the efficacy of clozapine in treatment-resistant patients is still unique, the newer atypical agents have a better overall safety profile, and they also produce fewer neurological side effects (reduced EPS and tardive dyskinesia) and appear to offer some advantages in cognition, relapse prevention, functional capacity, and quality of life

compared with typical APDs (for review, see Reference 52). Accordingly, the newer atypical APDs have, in most settings, become first-line agents for acute and maintenance therapy (53).

Although there is debate as to what constitutes atypicality, one defining feature of this class of agents is a wider separation between the dose that results in an antipsychotic effect and the dose that increases the risk of EPS. To date, two major theories have been proposed to account for an atypical profile: (a) The high 5-HT_{2A} receptor affinity of many atypical APDs is thought to mitigate EPS side effects associated with D₂ antagonism (48), and (b) lower mean levels of D₂ receptor occupancy (<80%) are associated with therapeutic doses of atypical APDs (55). Although both of these theories offer insight into the potential mechanisms of action of antipsychotic medications, neither fully accounts for the unique efficacy of clozapine.

The wide range of other receptor-binding activities shown by atypicals, including dopamine (D₁, D₃, D₄), serotonin (5-HT_{1A}, 5-HT_{2C}, 5-HT₆, 5-HT₇), muscarinic cholinergic, noradrenergic (α_1 , α_2), and histamine families, suggests that other receptor systems also contribute to the activity of these drugs (see **Table 1**; for review, see Reference 56). In addition, *in vitro* and *in vivo* evidence suggests that atypical APDs have neuroprotective effects, including production of neurotrophic factors (57), prevention of glutamate excitotoxicity, oxidative stress and apoptosis (58), and enhancing neurogenesis and connectivity (59), which could also contribute to the antipsychotic mechanism of action.

Revised Dopamine Hypothesis of Schizophrenia and Dopamine Partial Agonism

The original dopamine hypothesis, which posited that schizophrenia is associated with subcortical hyperactivity at the D₂ receptor, has been validated using positron emission

APDs: antipsychotic drugs

EPS: extrapyramidal side effects

Table 1 Relative neurotransmitter receptor affinities for antipsychotics at therapeutic doses (adapted from Reference 52)

Receptor	Haloperidol	Perphenazine	Clozapine	Risperidone	Olanzapine	Quetiapine	Ziprasidone	Aripiprazole
D ₁	+		+	+	++	-	+	+
D ₂	+++++	+++++	++	+++++	+++	+	+++	++++
D ₃	+++		+	++	+	-	++	++++
D ₄	+++	+	++	+++	++	-	++	++
5-HT _{1A}	-		+	-	-	-	+++	+++
5-HT _{1D}	-		-	+	-	-	+++	
5-HT _{2A}	+	+++	+++	+++	+++	+	+++	++
5-HT _{2C}	-		++	++	++	-	+++	++
5-HT ₆	-		++	-	++	-	+	+
5-HT ₇	-		++	+++	-	-	+++	++
α ₁	+++	++	+++	+++	++	+++	++	+
α ₂	-	-	+	++	+	-	-	-
H ₁	-		+++	+	+++	++	+	+
M ₁	-	-	+++	-	+++	+	-	-
DA Transporter			++		++			
NA Transporter			+		++		++	
5-HT Transporter							++	

- = minimal to none; + = low; ++ = moderate; +++ = high; ++++ = marked

tomography (PET) (60). This hypothesis has also been substantially updated. Imaging studies point to a dopaminergic imbalance involving a primary mesocortical hypodopaminergic state associated with hypofunctioning glutamate signaling, which results in hypostimulation of prefrontal D₁ receptors (61). Reduced D₁ function may lead to negative and cognitive symptoms, and a later-developed episodic hyperactivity of the mesolimbic dopamine system in turn leads to hyperstimulation of postsynaptic D₂ receptors and emergence of positive symptoms (4).

The use of partial dopamine agonists is a novel strategy to normalize dopaminergic dysregulation without the adverse effects of full D₂ antagonists. This class of compounds has lower intrinsic activity at D₂ receptors than full agonists have, allowing them to act as either an agonist or antagonist depending on the synaptic dopamine levels (62). In schizophrenia, an effective partial D₂ agonist is thought to act as a functional antagonist in the mesolimbic dopamine pathway to control positive symptoms and as a functional agonist in the mesocortical pathway to improve negative and cognitive symptoms. In addition, it maintains dopaminergic tone in the nigrostriatal and tuberoinfundibular pathways, avoiding the EPS and hyperprolactinemia associated with complete D₂ antagonism. Thus, partial D₂ agonist activity could stabilize the dopamine system in different areas of the schizophrenic brain (62).

Aripiprazole is the first partial dopamine agonist approved for use in treating schizophrenia (63). It has a very high affinity for D₂ and D₃ receptors (Table 1) and acts on both postsynaptic D₂ receptors and presynaptic autoreceptors. In addition, it displays partial 5-HT_{1A} agonism and 5-HT_{2A} antagonism, which could imply efficacy in anxiety, mood disturbances, cognitive deficit, and negative symptoms. PET studies in healthy volunteers indicate that although the

agent occupies up to 90% of striatal D₂-like dopamine receptors at clinical doses, it does not cause EPS. This finding suggests that its inherent agonism may provide a mechanism that protects against excessive blockade of the D₂ system (64).

Comparison of Clinical Profiles of Atypical Antipsychotics

There has been considerable debate as to the clinical superiority of atypical APDs over typical APDs. Leucht et al. (65) performed a meta-analysis of the atypical APDs risperidone, olanzapine, sertindole, and quetiapine compared with placebo and typical APDs. They suggested minor efficacy advantages for olanzapine and risperidone, moderate overall tolerability advantages for quetiapine and olanzapine, and lower EPS liability (as reflected in lower antiparkinsonian medication use) for all the atypical APDs compared to haloperidol. However, in a second meta-analysis comparing atypical APDs only to low-potency typicals, Leucht et al. (66) reported no advantage on EPS liability for the atypicals (other than clozapine), although a moderate superiority in efficacy was documented for the atypicals. The studies by Leucht et al. have been generally consistent with other recent meta-analyses, with several qualifications. Geddes et al. (67) asserted that the atypicals are equally efficacious as a homogeneous group, and Davis et al. (68) concluded that some atypicals (clozapine, amisulpiride, risperidone, and olanzapine) are superior to other atypicals (sertindole, quetiapine, ziprasidone, and remoxipride).

It should be noted that these meta-analyses lack data currently available to evaluate other relevant clinical dimensions (e.g., cognition, affect, quality of life). Moreover, pharmaceutical company sponsorship of studies, limited types of assessment measures used (e.g., last-observation-carried-forward analyses), and relatively short durations of trials could limit the generalizability of the results of previous efficacy studies for atypical APDs.

NMDA: N-methyl-D-aspartic acid

AMPA: alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

Primary Outcomes of the CATIE Schizophrenia Trial

The Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study sponsored by the National Institute of Mental Health was developed to determine whether the overwhelming use of atypical APDs represents a rational and appropriate approach to treating schizophrenia (69). CATIE was the largest, longest, and most comprehensive independent trial ever performed to examine existing therapies for schizophrenia. This double-blind randomized study compared the effectiveness of the atypical APDs olanzapine, quetiapine, risperidone, and ziprasidone, and one typical APD, perphenazine, for up to 18 months in 1493 patients with chronic schizophrenia (70). The study demonstrated that overall, all of the medications were comparably effective. The mean rate of all-cause discontinuation (i.e., discontinuation due to poor efficacy, side effects, or other reasons) was 74% prior to 18 months; the individual discontinuation rates were 64% for olanzapine, 74% for risperidone, 75% for perphenazine, 79% for ziprasidone, and 82% for quetiapine. Olanzapine had the lowest rate of all-cause discontinuation and also the lowest rate of discontinuation due to lack of efficacy. However, olanzapine was also associated with greater weight gain and metabolic side effects than were other medications. Somewhat surprisingly, perphenazine was similar in efficacy and tolerability to the other atypical APDs, suggesting that typical APDs remain a viable treatment option in chronic schizophrenia. Future reports from the CATIE study will address questions regarding the cost-effectiveness of the drugs, their effects on cognitive functioning, rates of recovery, the effectiveness of clozapine for patients with persistent symptoms, and the reversibility of drug-induced side effects (e.g., weight gain). Although the contribution of antipsychotics to longitudinal brain changes also remains an important area of investigation, the CATIE study could not include a neuroimaging component owing to funding constraints.

Novel Pharmacotherapeutic Approaches

In the United States, several novel antipsychotic compounds, including asenapine, bifeprunox, iloperidone, paliperidone, and ocapiperidone, are currently in phase II or III FDA clinical trials. Asenapine, iloperidone, paliperidone, and ocapiperidone have serotonin-dopamine (5-HT_{2A/D2}) antagonist properties; bifeprunox is a partial dopamine agonist/antagonist, as well as 5-HT_{1A} agonist.

With the emerging evidence for glutamatergic dysregulation in schizophrenia, a number of agents with direct or indirect activity on the glutamate system are being investigated, especially for their potential impact on cognitive and negative symptoms. Glutamate-based agents in various stages of development include agonists at the glycine site of the NMDA receptor, glycine reuptake inhibitors, glutamate release inhibitors, AMPA agonists and antagonists, and ampakines (for review, see Reference 56). The glycine site agonists appear to reduce negative symptoms and cognitive deficits in schizophrenia when used to augment antipsychotic treatment. In the case of AMPA ligands, it remains unclear whether agonists, antagonists, or partial agonists/modulators will be most successful.

It has also been suggested that the central cholinergic system is involved in the cognitive deficits observed in schizophrenia, and enhanced cholinergic activity may improve these deficits. Currently available treatments that may suit this purpose include acetylcholinesterase inhibitors (e.g., galantamine), muscarinic partial agonists (e.g., xanomeline), nicotinic agonists, and allosteric potentiators of nicotinic receptor function (for review, see Reference 71). Other potential cognitive enhancers for the treatment of schizophrenia include memantine (an NMDA receptor antagonist), modafinil (a wake-promoting agent currently used to treat narcolepsy), talnetant (a neurokinin-3 antagonist), and tolcapone (a catechol-*O*-methyltransferase

inhibitor), all of which are currently in phase II FDA clinical trials. Because the pathophysiology of schizophrenia remains largely unknown, new targets for drug development are likely to emerge as our understanding of the disorder improves.

SUMMARY POINTS

1. Synaptic dysconnectivity has emerged as a core neuropathological deficit in schizophrenia.
2. Recent data indicate that some of these deficits are progressive, at least around the onset of psychosis.
3. APDs appear to affect the progressive structural changes. Atypical APDs, but not typical APDs, exert a potential neuroprotective effect.
4. New developments in antipsychotic treatments include partial dopamine agonists and agents that target non-dopamine-based neurotransmitter systems. These offer the potential for improving dimensions of the illness, such as cognitive and negative symptoms, which are not adequately treated with currently available medications.

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