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Biological Mechanisms Underlying Risk for Emerging Psychopathology in Youth

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Abstract

For many years it was believed that the fundamental properties of the brain were sculpted mainly *in utero* and in the early postnatal years, but data from a range of disciplines have forced a reassessment of this notion. The transition from childhood to adulthood, especially the critical period of adolescence, involves a profound reorganization of both architecture and functionality of large-scale networks, which is likely to constitute a vulnerability for emerging psychopathologies and opportunities for intervention.

For youth (15–24 yr) and, in particular, adolescents (10–19 yr), dramatic changes occur (physically and behaviorally) during this critical period of development. Although most teenagers successfully navigate the transition from dependence on a caregiver to being a self-sufficient member of society, adolescence is also a time of increasing incidence of several classes of psychiatric illness, including psychosis, mood disorders, and substance abuse. The pathophysiology of these disorders is increasingly understood as arising from aberrations in the maturational changes that normally occur in the adolescent brain. This chapter reviews the neurobiological changes that occur during adolescence and discuss their possible relationship to the emergence of psychopathology.

How Do Genetic and Environmental Risk Factors Interact to Produce the Expression of Mental Disorders in Youth?

The causes of schizophrenia and related psychotic disorders are complex and heterogeneous, with a multitude of risk and protective factors being suggested (Radua et al. 2018). An extensive body of literature points to genetic and environmental risk factors and their interactions (Tandon et al. 2008; van Os et al. 2008). In reviewing this large literature, it is important to consider some key caveats. First, most of what we know for establishing causality comes from epidemiological data wherein guidelines exist about how to evaluate the

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strength of causal relationships (Hill 1965). These include the strength of association between a putative causal factor and its effect, consistency of the observations between populations and studies, specificity of the relationship (no other explanation for the relationship), temporality (cause precedes the effect), dose effect (the greater the exposure, the higher the association), the availability of a plausible mechanism (subject to what is known), and laboratory or experimental data showing the causal effect (e.g., animal models). These strict criteria (including well-known causal associations such as between cigarette smoking and cancer) are rarely met *in toto* in medicine, and even less so for complex, multidetermined conditions such as schizophrenia. They offer, however, a framework with which to evaluate the emerging literature on etiology of this illness.

Second, one needs to make the distinction between risk indicators and risk factors. In a recent overarching study involving 55 systematic reviews and meta-analyses of 683 individual studies and 170 risk or protective factors implicated in psychotic disorders, Radua et al. (2018) concluded that only prior ultra-high risk (UHR) state and being African-Caribbean in England emerged as convincing risk factors. However, premorbid antecedents such as the UHR state (a risk indicator) are not the same as actual risk factors (e.g., genetic factors, trauma, or substance abuse) which cause these antecedents in the first place.

Third, causal factors rarely work in isolation. For example, while ethnic minority status is likely to represent a true risk factor, several factors (e.g., social defeat, social isolation, substance abuse, and discrimination in health care) may all contribute interactively. Finally, a distinction needs to be made between cause (etiology) and mechanism (pathophysiology). Thus, while discussing causal factors, we do not delve into pathways of pathogenesis (e.g., inflammation, oxidative stress, alterations in brain circuitries, or neurochemistry).

Genetic Factors

Family studies have shown that biological relatives of schizophrenia patients are at higher risk for the disorder than the general population, proportional to the proximity of the relationship and number of affected relatives. While a familial relationship alone is not sufficient to establish the genetic contributions to these disorders, it incontrovertibly plays a major role in modulating risk for schizophrenia, often termed "vertical" transmission. Twin studies allow estimation of the etiologic variance contributed by shared genetic factors and environmental factors. Concordance of schizophrenia in monozygotic (MZ) twins (who share 100% of the genes) is about 40–50% whereas in dizygotic (DZ) twins the rate is around 15%. This suggests that even when genes are fully or largely shared, environmental factors play a major role. Schizophrenia is highly heritable: a meta-analysis of 12 twin studies showed, for example, an MZ/DZ ratio of 0.92/0.52, and heritability of 81% (Sullivan et al. 2003). Shared environmental effects were also significant, but smaller. Together, these

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findings, along with current estimates that less than one-third of schizophrenia risk arises from the sum of risks contributed by known gene variants, have led to a search for "missing heritability." Clearly, there is a large void in understanding the basic etiological processes of schizophrenia and related psychotic disorders.

It is worth noting that MZ twins also share their environment more than DZ twins. Adoption studies address this by examining children of schizophrenia probands who were adopted at birth by families with no history of schizophrenia, compared to children of nonschizophrenia probands who were adopted away at birth. Several adoption studies have shown that children of parents with schizophrenia have substantially increased risk for the disorder, as shown by significantly more schizophrenia in the adopted-away offspring of schizophrenia probands.

An important milestone in psychiatric genetics is the concept of endophenotypes. As proposed by Gottesman and colleagues (Gottesman and Gould 2003; Gould and Gottesman 2006; Hasler et al. 2006; Lenzenweger 2013), endophenotypes are stable, heritable, quantitative trait-like abnormalities that co-occur with psychiatric illnesses at higher frequencies in first-degree biological relatives than they do in the general population. Gottesman and Gould also proposed that the identification of endophenotypes would aid the search for underlying susceptibility genes for the disorder in question. Several endophenotypes have been proposed over the last two decades (Braff et al. 2008), including cognitive deficits and brain volume abnormalities (Prasad and Keshavan 2007; Stone and Seidman 2016).

Traditional approaches for identifying implicated genes have included linkage analysis and association studies. *Linkage analysis* seeks to investigate the loci *where* the risk genes may be located on *regions* of chromosomes that tend to travel together within the families due to recombination events during meiosis I of the germ cells. Linkage analysis is performed on affected sibling pairs, other relatives, small nuclear families, or larger pedigrees (Glatt et al. 2007). Several chromosomal regions such as 1, 2q, 5q, 3q, 4q, 5q, 6p, 6q, 8p, 10p, 13q, 15q, and 22q (p refers to the short arm, and q refers to the long arm of chromosomes) have been linked to schizophrenia risk (Levinson 2003; Tsuang et al. 2011). In contrast to linkage studies, *genetic association studies* inform about *what* genetic variations may underlie risk for neuropsychiatric disorders. *Functional candidate genes* may be selected based on *a priori* knowledge of a gene's biological function that may impact the trait or disease in question. An example is the gene which codes for the dopamine receptors (*DRD3*). Genome wide association studies (GWAS) employ a case-control design which tests tagged single nucleotide polymorphisms (SNPs) from all regions of the human genome for association with a disorder. It involves comparing the number of common variants (i.e., typically variants that occur in $\geq 5\%$ of the population) among those with versus those without the disorder, and making the appropriate adjustment for the large number of statistical tests performed. GWAS

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studies have strongly pointed to the human leukocyte antigen (HLA) locus, suggesting dysregulation of the immune system as a possible factor in schizophrenia etiology. *DNA sequencing* refers to determining the precise order of nucleotides in the genome or in a particular gene of interest. Whole genome sequencing attempts to sequence the entire genome, whereas exome sequencing focuses on protein-coding sequences. DNA sequencing studies have identified several genes that affect immune mechanisms, synaptic function, voltage-gated calcium ion channels, and synaptic plasticity, essential to learning and memory (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014).

Environmental Risk Factors

As noted earlier, genetic factors do not explain all of the variance associated with the onset of schizophrenia. Even among MZ twins, who share 100% of the genes, the risk for schizophrenia is about 40–50%. This suggests that a sizable portion of the etiological variance is not explained by genetic factors, and that schizophrenia is the result of an interaction between multiple genetic and environmental factors. There are several challenges in examining environmental factors. The number of known associated environmental factors has been increasing, thus widening the analytical space; environmental factors may also interact with each other which further complicates the analyses. A series of environmental factors associated with schizophrenia are given in Table 8.1.

Table 8.1 Environmental factors that are implicated in the risk for schizophrenia. Herpes simplex virus, type 2 (HSV2), catechol *O*-methyl transferase (COMT), alpha serine/threonine-protein kinase gene (AKT1).

Environmental Factors	Associated Risk	Caveats	Key References
Seasonality of birth	Winter birth (ca. 5–8%)	Highly replicated finding with unclear mechanisms	Torrey et al. (1997)
Perinatal complications	Hypoxia	Perinatal complications interact with each other, but are not always present	Geddes and Lawrie (1995)
Maternal infections	First and second trimester infections	Prenatal exposure to influenza, toxoplasmosis, and HSV-2 increase risk	Brown (2006)
Postnatal infection	Serious infections that require hospitalization	May increase risk independently as well as through interaction with autoimmune disorders	Benros et al. (2011)
Substance use	Cannabis	Adolescent exposure is associated with risk for schizophrenia; interaction with *COMT* and *AKT1* variants are reported	Semple et al. (2005)

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Table 8.1 (continued)

Environmental Factors	Associated Risk	Caveats	Key References
Nutrition	Malnutrition (1st and 2nd trimester); reduced Vitamin D, iron, and folate levels; increased homocysteine	Dutch and Chinese famine studies support the association between nutritional deficiencies and schizophrenia risk	Valipour et al. (2014)
Autoimmune disorders	Increases risk and interacts with serious postnatal infection	May be mediated through inflammation; autoantibodies to neuronal cell surface proteins may also lead to schizophrenia symptoms	Benros et al. (2011)
Childhood trauma	Trauma varieties before age 16 yr	Moderate evidence; more studies needed	Brown (2011)
Place of birth and residence	Urban birth associated with dose-dependent risk	Consistently replicated but reasons uncertain; urbanicity effects may be mediated, e.g., by exposure to infections, drugs, stress, and trauma	Pedersen and Mortensen (2001)
Socioeconomic status	Lower status associated with higher risk	Recent studies appear to show higher risk in relation to low social status at birth	Wicks et al. (2005)
Stress	Repeated, severe stress	Prenatal stress may constitute especially high risk	Morgan and Fisher (2007)
Social group	Ethnic minorities have elevated risk	Unclear; migration status may contribute	Cantor-Graae and Selten (2005)
Immigration	Recent immigrants have elevated risk	Observed even in the second generation	Radua et al. (2018)
Social support	Inadequate support increases risk	Poor social support may interact with stress	Veling et al. (2008)
Paternal age	Dose-dependent increase relative to advanced paternal age	Highly replicated association with risk	Miller et al. (2011)

Epigenetics and Gene–Environment Interactions

Challenging traditional inheritance paradigms, epigenetics involves several mechanisms that provide regulatory information to a genome without altering its primary nucleotide sequence, thus resulting in heritable gene expression changes and nonheritable, long-term transcriptional alterations (Allis et al. 2007). Epigenetics consists of interacting molecular mechanisms—including (a) DNA methylation, (b) histone modifications, and (c) noncoding RNA

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(ncRNA)-mediated regulation of gene expression through which dynamic changes to promoters, distal regulatory regions, imprinting, and X-chromosome inactivation occur during development or cellular differentiation (Allis et al. 2007; Avner and Heard 2001; Bourc'his and Bestor 2004; Colantuoni et al. 2011; Kouzarides and Berger 2007; Meissner et al. 2008; Numata et al. 2012; Tadokoro et al. 2007). Several epigenetic abnormalities have been reported in schizophrenia and related neurodevelopmental disorders, leading to altered gene expression during development and adulthood. Environmental factors that lead to epigenetic modifications may either reduce or exacerbate the expression of molecular and behavioral phenotypes associated with schizophrenia and related disorders.

How Can We "Connect the Dots" between Genes and Pathophysiology That Emerge in Early Adolescence and Adulthood

Schizophrenia is currently viewed as a disorder of disrupted connectivity across diverse neural circuitries, resulting from diverse pathophysiological processes. Currently, it is, however, unclear which of these processes is primary to the cause of the illness, and which ones are downstream consequences of a cascading pathogenic process that may begin early in development. While it is possible that all these processes may converge onto a final pathophysiological end result, which we call "schizophrenia," it is more likely that different subgroups of the illness may have distinct pathophysiological processes, and perhaps distinct causes. This latter view is supported by the enormous genetic heterogeneity observed in psychotic disorders.

The large phenotypic heterogeneity of schizophrenia (Tsuang 1975) makes a single causative gene, or a few genes of major effect, highly unlikely. More likely scenarios include a large number of common genetic variations of small effect (polygenic inheritance), rare genes of large effect, and copy number variations (CNVs) (Rees et al. 2015).

A large-scale GWAS study showed 108 schizophrenia-associated genetic loci involving 341 protein-coding genes reaching genome-wide significance (Schizophrenia Working Group of the Psychiatric Genomics Consortium 2014). Among these genetic loci were genes related to previously implicated theories of schizophrenia pathophysiology: several glutamatergic genes and one dopaminergic gene (DRD2). More recent GWAS studies and related extensions have confirmed previously implicated genes, identified new neurofunctional targets, and provided novel biological insights into the pathophysiology of schizophrenia. In addition, another large GWAS study of 11,260 cases and 24,542 controls identified 145 loci: 50 were novel and 33 were determined to contain candidate causal genes (Pardinas et al. 2018). These clustered into six independent gene sets associated with schizophrenia, which included targets of the fragile

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X mental retardation protein (FMRP), abnormal behavior, abnormal nervous system electrophysiology, voltage-gated calcium channel complexes, abnormal long-term potentiation, and the 5-HT2C receptor complex (Pardinas et al. 2018). Table 8.2 highlights a few of the more novel or consistent targets from these and other GWAS studies and directs readers to sources for more detailed discussions.

GWAS data can also be combined with other genomics approaches to yield insights into the underlying biological mechanisms of schizophrenia. For example, by combining GWAS data with expression quantitative trait loci (eQTL) analyses, Dobbyn et al. (2018) identified a number of candidate genes

Table 8.2 Disease and representative animal models for schizophrenia. THC: delta9-tetrahydrocannabinol; NMDA: N-methyl D-aspartate; DISC1: disrupted in schizophrenia.

Disease Model	Animal Model Example	Key Reference
Disease Expression Models		
• Impaired information processing	Altered sensory gating	Geyer and Braff (1987)
	Aberrant salience	Gray (1995)
Pathophysiology Models		
• GABA		Berretta et al. (2001)
• Dopamine	Stimulant-induced sensitization	Borison and Diamond (1978)
• Altered glutamatergic neurotransmission	Abnormal prepulse inhibition and neural oscillations with NMDA antagonists	Ehrlichman et al. (2009), Geyer et al. (2001), Javitt et al. (1995)
Etiology Models		
• Genetic	DISC1 mutant mice with working memory deficits; 22q deletions in mice	Koike et al. (2006), Paylor et al. (2001)
• Infection/ inflammation	Maternal immune activation model	Nyffeler et al. (2006)
• Peri/neonatal lesions	Methylazoxymethanol acetate; neonatal ventral hippocampal lesions	Lavin et al. (2005), Lipska et al. (1992)
• Nutrition	Dietary omega-3 fatty acid deficiency effects on adolescent behavior and dopamine availability	Bondi et al. (2014)
• Cannabis	THC-induced sensitization of amphetamine motor effects in mice	Gorriti et al. (1999)
• Social stress	Social defeat effects on behavior in Disc1 mutant mice	Haque et al. (2012)

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for which genetic variation for expression colocalizes with genetic variation for schizophrenia risk, including *IREB2* and *STAT6* among others. This suggests that the implicated genes may play a causal role in schizophrenia. Gusev et al. (2018) integrated schizophrenia GWAS data with expression data from brain, blood, and adipose tissues in a transcriptome-wide association study (TWAS) to identify multiple novel gene targets implicated in schizophrenia, such as *MAPK3*. They found that total brain expression of *MAPK3* was associated with schizophrenia. Since *MAPK3* induced neurodevelopmental changes in zebra fish (Pardinas et al. 2018), this makes it an attractive target for further investigation. In another fascinating study using a combination of GWAS analyses and single-cell RNA sequencing, Skene et al. (2018) found that the common genetic findings for schizophrenia mapped most consistently "to just 4 of 24 main brain cell types: medium spiny neurons, pyramidal cells in hippocampal CA1, pyramidal cells in the somatosensory cortex, and cortical interneurons," suggesting that these discrete cell types are central to the etiology of schizophrenia.

Other recent developments suggest that several *de novo* mutations may also contribute to schizophrenia risk. *De novo* mutations can arise from mutations occurring in the germ cell for the first time in one of the parents. Alternatively, such mutations can occur in the fertilized egg during embryogenesis. It is too early to comment on what proportion of schizophrenia patients carry *de novo* mutations compared to the mutations transmitted by the parents. Overall, such emerging data could partly address "missing heritability."

One series of observations has generated particular attention, connecting the dots with previous theories and observations. First, based on the typical onset of schizophrenia during adolescence, Feinberg (1982) initially suggested aberrant peri-adolescent pruning of synapses (too much pruning, too little pruning, or pruning of the wrong synapses) to underlie the pathogenesis of schizophrenia. We (Keshavan et al. 1994) subsequently suggested an exaggerated pruning of synapses in this illness. While there is no direct evidence of excessive pruning, there are several compelling observations which indirectly support this view, such as decreased dendritic spine density in postmortem brains of schizophrenia patients (Glantz and Lewis 2000) compared to healthy subjects and individuals with major depressive disorder. As mentioned earlier, GWAS studies have replicated the association of the HLA region in relation to risk for schizophrenia. Since the HLA region is highly complex and gene dense, further studies by Sekar et al. (2016) showed that a CNV within the HLA region accounted for a portion of the risk for schizophrenia (Sekar et al. 2016). Interestingly, Beth Stevens and colleagues demonstrated that complement proteins, known components of the innate immune system, were repurposed for another role; namely, tagging the synapses for phagocytosis (Stephan et al. 2012) and, hence, in synaptic pruning processes during adolescence (Sekar et al. 2016). *Complement genes C4A* and C4B that share 99% sequence homology are part of this gene location, and individuals with higher copy numbers of

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the *C4A* long form (*C4AL*) showed a stronger association with schizophrenia. They also showed that both *C4A* and *C4B* mRNA levels were elevated in five selected regions of the brains of schizophrenia patients compared to healthy controls; approximately 40% higher expression was reported. In addition, they showed that *C4* knockout mice (i.e., without *C4* activity) had decreased synaptic pruning during brain development. A recent study using phosphorus magnetic resonance spectroscopy on schizophrenia patients and controls revealed that increasing *C4A* copy numbers was associated with greater neuropil contraction, suggesting a gene dosage effect on the possibility of increased synaptic pruning (Prasad et al. 2018). Taken together, these observations point to the possibility of identifying subgroups of psychotic disorders where a known set of risk genes work via a known pathophysiological mechanism to produce an observable illness phenotype.

A continuing challenge in understanding the causes of psychotic disorders is that many biological findings (Tamminga et al. 2014) and the implicated susceptibility genes overlap between psychotic disorders as well as between psychotic, affective, and developmental disorders (Cross-Disorder Group of the Psychiatric Genomics Consortium 2013). For this reason, the Research Domain Criteria (RDoC) approaches outlined earlier are needed to advance the field, as they permit examination across multiple disorders and can capture the continuous variation between health and disease. Recent studies such as the Bipolar and Schizophrenia Network for Intermediate Phenotypes (B-SNIP) are beginning to show that it is possible to identify biological subtypes that cut across DSM psychotic disorders; this may lead to better validation by external validators such as neuroimaging data (Pearlson et al. 2016). Transdiagnostic overlaps are seen in gene expression as well. Using transcriptomic profiling of molecular brain-based phenotypes across autism, schizophrenia, bipolar disorder, depression, and alcoholism, compared with matched controls, Gandal et al. (2018) showed shared polygenic overlap underlying a substantial proportion of cross disorder expression.

What Are the Core Modifications to Circuit Properties During the Transition from Childhood to Adulthood?

Alterations in neuroplasticity underlie several major psychiatric disorders, such as schizophrenia and autism. The typical onset of psychotic symptoms and cognitive decline during adolescence as well as observations of pronounced gray matter reductions around the onset of this illness have led to the hypothesis that schizophrenia may be related to an exaggeration of the normative synaptic pruning processes around adolescence. This view, originally proposed by Irwin Feinberg (Feinberg 1982; Keshavan et al. 1994), has received subsequent support through observations of dendritic loss and synapse reductions in postmortem studies (Glantz and Lewis 2000). Reduced synaptic redundancy

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may also be expected to lead to diminished brain plasticity, which can account for the cognitive deficits, negative symptoms, and functional disability central to this illness.

Evidence to support reduced cortical plasticity in schizophrenia comes from novel neuroimaging experiments that incorporate brain stimulation and electroencephalography. Transcranial magnetic stimulation (TMS) has been used to study *in vivo* cortical plasticity in schizophrenia. This method uses focal magnetic fields to penetrate the cranium. The resultant electric currents then depolarize the underlying cortex, thus inducing action potentials in targeted brain regions. The output of cortical activation (in this case motor cortex) is measured using electromyographic recordings of hand muscle contractions. The most common method has been to compare motor-evoked potentials (MEP) and motor thresholds (MT) before and after repetitive brain stimulation with repetitive TMS (rTMS) or transcranial direct current stimulation (tDCS), which uses direct currents to shift the resting membrane potentials of underlying neurons. These techniques use synaptic plasticity-inducing protocols that result in cortical excitability changes mirroring LTP (high-frequency rTMS and anodal tDCS) or LTD (low-frequency rTMS and cathodal tDCS).

Compared to healthy controls, LTD-like plasticity is reduced in schizophrenia, as evidenced by lack of expected low-frequency rTMS-induced changes in MEP amplitude. Schizophrenia patients also show lesser facilitation of visual- and auditory-evoked potentials in schizophrenia patients as compared to healthy controls. Evidence to support reduced cortical plasticity in schizophrenia also comes from novel neuroimaging experiments that incorporate brain stimulation and electroencephalography. Deficient cortical plasticity may link these deficits to impairments in cognitive functions, like learning and memory (Frantseva et al. 2008; Wamsley et al. 2012). Aberrant hyperplasticity may also underlie psychotic symptoms (Keshavan et al. 2015).

Genes, Environment, and Impaired Plasticity in Schizophrenia

Schizophrenia is highly heritable. In recent years, several genetic loci with small to moderate effects have been identified in GWAS. Interestingly, not only do these genes regulate glutamatergic, GABAergic, and dopaminergic transmission, they also regulate several aspects of brain development and plasticity (discussed above). One novel line of work has used human-induced pluripotent stem cells to examine alterations in neurogenesis in schizophrenia. In this method, fibroblasts are obtained from individuals and reprogrammed into pluripotent stem cells. In one such study in patients with schizophrenia, these neurons displayed a significant decrease in the number of neurites and neuronal connectivity (Brennand et al. 2011).

Environmental factors may mediate the dendritic spine reductions observed in schizophrenia. Chronic stress and prenatal stress have been correlated with reduced dendritic arborization in animal models (Markham et al. 2013), while

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environmental enrichment and learning are associated with increased dendritic arborization (O'Malley et al. 2000). In summary, plasticity in schizophrenia may be abnormal due to genetically mediated changes in NMDA receptor function, GABA-mediated inhibition, and neurogenesis. These abnormalities eventually lead to observable neuropathological abnormalities in dendritic spine density and complexity. Epigenetic factors may also mediate the impact of environmental factors on plasticity processes via noncoding RNAs (Spadaro and Bredy 2012).

How Might Animal Models Guide Our Understanding of Psychopathology and the Development of Interventions?

Animal models of schizophrenia initially focused on the dopaminergic theory of this illness based on observations that all antipsychotics work by blocking dopamine receptors. Amphetamine-induced stereotypic behaviors provide one example. Dopamine-blocking antipsychotics consistently block this behavior, and this effect directly correlates with the antipsychotic potency of the drugs in clinical settings. While they were helpful in screening new compounds for antipsychotic efficacy, most of these models, however, lacked face, construct, and predictive validity. To be valid, an animal model needs to reveal the complex presentations of the illness (face validity), resemble the neurobiological observations seen in the disease (construct validity), and replicate causal relationships between the risk factors observed in the human condition and the phenotypic manifestations (predictive validity). Few extant animals do this.

As knowledge has increased on the physiology of psychotic disorders involving brain development, glutamate and the genetic factors, so too have animal models focused on these new insights. Etiological models have been designed based on known susceptibility genes and environmental risk factors for the illness (e.g., as obstetric complications, malnutrition, inflammation, and intrauterine exposure to alcohol); see Table 8.2 for information regarding well-known animal models of schizophrenia. Each animal model recapitulates one or another proposed disease model of the illness, regardless whether it is based on known aspects of clinical expression, pathophysiology, or presumed etiology. None of the models, however, recapitulates all aspects of this heterogeneous disease entity.

What Are the Implications of Causal Understanding for the Development of Biomarkers During this Period? How Can This Inform the Development of Interventions?

What we know about the etiology of schizophrenia may already be yielding better approaches to diagnosis, treatment, and prediction. Using a combination

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of risk markers and indicators in the clinical or familial high risk for schizophrenia, it is possible to predict conversion to psychotic disorders with a moderately high level of specificity (Carrión et al. 2016; Padmanabhan et al. 2017). A small minority of schizophrenia patients have rare large effect gene mutations or CNVs; this points to the value of genetic counseling (Gershon and Alliey-Rodriguez 2013). Several studies now suggest the value of pharmacogenetic prediction of side effects (e.g., agranulocytosis with clozapine) and the efficacy of antipsychotics, which may be increasingly used in clinical practice (Zai et al. 2018).

Understanding causes will clearly help in developing innovative therapeutic targets and potentially better diagnosis and treatments for complex illnesses like schizophrenia. Using large-scale GWAS datasets from the Psychiatric Genomics Consortium, potential "druggable" genes have been identified that encode proteins which can serve as targets of currently approved medications elsewhere in medicine (e.g., glaucoma, epilepsy, and hypertension) (Lencz and Malhotra 2015). Some of the 20 genes identified are known to be implicated in neuropsychiatric disorders, such as *DRD2* (dopamine), *CACNAC1c* (calcium channels), *GRIN2A* (glutamate receptors), and *HCN1* (voltage-gated potassium channels). GWAS studies also allow the characterization of disease gene networks to elucidate drug-disease relationships. Kauppi et al. (2018) recently examined protein interactomes to map antipsychotic drug targets to gene networks related to schizophrenia. Antipsychotic drug targets overlapped with the core disease gene network modules, comprising several pathways not limited to dopamine. Other risk genes not connected to antipsychotics may be targets for novel compounds that address unmet treatment goals, such as cognitive and negative symptoms.

Continuing challenges in this field include the lack of specific or satisfactory treatments, and the paucity of actionable biomarkers or laboratory tests for early detection, outcome prediction, prevention, and differential treatment selection. We still do not understand much of the heritability of psychotic disorders; known liability genes have relatively small effect sizes, accounting only for a small proportion of the genetic risk. Most of the implicated risk genes are noncoding genes (i.e., intergenic or intronic), whose functional significance remains unclear. A large part of the "missing heritability" in schizophrenia may be caused by unknown gene–gene interactions (epistasis). The lengthy drug development process and diminishing investment by industry in psychopharmacological research are factors that contribute to delays in treatment development (Keshavan et al. 2017).

Several recent initiatives offer promise. Progress toward bridging the "missing heritability" will benefit from the PsychENCODE initiative by NIMH (Akbarian et al. 2015). This initiative seeks to characterize the function of noncoding genomic elements in cell- and tissue-specific samples in the brain in health and neuropsychiatric illness. New bioinformatics and analytical tools are helping to clarify the interactions between genomic data with

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environmental, proteomic, epigenomic, and interactomic data to better understand disease mechanisms. These insights will help identify better therapeutic targets than single gene products (Gebicke-Haerter 2016). Finally, induced pluripotent stem cells from patient populations can yield cell-based *in vitro* phenotypes to model human illness and generate novel biomarkers for diagnosis and treatment development (Haggarty et al. 2016).

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