Chapter 4
Pathophysiology of Schizophrenia

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Introduction

The neurobiological basis of schizophrenia has been suspected for over a century, beginning with Kraepelin's description of *dementia praecox* [1]. Unlike other neurological disorders such as Alzheimer's disease, however, few clear-cut neuropathological observations emerged. This led to an eminent neurologist's comment that "schizophrenia is the graveyard of neuropathologists" [2]. Scientific research in this area stagnated for much of the early twentieth century as psychodynamic theories dominated our understanding of mental illness. Beginning in the 1960s, however, neurobiological approaches to schizophrenia reemerged, starting with the landmark finding of ventricular enlargement [3].

As Weinberger stated, the challenge of finding verifiable brain changes in schizophrenia no longer exists given the advent of sophisticated neuroimaging, electrophysiological, and neuropathological techniques over the past three decades which led to an improved, albeit incomplete, understanding of the pathophysiology of this illness [4]. Thus, we review the current understanding of the neurobiology of schizophrenia with a focus on the substantive body of literature largely accumulated over the past 30 years. We conclude with a summary of the prevailing theoretical models of its pathophysiology, gaps in our knowledge, and promising directions for future research (Box 4.1).

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Box 4.1 Key Facts in the Pathophysiology of Schizophrenia

- Structural brain findings:
  - Ventricular enlargement [3]
  - Subtle reductions in total gray matter volume [6]
  - Reductions in gray matter volume of the hippocampus and other medial temporal and limbic regions [7]
- Functional brain findings:
  - Decreased activation of prefrontal cortex (hypofrontality) [27]
  - Increased activation of temporal regions during hallucinations [31]
- Electrophysiological findings:
  - Diminished prepulse inhibition of startle response (PPI) [39] and diminished P50 suppression [46]
  - Decreased amplitudes of the P300 response [34] and mismatch negativity [54]
  - Abnormalities in gamma oscillations [58]
- Neuroendocrine, Oxidative, and Immunological
  - Elevated markers of oxidative stress, varying by clinical status [62]
  - Dysfunction of the hypothalamic–pituitary–adrenal axis (abnormal dexamethasone suppression) [74, 131]
  - Abnormal levels of inflammatory cytokines [68]
- Neuropathology
  - Reductions in dendritic spines and size of pyramidal neurons [98]
  - Relative preservation of total number of neurons [97]
  - The absence of gliosis and other neurodegenerative features [89, 97]
  - Reduced expression of GAD-67 in the dorsolateral prefrontal cortex [88]
- Neurochemical
  - Reduced *N*-acetyl aspartate in frontal and temporal regions [77]
  - Reduced PME (marker of membrane phospholipid synthesis) in prefrontal regions [80]
  - Elevated presynaptic dopamine function [83]

Brain Structure

Gray Matter

There are a number of well-established structural brain alterations in schizophrenia. The most consistent findings include enlargement of the third and lateral ventricles and slight reductions in total brain volume and total gray matter volume [5–7].

Additionally, regional reductions are reported consistently in the hippocampus, amygdala, parahippocampus, superior temporal gyrus, anterior cingulate, insula, and inferior and medial frontal gyri [7, 8].

Patients with first-episode psychosis also exhibit volumetric reductions in whole brain and hippocampus; enlargement in the third and lateral ventricles; and longitudinal loss of total cortical gray matter and gray matter in frontal, temporal, and parietal regions [9, 10]. Although further study is required, first-generation antipsychotic (FGA) exposure appears to correlate with enlargement of the caudate over time, while cumulative antipsychotic exposure may be associated with gray matter loss over time [11, 12].

Alterations are observed in other aspects of structural morphology. These include reductions in cortical thickness of the temporal and frontal lobes and reduced cortical surface area in multiple regions [13, 14]. Cerebral asymmetry is also reduced in both affected individuals and healthy relatives, particularly in the planum temporale which shows diminished left–right asymmetry in patients with schizophrenia compared with healthy controls [15].

Structural measures show some correlations with severity of symptoms and cognitive deficits. The most consistent finding is the association between gray matter reductions of the superior temporal gyrus and positive symptom severity, specifically hallucinations [16]. Hippocampal volume reduction is correlated with greater severity of positive and negative symptoms and poorer social function [17]. Prefrontal alterations are associated with impaired executive function, while temporal and hippocampal structural abnormalities correlate with deficits in performance speed, working memory, and abstraction [18].

High-risk individuals (variously defined as individuals with prodromal symptoms or a family history of schizophrenia) also exhibit reduced volume in structures such as the insula, superior temporal gyrus, and cingulate [19, 20]. Conversion to psychosis among high-risk individuals is associated with relative gray matter deficits in frontal, temporal, and parahippocampal regions, although this finding is not consistent [20, 21]. Nonpsychotic relatives of individuals with schizophrenia also demonstrate volumetric reductions in the anterior parahippocampus and hippocampus and enlargement of the third ventricle when compared with healthy controls [22, 23].

White Matter

White matter changes are documented in schizophrenia through use of diffusion tensor imaging (DTI), a form of magnetic resonance imaging (MRI) that evaluates its structure by measuring characteristics of water diffusion in the brain. DTI studies in schizophrenia have identified numerous regions with decreased fractional anisotropy (FA), a measure that reflects axonal diameter and myelination in white matter [24]. Meta-analyses of DTI studies in schizophrenia report FA reductions of the left deep frontal lobe, right deep frontal lobe (including the right cingulum), and left deep temporal lobe [24, 25]. FA is also generally reduced in the corpus callosum, suggesting deficits in interhemispheric communication [24]. These white matter

changes were used to propose a model of schizophrenia as a syndrome of "functional disconnection," resulting from abnormalities in the connectivity between brain regions which may ultimately be relevant in understanding the cognitive deficits in this disorder.

Summary

Although structural imaging has produced a rich data set uncovering a number of consistent brain alterations, several questions merit further study. The neurodevelopmental timeline of observed alterations is not fully understood. Though there has been an increasing focus on high-risk and first-episode patients, further longitudinal data is needed to determine which brain alterations mark the conversion to psychosis. Additionally, it is unclear whether structural changes result from intrinsic disease pathology or reflect adaptations to the disease state. Continued research with healthy relatives and first-episode populations may disentangle the effects of environmental factors (e.g., antipsychotic exposure) from intrinsic disease effects on brain structure. Lastly, the current knowledge base is limited regarding the relationship between structural brain changes and long-range network connectivity. Ongoing integration of structural data with functional imaging may provide insight into these issues.

Brain Function

Functional and Molecular Imaging

Over the past several decades, functional MRI (fMRI) has been used extensively to examine brain activation in schizophrenia during specific cognitive and emotional processes (e.g., tasks of working memory, attention, and decision-making) [26]. One of the most consistent findings is diminished activation of frontal regions during cognitive tasks (i.e., "hypofrontality"), with meta-analyses of both first-episode and multiepisode patients finding reduced activation in the dorsolateral prefrontal cortex during these tasks [27–29].

Further, functional studies of social cognition and emotional processing suggest dysfunction of the amygdala and hippocampus. Individuals with schizophrenia demonstrate decreased limbic activation during tasks, but abnormally increased limbic activation when presented with fear-inducing stimuli such as pictures of angry faces [30]. Functional studies also focus on neural correlates of hallucinations and other symptoms, demonstrating that real-time auditory hallucinations correlate with increased activation of fronto-temporal regions such as Broca's area and the middle and superior temporal gyri [31]. Another area of research focuses on the

"default mode network" which is active during rest. While activity in these regions is normally suppressed during cognitive tasks, it is under-suppressed in schizophrenia, perhaps reflecting attentional and other cognitive impairments [32].

Summary

Schizophrenia is associated with abnormal limbic activation in response to emotional stimuli and frontal dysfunction during cognitive tasks. Despite its extensive research use, functional imaging is far from achieving clinical utility in diagnosis or treatment for several reasons. fMRI signals are subtle and require specialized analysis, making it difficult to detect robust signals at the level of the individual patient [33]. Lack of standardized image acquisition and analysis techniques also impedes efforts to establish the clinical utility of fMRI [33]. As with structural alterations, the pathogenesis of functional alterations is poorly understood. Two lines of research which may address these issues are multimodal studies integrating functional imaging with structural imaging, DTI, or electrophysiology and functional connectivity analyses evaluating temporal correlations in networks of brain regions [26]. These developments may ultimately yield clinically relevant biomarkers which are robust enough to identify high-risk individuals and guide treatment choices.

Neurophysiology

Neurophysiological research in schizophrenia largely focuses on event-related potentials (ERPs), which are electrophysiological responses observed in an EEG after presentation of a stimulus. ERP data is collected by applying electrodes to the scalp and recording brain electrical activity during tasks or stimuli. Electrophysiological markers are based on variations in latency, amplitude, and scalp localization of waveforms generated by various auditory stimuli. These markers differ in their anatomical substrate, their association with cognitive and clinical measures, and their putative genetic influences. Electrophysiology has several important advantages as a clinical and research tool: it is noninvasive, presents fewer technical challenges than functional and molecular imaging methods, and has a long history of use with established paradigms and analysis methods.

P300

P300 is one of the most studied electrophysiological markers. It is a large, positive voltage response evoked about 300 ms after presentation of a salient stimulus.

Its amplitude is consistently lower in individuals with schizophrenia compared with healthy controls [34]. A subset of the P300, the P3b, localizes to the inferior parietal cortex, while the other component of the P300, the P3a, localizes to frontal regions [35]. P300 abnormalities may correlate with negative symptoms, cognitive dysfunction, and gray matter reductions in temporal regions [36]. A meta-analysis of 46 studies of P300 alterations in schizophrenia found a pooled effect size of 0.85 for the amplitude of the P300 measure but did not find any impact of antipsychotic medication on this measure [37]. P300 reduction is also observable in relatives of patients with schizophrenia and in other psychiatric disorders [38].

Prepulse Inhibition of Startle

Abnormal prepulse inhibition of a startle response (PPI) is a well-established electrophysiological finding in schizophrenia. The startle response is typically measured as the amplitude of electromyographic response of the orbicularis oculi muscle when it contracts after an unexpected stimulus. PPI is the reduction in the amplitude of this wave which occurs when the startling stimulus is preceded by a weak stimulus [39]. Individuals with schizophrenia do not exhibit the same degree of reduction in the startle response as healthy controls, suggesting defects in the brain's ability to selectively filter stimuli [39]. This abnormality correlates with thought disorder and disruption in global functioning but may normalize with second-generation antipsychotic (SGA) treatment [40, 41]. Abnormal PPI is highly heritable and present in unaffected first-degree relatives [42, 43]. PPI also has a direct association with gray matter volume in the right superior parietal cortex of first-episode patients and healthy controls [44].

P50 Auditory-Evoked Potential Suppression

The P50 wave is an evoked potential which occurs 50 ms after a stimulus. When two auditory clicks are presented 500 ms apart, generating two P50 waves, the amplitude of the second wave is reduced in comparison to the first. This phenomenon is known as P50 suppression and is abnormal in patients with schizophrenia who demonstrate a smaller reduction in amplitude of the second P50 wave compared with normal controls [45, 46]. Cholinergic neurotransmitter pathways may mediate P50 suppression, as indicated by the apparent ability of nicotine to briefly normalize suppression in people with schizophrenia [47]. P50 suppression localizes to the hippocampus, is estimated to have a heritability around 68 %, and is observed in first-degree relatives of patients with schizophrenia [48–50]. Treatment with clozapine, but not other antipsychotics, may normalize P50 suppression [51].

Mismatch Negativity

Mismatch negativity (MMN) refers to an ERP component which is measured when a series of repetitive auditory stimuli are punctuated by deviant or "oddball" stimuli. MMN is believed to reflect pre-attentive sensory processing and the response of the brain to changes in consecutive stimuli [52]. It localizes to the primary and secondary auditory cortices, as well as the dorsolateral prefrontal cortices [53]. MMN abnormalities appear specific to schizophrenia among psychiatric disorders and are consistently associated with cognitive activity and the ability to function independently [54, 55].

Cortical Oscillations and Neural Synchrony

Neural oscillations allow networks of brain regions to coordinate activity essential for cognitive processes. Gamma band oscillation, which is normally in the range of 30–80 Hz, reflects coordination of neuronal activity and appears highly heritable [56, 57]. Compared to healthy controls, individuals with schizophrenia demonstrate reduced power of gamma band oscillations and are less able to modulate these oscillations in frontal regions during tests of cognitive function [58, 59]. Because cortical synchrony matures during adolescence, gamma band abnormalities may reflect a failure of normal neurodevelopment. A number of studies support a correlation between positive symptoms, particularly auditory and visual hallucinations, and changes in gamma band activity [60].

Summary

The existence of electrophysiological abnormalities in schizophrenia is well established but their clinical and research implications require further study. Electrophysiological markers hold the potential to serve as "endophenotypes" (i.e., heritable, objective disease characteristics that bridge the gap between genetic factors and clinical phenotype). These markers fulfill some of the criteria for endophenotypes as they appear to be highly heritable and present in unaffected relatives. They do not, however, consistently fulfill other endophenotype criteria such as stability over time. In addition, the clinical utility of electrophysiological markers is currently limited because of the expense of EEG equipment, the need for subjects to cooperate with complex task instructions (for some markers), and the lack of diagnostic specificity or treatment implications for most existing markers [61]. Nevertheless, electrophysiology is highly relevant for future study, as markers may correlate with elements of early information processing disrupted in schizophrenia. Electrophysiology can also be applied to the study of simple neural processes in other mammals, thus expanding the role of animal models in schizophrenia research.

Oxidative, Immunological, and Neuroendocrine Abnormalities

Schizophrenia may involve abnormalities in the oxidative stress response. Oxidative stress results from the body's inability to fully neutralize free radicals generated by normal metabolic processes [62]. This can ultimately lead to cell membrane damage and impaired neurotransmission. Markers of elevated oxidative stress are observed in schizophrenia (e.g., diminished levels of the antioxidant glutathione in the brain and cerebrospinal fluid) [63]. A meta-analysis found decreased levels of the antioxidant red blood cell superoxide dismutase across the illness course, implying it may be a trait marker for schizophrenia [62]. Other antioxidants in this study varied by patients' clinical status or stage of disease. Antioxidant deficits may affect interneuron function and cortical synchrony. For example, in a mouse model, impaired synthesis of glutathione led to reductions in high-frequency gamma oscillations [64]. Thus, oxidative stress may play a critical role in the neurodevelopmental pathways leading to schizophrenia, while enhancement of antioxidant function may represent a novel therapeutic pathway. Further investigation is needed to explore whether antioxidant abnormalities explain the link between schizophrenia and certain environmental risk factors (e.g., psychosocial stress or viral infections) [65]. Additional trials also are necessary to validate the clinical potential of antioxidant treatment, although studies using *N*-acetyl cysteine show promise in the treatment of negative symptoms (see Chap. 7) [66].

Immunological theories propose that autoimmune dysfunction or infections may contribute to the etiology of schizophrenia. Epidemiological studies observe a correlation between prenatal exposure to infections and later development of schizophrenia [67]. Studies report a number of immunological findings, including changes in the levels of cytokines (signaling molecules that coordinate the inflammatory response), elevated levels of autoantibodies, and associations between autoimmune disorders and risk for schizophrenia [68–70]. A meta-analysis found that some cytokines (such as IL-6 and TGF-β) were associated with psychotic exacerbations, while others (IL-12, TNF-α) may be trait markers for schizophrenia [68]. In addition, anti-inflammatory medications may augment antipsychotic response and improve psychotic symptoms in randomized controlled trials (see Chap. 7) [71]. These findings lend support for immunological theories of schizophrenia and fit well with known prenatal risk factors. The current literature on immunological markers is often limited by inadequate control for confounding factors such as clinical status, body mass index, and smoking. Thus, many studies were unable to determine if abnormalities represented state or trait markers [68]. Additional research is necessary to clarify the role of cytokines in the pathogenesis of schizophrenia and whether they hold potential as therapeutic targets in addition to biomarkers.

Dysfunction in the hypothalamus–pituitary–adrenal (HPA) axis may mediate interactions between stress and psychosis. The stress response appears blunted in individuals with schizophrenia, as reflected in studies showing decreased cortisol response to psychological and physical stress [72, 73]. Multiple studies also demonstrate a relatively high rate of dexamethasone non-suppression (i.e., the absence of

cortisol suppression after a dexamethasone suppression test) in chronic schizophrenia, indicating failure of the HPA negative feedback mechanism [74]. Subgroups of patients (e.g., those with primary polydipsia) have higher rates of dexamethasone resistance and HPA overactivity which may result from abnormal hippocampal regulation of the stress response (see Chap. 11) [75]. Function of the HPA system is likely preserved overall, despite some abnormal input from the limbic system. One major challenge for neuroendocrine research in schizophrenia is distinguishing adaptive responses from intrinsic disease pathophysiology. To place neuroendocrine findings in an appropriate context, future studies will need to identify where abnormalities occur in the regulatory pathway and connect observed abnormalities with clinical symptoms.

Neurotransmitter Systems

Neurochemical Imaging

Proton magnetic resonance spectroscopy (^{1}H MRS) is a noninvasive imaging method which assesses the chemical composition of brain tissue in vivo by measuring magnetic resonance signals produced by atomic nuclei within molecules [76]. This form of imaging can estimate concentrations of several biologically relevant compounds including *N*-acetyl aspartate (NAA) which is a marker of neuronal integrity; glutamate and glutamine (Glu + Gln), which correlate with glutamatergic neurotransmission; and choline metabolites (Cho) which are an indicator of cellular turnover [76]. One of the most consistent findings in this area is a reduction in NAA in frontal, temporal, and thalamic regions. This is seen in both first-episode and multiepisode patients, indicating neuronal abnormalities in these regions [77]. Another consistent finding, which was reported in a meta-analysis of studies on Glu + Gln, is a reduction in frontal glutamate and increase in glutamine [78]. Possible reasons for reduced glutamatergic function include hypo-activation of *N*-methyl-D-aspartate (NMDA) receptors and abnormal expression of glutamate transporters [78]. These hypotheses require clarification, however, perhaps through animal models.

The current MRS literature is also limited by the paucity of longitudinal studies, making it difficult to assess the relationship between neurochemical alterations and disease course [78]. Because of long scanning times, studies typically limit themselves to small samples of cooperative subjects [79]. Scanner resolution is constrained by the size and strength of spectroscopy magnets [79]. Studies also differ in their choice of MRS techniques, and many did not control for variables such as antipsychotic medication status or duration of illness [76, 78]. Future studies will need to develop and use more standardized methods. Newer forms of MRS (e.g., proton echo-planar spectroscopic imaging (PEPSI)) are able to scan multiple brain regions in a short amount of time. These advances allow for the imaging of

agitated or uncooperative subjects, enhancing the potential clinical utility of MRS. Recent studies are also using more powerful magnets which permit greater spatial and temporal resolution [79].

MRS with ^{31}P (phosphorus-31) is also used to examine cell membrane phospholipids (i.e., PME (phosphomonoester), a phospholipid precursor; and PDE (phosphodiester), a metabolite of phospholipid breakdown). PME and PDE can provide information about membrane phospholipid synthesis and turnover which in turn may reflect the condition of neuronal membranes [80]. Studies utilizing ^{31}P have reported reductions in PME in prefrontal and medial temporal regions in schizophrenia, implying reduced production of membrane phospholipids [80]. As with ^{1}H MRS, studies with ^{31}P are limited by small sample sizes, inconsistencies in imaging and analysis techniques, and differences in subject populations [79]. ^{31}P MRS, however, continues to be relevant given its unique ability to examine processes of lipid metabolism and cell membrane turnover.

Two forms of molecular imaging are used to explore neurotransmitter systems in schizophrenia: positron-emission tomography (PET) and single-photon emission-computed tomography (SPECT). In both methods, radioactive-labeled tracers are injected into the bloodstream and emitted rays are measured. PET demonstrates better spatial resolution and more sensitivity to subtle brain changes than SPECT, and presently appears to be a more powerful brain imaging technique [81]. Two meta-analyses of SPECT and PET studies found elevations in striatal dopamine synthesis capacity but found no significant difference in dopamine transporter availability [82, 83]. Additionally, prefrontal hypo-activation is correlated with increased striatal dopamine function [84]. These findings support a modified version of the "dopamine hypothesis" (to be discussed below) in schizophrenia. Altered striatal dopamine synthesis may hold potential as a biomarker for risk of psychosis, but additional research is needed to determine how it changes over the illness course and whether it is specific to schizophrenia rather than affective psychosis [82]. In addition to clarifying these issues, future studies could integrate PET and SPECT methods with electrophysiology and structural imaging to identify dysfunctional networks [85]. As with MRS, PET and SPECT research is limited by small sample sizes, differences in technical methods, and variations in subject characteristics.

Dopamine

The dopamine hypothesis has persisted as a pathophysiological theory of schizophrenia for several decades. Various lines of evidence support this theory. These include the efficacy of D2 receptor antagonists in treating the acute symptoms of psychosis, as well as the ability of amphetamines to stimulate psychosis by increasing extracellular dopamine. Initial models theorized simply that increased dopamine transmission led to psychosis, and later, that defects in mesocortical dopamine activity resulted in overactivity of the mesolimbic system [86]. Further, depletion in prefrontal dopamine was believed to disinhibit subcortical regions, resulting in

dopaminergic excess in striatal regions [87]. More recent models proposed that presynaptic dopamine dysfunction is the primary path to psychosis, in accordance with recent PET studies [82, 83]. These more recent findings point to presynaptic dopamine synthesis as a potential therapeutic focus (see Chap. 7) [83].

The ultimate place of dopaminergic dysfunction in the pathogenesis of schizophrenia is unclear with the literature increasingly implying that dopamine dysfunction is a downstream consequence of other deficits. One weakness of initial dopamine models was their relative difficulty in accounting for cognitive deficits and negative symptoms in schizophrenia. Altered D1-mediated transmission in the prefrontal areas or changes in glutamatergic neurotransmission may influence striatal dopamine systems and could underlie cognitive and negative symptoms [83, 84]. However, these theories await further confirmation.

Gamma Aminobutyric Acid

Gamma aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain and an increasing focus of attention in the pathophysiology of schizophrenia. Inhibitory control by GABA interneurons is believed to coordinate subsets of pyramidal neurons which comprise the majority of cortical neurons [56]. Thus, GABA interneurons are crucial for synchronized neural activity [56]. While the overall number of GABA interneurons is not reduced in schizophrenia, those which contain parvalbumin demonstrate reduced production and uptake of GABA [88]. In particular, levels of glutamic acid decarboxylase 67 (GAD-67), an essential enzyme for GABA synthesis, are diminished in several cortical regions in parvalbumin-containing GABA interneurons [88]. Deficiencies in GAD-67 and decreased expression of parvalbumin appear to correlate with alterations in gamma band oscillations, thus linking electrophysiological phenomena and neurotransmitter systems. Synaptic alterations in the dorsolateral prefrontal cortex may disrupt the balance of inhibitory control by GABA interneurons, leading to deficits in working memory [89]. It is not known whether the observed abnormalities in the GABA-ergic system represent primary deficits in schizophrenia or compensatory mechanisms for other deficits [56]. For example, increases in postsynaptic GABA-A receptors and reductions in presynaptic parvalbumin may compensate for reduced GABA release from chandelier neurons which serve to inhibit pyramidal neurons [90]. This viewpoint is supported by evidence from animal models showing that such alterations tend to improve GABA transmission [91].

Glutamate

Unlike dopamine, glutamate is present throughout the entire nervous system and is the main excitatory neurotransmitter in mammals [92]. The potential relevance of glutamate to the pathophysiology of schizophrenia was discovered through research

on NMDA receptor antagonists such as phencyclidine (PCP) and ketamine. NMDA receptors are normally activated through the binding of glutamate or aspartate, but synthetic NMDA antagonists bind specifically to the NMDA receptor. When administered to healthy subjects, NMDA antagonists can induce psychotic symptoms, cognitive deficits, and defects in MMN which mimic those observed in schizophrenia [93, 94]. From this and other data, it was initially proposed that schizophrenia involved diminished function or density of NMDA receptors caused by abnormalities in glutamate neurotransmission [92]. Studies on postmortem brains report reductions in the NMDA receptor density in the prefrontal cortex and hippocampus [95]. Reduction in the density of dendritic spines, which receive excitatory glutamatergic synapses, may also reflect inadequate glutamate neurotransmission and resulting defects in connectivity [96]. Subsequent research, however, suggests that glutamatergic excess may actually be a driving force in the disease process. One promising pharmacotherapeutic application is the use of metabotropic glutamate 2/3 receptor agonists, which could balance excitatory and inhibitory systems by normalizing presynaptic glutamate levels (see Chap. 7) [92].

Summary

Dopaminergic dysfunction remains a consistent finding in schizophrenia and may be due primarily to alterations in presynaptic synthesis and transmission. While the relative place of dopaminergic dysfunction in the pathogenesis of schizophrenia remains unclear, it may play an early role in neurodevelopmental processes or it may reflect downstream consequences of other abnormalities. Recent investigations focusing on glutamatergic and GABA-ergic neurotransmitter systems may generate novel therapeutic targets.

Neuropathology

Schizophrenia is historically a challenging area in neuropathology, initially yielding few definite findings. As stated earlier, it is associated with subtle reductions in total brain volume and total gray matter volume [6]. Notably, these reductions are not attributable to loss of neurons, but to reductions in the size of neuronal cell bodies and in cortical neuropil [97]. Specifically, pyramidal cell bodies are about 10 % smaller in layer three of the dorsolateral prefrontal cortex and dendritic shafts and spines are reduced, resulting in diminished dendritic arborization [98]. Dendritic spines receive excitatory synapses throughout the central nervous system and reductions in their density may underlie connectivity defects between regions [96]. In addition, reductions and altered gene expression in the microglia, support cells of the nervous system which include astrocytes and oligodendrocytes, may contribute to white matter abnormalities [99].

Another consistent finding is the lack of gliosis. This is the proliferation of glial cells in response to nervous system damage which is observed in many neurodegenerative disorders [89]. Its absence in schizophrenia suggests a neurodevelopmental rather than a neurodegenerative process at work [97]. Postmortem studies observe higher densities of cortical neurons in deep rather than superficial layers of the limbic and prefrontal regions. This indicates that there may be early failures in the migration of neuronal precursor cells from subcortical to cortical regions during gestation [100]. Neuropathological studies have a number of limitations including the effects of variable postmortem intervals, heterogeneity within the schizophrenia diagnostic spectrum, and the confounding effects of antipsychotic medication [97].

Neuroplasticity

The presence of widespread gray matter deficits and synaptic alterations without apparent neuronal loss raises the question of whether these abnormalities are remediable. Neuroplasticity refers to the ability of the brain to adapt to the environment and reorganize aspects of neuronal circuits, such as synaptic density [101]. Neuroplasticity may be abnormally reduced in schizophrenia, as suggested by studies showing diminished long-term potentiation in response to transcranial magnetic stimulation and lowered stimulus-specific plasticity in response to electrophysiological tetanic stimulation [101, 102]. Recent findings indicate that levels of brain-derived neurotrophic factor (BDNF), a protein responsible for neuronal development and synaptic plasticity, may be altered in schizophrenia [103]. BDNF may closely interact with glutamatergic, dopaminergic, and GABA-ergic neurotransmitter systems and may mediate the gray matter improvements observed following cognitive remediation [104, 105].

Models of Pathogenesis

Although various neurobiological abnormalities are now well established in the schizophrenia literature, it is important to synthesize these findings to develop models of pathogenesis. The majority of evidence supports the conceptualization of schizophrenia as a neurodevelopmental disorder. This evidence includes the onset of schizophrenia in adolescence and the presence of premorbid cognitive deficits, minor physical anomalies, and neuromotor abnormalities during childhood [106–108]. The timeline of neurodevelopmental alterations, however, remains unclear.

One model posits that the pathogenesis of schizophrenia begins pre- or perinatally, perhaps through early environmental insults or genetically mediated defects in neuronal migration [86]. As mentioned earlier, postmortem studies imply alterations in neuronal migration from subcortical to cortical regions, a process which occurs during the second trimester [100]. Studies of high-risk individuals find a

high prevalence of motor coordination issues in childhood, further supporting an early timeline of pathogenesis [108]. An exclusive focus on perinatal or prenatal abnormalities, however, does not explain why the characteristic symptoms of schizophrenia emerge in late adolescence.

Another model addresses this issue by focusing on neurodevelopmental abnormalities in late adolescence. Excessive synaptic or axonal pruning may underlie longitudinal changes reported in young high-risk and first-episode patients. These include gray matter reductions and reductions in NAA observed in MRI studies [10, 77]. Findings from neuropathology, such as reductions in dendritic arborization and synaptic density, are also consistent with this model [98].

Schizophrenia does not appear to be a neurodegenerative disorder, as demonstrated by lack of gliosis or other neurodegenerative signs in postmortem studies [97]. There still remains a question of whether a subgroup of individuals experience progressive deterioration. The first few years of illness in particular are marked by a decline in function and some individuals recover incompletely or take longer to recover after each successive psychotic episode [109].

Diminished neuroplasticity may fit well with existing neurodevelopmental models of pathogenesis. Dysfunction in GABA-ergic systems could reduce plasticity in cortical areas, while changes in NMDA receptor-mediated neurotransmission may disrupt long-term potentiation, a crucial process for learning and memory [101, 110]. Altered neuroplasticity may serve as a biological mechanism for environmentally mediated longitudinal changes in schizophrenia.

Summary

Although divergent in their timelines, these models could be integrated with the current understanding of neurotransmitter systems to create a "three-hit" model that longitudinally describes the pathogenesis of schizophrenia [111]. Early genetic or environmental "hits" may disturb glutamate-mediated processes of neuronal migration and survival during gestation. This could lead to cell death and loss of glutamatergic neurons, manifesting as premorbid cognitive and neuromotor deficits. In adolescence, hypofunction of NMDA receptors, whose sustained activity is necessary for synaptic survival, could result in excessive synaptic pruning and reduced neuroplasticity. Diminished neuronal connectivity could worsen cognitive and social function during this time period. Additionally, glutamatergic dysfunction could disrupt phasic and tonic dopamine release and upregulate subcortical dopaminergic neurons, ultimately precipitating the onset of psychotic symptoms [111, 112]. During the years following the first episode of psychosis, glutamatergic dysfunction could lead to increased phasic dopamine release during psychotic episodes, which could then *increase* glutamate release, resulting in oxidative stress and neuronal damage. Neurotoxicity caused by glutamatergic excess could then account for disease progression during the first years of illness. In addition, deficits in neuroplasticity may help explain chronic cognitive impairments. This model draws support from genetic

studies showing association of schizophrenia with glutamate- and neuroplasticity-related genes (see Chap. 5). Further research using animal models and longitudinal brain imaging is likely to refine neurodevelopmental theories of pathogenesis.

Conclusion

Knowledge Gaps and Future Steps

As this review indicates, many facts about the pathophysiology of schizophrenia are being discovered at a rapid pace. This progress, however, is not matched by their translation to advances in treatment of schizophrenia. In general, treatments for schizophrenia were largely discovered by astute, yet serendipitous, observations. Thus far, few treatments are based on knowledge of pathophysiology (Fig. 4.1). Yet, some trends may be delineated.

Toward neuroscience-based classification of psychoses. While successive revisions of the Diagnostic and Statistical Manual of Mental Illness (DSM) serve to improve the reliability and clinical utility of a symptom-based classification of psychiatric disorders, there remains a critical lack of *validity* in the current categorization of psychoses. The century-old distinction between schizophrenia and affective psychoses remains in the DSM-5 despite the considerable overlap in symptoms, cognition, neurobiology, genetics, treatment response, and outcome characteristics across these disorders [113–117]. Emerging new data on pathophysiology of the psychotic disorders spectrum can eventually help move the field

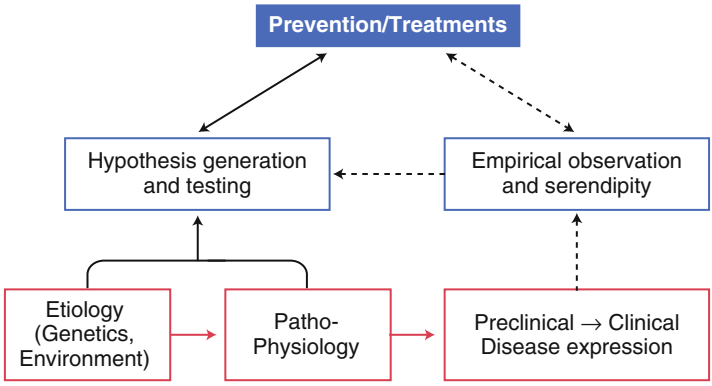

Fig. 4.1 Pathways to treatment discovery. Treatments for schizophrenia have traditionally been developed by clinical observation and serendipity (*dashed lines*) but need to be increasingly informed by etiopathological observations and hypothesis testing (*solid lines*) (Adapted from Tandon et al. [132])

toward a neuroscience-informed nosology. Such progress is only possible if disease dimensions of what we now call schizophrenia, spanning molecular to behavioral domains across the psychosis spectrum, are deconstructed [118, 119]. The cross-cutting pathophysiological dimensions can then be used to identify new, perhaps more valid categories of the psychosis spectrum. Relevant to the pursuit of this goal are the NIMH Research Domain Criteria (R-DoC) which seek to map translationally relevant behavioral phenotypes to biomarkers in physiological and molecular domains [120]. The introduction of dimensional measures which cut across diagnoses in DSM-5 is a good step in this direction. It is critical for the field, however, to utilize such measures in large populations, agnostic to DSM diagnoses, and examine their relationships to biology [121].

Toward diagnostic and predictive biomarkers. Despite accumulating data on several altered biological processes, few diagnostic or predictive biomarkers exist for psychiatric disorders, other than those to rule out "other" medical disorders (e.g., testing to rule out hypothyroidism). Even "proxy" biomarkers such as cognitive deficits, which are widely prevalent, pervasive across multiple domains, persistent, map onto biology, and may predict outcome in schizophrenia, are not yet incorporated into standard psychiatric assessments [122]. At least in part, this impasse stems from a continued reliance on symptom-based categories as the gold standard for developing diagnostic tests [121, 123]. In striking contrast, there is unprecedented progress in imaging, genomics, and computational abilities which could deliver clinically useful tests in the near future. Given the lack of validity of symptom-based classifications in psychiatric disorders as discussed earlier, simple comparisons of imaging or other biomarker data between diseases and between disease and healthy subjects are unlikely to yield much. In contrast, examining etiological differences across biologically defined subgroups of disease may be much more valuable. For example, using data-driven approaches on phenotypically diverse subjects, it may be possible to derive subgroups characterized by distinctive biological features, quantifiable through neuroimaging and electrophysiology. These subgroups could then be compared in etiology and pathophysiology, ultimately generating targeted therapeutic approaches.

Multimodal approaches and automated machine learning algorithms (e.g., support vector machines (SVMs) which utilize multivariate pattern recognition methods) can robustly distinguish early course of schizophrenia and its progression [124]. Such classification approaches in the future may also incorporate information from other biomarker domains, including electrophysiology, metabolomic, proteomic, genomic, and gene expression profiles. Cellular markers derived from induced pluripotent stem cells are another exciting direction in the not-too-distant future [125].

Toward theory-driven therapeutic interventions. Stratifying psychosis spectrum disorders into neurobiologically separable entities will help develop more targeted interventions [119]. Molecular stratification of disease is already standard practice in the rest of medicine. Thus, the presence of "actionable" mutations such as BRCA1 gene in breast cancer can lead to prevention efforts [126]. In another example,

specific treatments can lead to substantial clinical benefit for cystic fibrosis for individuals with CFTR mutations [127]. Several examples of such theory-driven interventions in schizophrenia may now be mentioned. It is important to look beyond simply modulating the dopamine receptor. Recent thinking on the role of glutamatergic and GABA pathways discussed earlier suggests trials of several novel pharmacological agents which may impact these systems (see Chap. 7) [128]. One needs to look beyond neurotransmitter systems as well to treatments which address increased oxidative stress, such as *N*-acetyl cysteine [66]. Anti-inflammatory agents such as aspirin may be of value in treating psychosis [129]. Improvement in cognitive deficits in schizophrenia patients positive for herpes simplex antibody titers is reported with the antiviral agent valacyclovir [130]. Treatments that directly upregulate BDNF or improve neural plasticity, such as computer-based cognitive enhancement therapies, also hold promise as novel therapeutic approaches [105].

In conclusion, our understanding of the pathophysiology of schizophrenia has made remarkable progress, but much work remains to translate these observations into real differences for managing and potentially preventing this devastating illness. Future researchers will benefit from both a creative application of cutting-edge neuroscience knowledge and having an open mind to look beyond current conceptual models of this disease.

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