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Neurodevelopmental Animal Models of Schizophrenia: Role in Novel Drug Discovery and Development

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Abstract

Schizophrenia is a devastating mental illness that is associated with a lifetime of disability. For patients to successfully function in society, the amelioration of disease symptoms is imperative. The recently published results of two large antipsychotic clinical trials (e.g., CATIE, CUtLASS) clearly exemplified the limitations of currently available treatment options for schizophrenia, and further highlighted the critical need for novel drug discovery and development in this field. One of the biggest challenges in schizophrenia-related drug discovery is to find an appropriate animal model of the illness so that novel hypotheses can be tested at the basic science level. A number of pharmacological, genetic, and neurodevelopmental models have been introduced; however, none of these models has been rigorously evaluated for translational relevance or to satisfy requirements of “face,” “construct” and “predictive” validity. Given the apparent polygenic nature of schizophrenia and the limited translational significance of pharmacological models, neurodevelopmental models may offer the best chance of success. The purpose of this review is to provide a general overview of the various neurodevelopmental models of schizophrenia that have been introduced to date, and to summarize their behavioral and neurochemical phenotypes that may be useful from a drug discovery and development standpoint. While it may be that, in the final analysis, no single animal model will satisfy all the requirements necessary for drug discovery purposes, several of the models may be useful for modeling various phenomenological and pathophysiological components of schizophrenia that could be targeted independently with separate molecules or multi-target drugs.

Keywords

Schizophrenia; Animal Models; Neurodevelopment; Drug Discovery

Introduction

Schizophrenia is a severe chronic brain disorder that afflicts approximately 1% of the world’s population. The heterogeneous disorder produces a lifetime of disability, and afflicts all areas of the patient’s life, ranking as one of the leading causes of disability in the United States and other developed countries (1). Symptoms of schizophrenia are commonly divided

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into three domains: positive (e.g., delusions, hallucinations, agitation); negative (e.g., depression, anhedonia); and, cognitive dysfunction (e.g., poor attention, deficits in executive function, disorders of working and spatial memory). Whereas positive and negative symptoms of schizophrenia tend to be episodic, cognitive deficits often precede the manifestation of psychosis and usually persist throughout the course of the illness (2). Furthermore, cognitive dysfunction is now recognized to be central to the functional disability of the disorder, having the most substantial impact upon the long-term outcome of the illness, yet the focus on developing therapeutic treatments for management of cognitive symptoms has been limited (3, 4).

Current Treatment and Limitations

Treatment options for patients with schizophrenia include typical (first-generation) and atypical (second-generation) antipsychotics. A range of adverse reactions (e.g., extrapyramidal side effects, sedation, anhedonia) of the first-generation antipsychotics led to the development of second-generation antipsychotics with lower D2 receptor affinity and a higher affinity for the 5-HT2A receptor. Results of industry-funded trials suggested that second-generation compounds offered significant advantages over the first-generation drugs, including better efficacy for positive and negative symptoms, enhanced cognitive effects, and improved tolerability (5). However, it is now recognized that these newer atypical agents also have a range of side effects (e.g., weight gain, endocrine disturbances, anticholinergic effects, hypotension, seizures) that can lead to morbidity, impaired quality of life and poor compliance (6, 7).

With rising cost of mental healthcare and lack of evidence of patients with improved outcomes, the NIMH in the U.S. and the NHS Health Technology Assessment R&D Office in the U.K. funded clinical trials to determine clinical superiority of second-generation antipsychotics (5). In terms of effectiveness, results from the U.S. Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) showed no difference between second-generation antipsychotics (with the exception of olanzapine) and the first-generation antipsychotic perphenazine, the primary outcome being discontinuation of the drug and switching to another antipsychotic (8). Longitudinal assessment of neurocognition and psychosocial functioning indicated no evidence of superiority in the treatment for negative and cognitive symptoms (9). Similarly, the U.K. Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS) showed no advantages of second-generation antipsychotics in terms of symptoms or quality of life, the primary outcome being the total score on the Quality of Life Scale (QLS) and Positive and Negative Syndrome Scale (PANSS) score being a secondary outcome measure (5, 10). These results suggest that no new drugs have achieved superior efficacy for psychosis, nor have they successfully addressed the cognitive and negative symptoms of the disorder (11).

Schizophrenia-Related Animal Models in Drug Discovery and Development

Despite fifty years of drug development research, discovery platforms of schizophrenia have (to date) repeatedly produced compounds with similar mechanisms of action (i.e., primarily dopamine receptor antagonism and, to a secondary extent, serotonin receptor antagonism).

This is most likely due to our relatively poor understanding of the etiology and pathophysiology of schizophrenia, as well as the lack of appropriate animal models for screening new compounds. As more knowledge of the pathophysiology of schizophrenia accrues, it is essential that appropriate animal models of the illness be developed that have better translational value. Typically, animal models of human illness are expected to meet the requirements of "face," "construct" and "predictive" validity (see reviews 12–14).

Face Validity

The degree of phenomenological similarity between the animal model and the human condition it is meant to simulate is known as "face validity." In the context of schizophrenia, challenges to face validity immediately arise due to the nature of the symptoms of the illness. For examples, some features of schizophrenia are uniquely human (e.g., language disorders) and others (hallucinations, delusions) are impossible to determine in animals. However, several symptoms known to have an important impact on illness outcome in schizophrenia can be modeled successfully in animals. These include deficits of information processing (e.g., prepulse inhibition) and several domains of cognition (e.g., attention, working memory). Other symptoms that can be modeled successfully in animals include hyperactivity, sensitivity to psychostimulants, and deficits in latent inhibition.

Construct Validity

The level of homology in pathological mechanisms (i.e., between the animal model and the human illness) that underlies disease symptoms is known as "construct validity." Demonstrating construct validity for animal models of schizophrenia is difficult since neither the underlying neurobiological substrates of the behavioral symptoms nor the cognitive deficits have been clearly established. However, several animal models exhibit some pathophysiological features that have been detected in schizophrenia (e.g., neurotransmitter deficits, enlarged ventricles, decreased hippocampal volume, decreased synaptic connections).

Predictive Validity

The most critical (but most difficult to achieve) feature of an animal model for drug discovery purposes is predictive validity. Predictive validity in drug discovery is primarily defined by the degree to which the model can be used to predict efficacy of a new therapeutic agent in humans (reviewed, 13). Typically, in drug discovery research, assessing the effects of positive-control compounds provides this type of validation. In schizophrenia, positive controls for some of the symptoms of schizophrenia (e.g., efficacy in prepulse inhibition [PPI]) impairment models, amphetamine locomotor assays, etc.) have been identified; however, this has not been the case for negative and cognitive symptoms since drugs that reliably improve these symptoms in human patients are not currently available.

As noted above, schizophrenia is a very complex and heterogeneous disease, and, therefore, efforts to model the illness in its entirety are probably unrealistic. There are, however, a number of distinct behavioral, structural and molecular components of schizophrenia that can be modeled in animals (summarized in Table 1; see also reviews 14–18). Thus, focusing on specific symptoms of the disorder or modeling changes in neurobiological substrates that

are known to be involved in schizophrenia may represent the most rational approach to establishing face and construct validity in animals models (14, 19).

Elevations in locomotor activity and increased sensitivity to dopaminergic psychostimulants are commonly described characteristics of a useful schizophrenia-related animal model. Amphetamine-induced hyperlocomotion has been especially useful in preclinical research for screening new drugs with potential antipsychotic activity (20). The model is thought to mimic the hyperdopaminergic tone and the related stereotypical behaviors often observed in schizophrenic patients (21). Some have challenged the face and construct validity of this approach, however, and argue that a focus on these characteristics was primarily inspired by antipsychotic (i.e., antidopaminergic) pharmacology and not schizophrenia symptoms per se (22). More recently, an elevation in locomotor activity due to glutamate (NMDA) antagonists (e.g., phencyclidine) is recognized as a desirable feature of a schizophrenia-related model and based on N-methyl-D-aspartate (NMDA) alterations that have been observed in postmortem schizophrenia brains. Abnormal sensory gating, deficits in habituation, impaired social behavior, deficits in latent inhibition and cognitive dysfunction are behavioral features that correspond well with schizophrenic symptomatology. Sensory gating deficits (i.e., the inability to properly filter sensory stimuli) are most commonly assessed via measurements of prepulse inhibition (reduction of startle reaction to a sensory stimulus when preceded by weaker stimulus) and the N40 potential (analogous to human P50 event- related potential). Habituation (often assessed in open field locomotor activity assays in rodents) refers to the reduction of response associated with repeated exposure to unimportant stimuli, necessary for the development of selective attention. Latent inhibition (often assessed in operant tasks, drinking behavior- and shock response-related tasks, etc.), in contrast, refers to the retardation in learning about the significance of stimuli due to nonconsequential repeated pre-exposures. Deficits in social interaction and social recognition reflect abnormalities in social cognition and are indicative of the negative sympotomatology of schizophrenia. Attention, speed of processing, visual learning and memory, working memory, and reasoning and problem solving are cognitive domains of schizophrenia that can be modeled via a variety of methods in animals (e.g., 5-choice serial reaction, attentional set-shifting, novel object recognition, water maze tasks).

A number of important structural and molecular abnormalities in the brains of schizophrenic patients has been identified through postmortem studies and, more recently, brain imaging technology. Such features in an animal model help establish construct validity, and include abnormalities in the neuronal organization of the prefrontal cortex (e.g., reduced volume, reduced neuropil, altered laminar distribution of neurons, elevated neuronal density), abnormalities in cortical neurotransmitter function (e.g., alterations in GABA neurons, decreased axons immunoreactive to an essential enzyme for the conversion of dopamine—tyrosine hydroxylase, changes in gene expression of subunits of the glutamate NMDA receptors), as well as enlarged ventricles, decreased gray matter, and enlarged caudate nucleus (16, 17). However, it is important to note that the features listed here are not all inclusive; and, though the behavioral, structural, and molecular abnormalities mentioned are indicative of schizophrenia, they can be observed in patients who do not suffer from schizophrenia.

Neurodevelopmental Hypothesis

The neurodevelopmental hypothesis of schizophrenia posits that the behavioral outcome of the disorder is due to an abnormality in neurodevelopmental processes from early (prenatal or perinatal) insult that begin long before the onset of clinical symptoms (23–25). This hypothesis has been modified more recently to include the role of genetic predisposition and environmental influences (26). Numerous studies have reported developmental delays, social impairments, and general cognitive deficits in preschizophrenic children (27). Studies of brain pathology have revealed abnormalities in neuronal migration, enlargement in cerebroventricular systems, and changes in gray and white matter (18, 28). Several gene candidates (discussed further in the “Genetic Models” section) implicated in schizophrenia are involved in neurodevelopment (e.g., neuronal migration, cell proliferation, axonal outgrowth, and synaptogenesis) and include neuregulin 1 (NRG1), glutamic acid decarboxylase 1 (GAD1), disrupted-in-schizophrenia-1 (DISC1), and dysbindin (DTNBP1) (29–33). The emergence of this considerable amount of evidence has strengthened the link between maldevelopment and schizophrenia.

There has also been a significant amount of research on the role of ecogenetics (i.e., interactions between genetic vulnerability and environmental risk factors) in schizophrenia (34). The incidence of schizophrenia is 2–6% in second degree relatives (e.g., grandparent, aunt, uncle), 6–17% in first degree relatives (e.g., parents, siblings) and nearly 50% in monozygotic twins (35). Although the etiology of schizophrenia is clearly related to genetic factors, the degree of concordance among monozygotic twins and the large percentage of schizophrenic individuals with no affected relative suggest that genetic liability alone is not sufficient for the development of the disorder, and that environ- mental influences also play a critical role. Maternal malnutrition, maternal infection, and labor-delivery complications significantly increase the risk of the offspring developing schizophrenia later in life (36). Studies have also shown that individuals with schizophrenia are more likely to have experienced prenatal adverse events, obstetric complications, or exposure to harmful stressors in comparison to healthy individuals (27). In light of the considerable amount of evidence supporting the neurodevelopment hypothesis, animal models focusing on the role of ecogenetics and mal- development in schizophrenia may be crucial in under- standing the pathophysiology of the disorder, as well as in drug discovery.

Neurodevelopmental Animal Models of Schizophrenia

Disadvantages of using conventional pharmacologic and lesion models of schizophrenia in drug discovery research include a lack of etiological validity, a lack of subtle changes across several neural systems that more accurately reflect the pathophysiology of the disorder, and limitations related to the novel therapeutic agent directly attenuating the effects of the animal manipulation itself (i.e., the drug- or lesion-related effect) instead of what may be disrupted in schizophrenia. Neurodevelopmental animal models, in contrast, have etiological validity, can mimic the delayed onset of symptoms, and produce abnormalities in multiple neural systems associated with schizophrenia; thus, better approximating the pathophysiology of the disorder (3). Several neurodevelopmental animal models have been developed that reflect environmental stressors thought to increase the risk of developing

schizophrenia later in life. For the purpose of this review, neurodevelopmental animal models were grouped based on experimental design into prenatal stress models, prenatal/neonatal immune challenge models, perinatal/neonatal stress models, pharmacological/lesion models, and genetic models.

Prenatal Stress Models

Several studies have shown that maternal stress due to famine, war, and natural disasters during pregnancy increases the risk of a child developing schizophrenia later in life (36–38). Schizophrenia-related rodent models developed to study the effects of prenatal stress include restraint stress, variable stress, maternal protein malnutrition, and vitamin D deficiency (see Table 2).

Restraint Stress—Offspring of pregnant females exposed to restraint stress during the last week of pregnancy show several behavioral changes and alterations in neurochemistry. For example, several studies have indicated that restraint stress increases sensitivity to amphetamine-induced locomotor activity in offspring. This is often interpreted as a sign of a functional imbalance in dopaminergic transmission, which is thought to underlie several symptoms of schizophrenia (39). One study found that restraint stress resulted in alterations of dopamine receptor densities in the meso-limbic dopaminergic system, possibly the cause of the increased amphetamine sensitivity in the animals (40). Prenatal restraint stress also induced impairments in the Morris water maze (a hippocampal-related spatial learning task) and reduced neurogenesis in the dentate gyrus (41). Restraint stress also increased HPA axis response, altered dopamine and norepinephrine levels, and was associated with deficits in the forced swim test and in home cage emergence, results thought to correspond to depressive- and anxiety-like behaviors, respectively (42–45).

Variable Stress—Variable prenatal stress models were developed in response to evidence that repeated application of the same type of stress allows an animal to adapt over time, resulting in reduced activation of the HPA axis. In contrast, unpredictable stress exposure induces a more robust HPA axis response (46). Similar to restraint stress, variable stress produced increased sensitivity to amphetamine-induced locomotor activity and deficits in prepulse inhibition (PPI), considered a measure of sensorimotor gating which is often deficient in schizophrenia patients (46). Animals exposed to variable prenatal stress also showed a reduction in social interaction and dysregulation of genes involved in NMDA, GABAergic, and synaptic function in the frontal pole and hippocampus (47–49).

Maternal Protein Malnutrition—Protein malnutrition throughout pregnancy was also found to produce PPI deficits in rodents; however, unlike variable prenatal stress, the deficits were age and sex dependent occurring only in females (50). Maternal protein malnutrition induced sex dependent increases in NMDA and DA receptor binding in the striatum and hippocampus, increased stereotypic response to apomorphine, and increased locomotor response to amphetamine in female rats (51). Prenatal malnutrition altered extracellular DA and 5-HT levels in response to stress as well (52).

Vitamin D Deficiency—Vitamin D is known to be involved in normal brain development, and deficiency of this vitamin has been proposed as a risk factor for the development of schizophrenia. Studies show dysregulation of proteins involved in mitochondrial function, synaptic plasticity and neurotransmission in rodents exposed to prenatal vitamin D deficiency (53–55). Vitamin D deficiency produced enlarged lateral ventricles and reduced cortical thickness in rodents as well, resembling structural changes observed in schizophrenic patients (56). PPI deficits were only seen with additional chronic postnatal vitamin D deficiency (57). In addition, increased MK-801 sensitive locomotor activity was observed in prenatal vitamin D deficient animals (58). The model also showed impairments of latent inhibition (often observed in patients with schizophrenia), which reflects the ability to ignore stimuli that historically predicted no significant consequence (59).

Prenatal/Neonatal Immune Challenge Models

The original report of Mednick et al. (1988), indicating that persons in Helsinki exposed to the 1957 A2 influenza epidemic during their second trimester of fetal development were at an elevated risk of schizophrenia, has stimulated a considerable amount of interest in the role of maternal infection (37, 60). Rodent models developed to study the effects of prenatal and neonatal infection (i.e., in the context of schizophrenia-related symptoms or pathophysiology) include maternal exposure to the human influenza virus, neonatal exposure to the Borna disease virus, maternal immune activation by bacterial endotoxin lipopolysaccharide (LPS), and maternal and neonatal immune activation by synthetic double-strand RNA polyriboinosinic-polyribocytidilic acid (Poly I:C) (see Table 3).

Human Influenza Virus—Maternal human influenza infection produced offspring with behavioral deficits in social interaction and exploratory behavior in an open field, as well as deficits in PPI that were reversible by clozapine and chlopromazine (61). Dysregulation of genes involved in cell structure and function suggests that prenatal influenza infection may cause permanent changes in brain morphology and function; indeed, significant brain atrophy has been observed in rodents using this model approach (62, 63). Studies also show a decrease in reelin-positive cell counts in the cortex and hippocampus, thought to play a key role in neuronal migration of the developing brain (64).

Borna Disease Virus—Neonatal Borna disease virus infection caused severe alteration in the cerebellum, including reduced size, substantial loss of Purkinji cells, and increased extracellular levels of norepinephrine and serotonin (65, 66). Neonatal exposure to the Borna disease virus produced alterations in the hippocampus of offspring as well, with impaired synaptogenesis and defects in synaptic organization (67). Behavioral changes in social interaction, locomotor activity, habituation and PPI were observed; however, these changes were found to be dependent on the strain of the rat, possibly demonstrating that the same environmental insult can produce differential neuroanatomical and behavioral abnormalities dependent on genetic vulnerability (68, 69).

Lipopolysaccharide—Prenatal immune activation by bacterial endotoxin lipopolysaccharide (LPS) produces several of the behavioral deficits previously described that are thought to be relevant to schizophrenia. Studies have shown increased

amphetamine-induced locomotor activity, deficits in social interaction, increased anxiety and haloperidol-sensitive, age-dependent disruptions in PPI (70–73). Prenatal LPS also produced age-specific changes in accumbal dopamine levels (74, 75). Observations of dendritic changes in the medial prefrontal cortex and hippocampus suggest that LPS prenatal immune activation affects development of pyramidal neurons that may potentially lead to abnormal neuronal connectivity and function (76).

Poly I:C—Immune activation (maternal and neonatal) with the synthetic double-strand RNA polyriboinosinic-polyribocytidilic acid (Poly I:C) has been suggested to be more appropriate in mimicking viral infection than LPS because it is thought that double-strand RNA is important in interferon induction (77). Studies of prenatal and postnatal Poly I:C immune activation produced similar behavioral results as LPS immune activation in rodents, including increased amphetamine-induced locomotor activity, deficits in social interaction, increased anxiety and disrupted PPI (78, 79). Other behavioral changes observed in maternal exposure to Poly I:C included postpubertal emergence of latent inhibition and impaired spatial working memory, while neonatal Poly I:C immune activation impaired object recognition (79–81). Deficits in latent inhibition and novel object recognition were improved by clozapine, but not affected by haloperidol (77). Maternal immune activation during pregnancy by Poly I:C also produced dopamine-related pharmacological abnormalities and increased GABAA receptor subunit α2 in the ventral dentate gyrus and basolateral amygdala (78, 82).

Perinatal/Neonatal Stress Models

Various forms of psychopathology have frequently been associated with obstetric complications or exposure to a traumatic experience during childhood (83, 84). Rodent models developed to study the effects of perinatal and neonatal stress include 24-hour maternal deprivation, isolation rearing, and birth insults (see Table 4).

24-Hour Maternal Deprivation—A single 24-hour episode of maternal deprivation produced postpubertal deficits in PPI that were reversible by haloperidol and risperidone (85). However, it was found that the deficits in PPI, as well as sensitivity to apomorphine, were strain dependent, similar to what was seen in prenatal exposure to the Borna disease virus (86). Maternal deprivation was also found to be associated with neuronal degeneration and an increased number of astrocytes in the cerebellum, which interestingly was attenuated by inhibitors of endocannabinoid inactivation, suggesting a possible role of the endocannabinoid system in neural development (87, 88). Increased numbers of astrocytes in the hippocampus were also observed in animals exposed to maternal deprivation; however, these results were sex dependent (89).

Isolation Rearing—A large amount of research has been dedicated to the effects of early social isolation in rodents. Behavioral deficits observed in animals exposed to isolation rearing include strain-dependent PPI, increased aggression, increased anxiety, increased locomotor activity, increased food hoarding behavior, and impaired object recognition (90–96). Treatment with methylphenidate was found to improve deficits in anxiety, and treatment with clozapine and fluoxetine was found to improve aggressive behavior in these

animals (97). Isolation rearing is also associated with impaired performance in an attentional set-shifting task, a deficit seen in patients with chronic schizophrenia and thought to reflect impaired reasoning and problem solving (98). Exposure to social isolation in rodents produces several neurochemical and neuroanatomical alterations as well, including reduced arrays of chandelier axons in the prelimbic cortex, reduction in the volume of the medial prefrontal cortex, decreased cortical and hippocampus synaptic plasticity, and an increase in the number of striatal dopamine receptors in the functional high affinity state (95, 99–102).

Birth Insults—To determine the possible effects of obstetric complications, a rodent model of anoxia during Caesarean section birth was developed. Exposure to anoxia during birth increased age-dependent amphetamine-induced locomotor activity (103, 104). Altered dendritic morphology in the prefrontal cortex and hippocampus, changes in dopamine turnover in the prefrontal cortex and nucleus accumbens, and a decrease in hippocampal dentate granule cells were observed in animals exposed to anoxia as well (104–107).

Pharmacologic/Lesion Models

Pharmacologic and lesion models have played an important role in biomedical research. An advantage of these models is the ability to provide information about changes in transmitter systems and neural circuits from a specific alteration (3). Rodent models developed to study the effects of specific pharmacological and lesion manipulations on neurodevelopment (and how the effects may relate to schizophrenia) include neonatal PCP exposure, neonatal ventral hippocampus lesion, neonatal exposure to NOS inhibitors, and exposure to antimitotic agents (see Table 5).

Neonatal PCP—Neonatal administration of phencyclidine (PCP), an NMDA antagonist, has been shown to cause schizophrenia-like symptoms in humans and to impair attentional set-shifting in adult rats (108). The antipsychotic, sertindole, and ampakine CX516 (an AMPA receptor modulator) were able to attenuate these deficits in attentional set-shifting (109). Neonatal PCP administration was also associated with apoptosis of GABAergic interneurons in the primary somatosensory, motor, and retrosplenial cortices as well as neurodegeneration in the striatum and hippocampus, an effect that could be attenuated by treatment with lithium (110, 111).

Neonatal Ventral Hippocampal Lesion—Perhaps the most thoroughly characterized neuro-developmental model of schizophrenia to date is the neonatal ventral hippocampal lesion (NVHL) model first introduced by Lipska and Weinberger (112). Lesions of the ventral hippocampus in neonatal rats (typically produced by ibotenic acid) produce a complex syndrome that is postadolescent in onset and characterized by frontal cortical-striatal dysfunction. The syndrome in rats is expressed as a variety of symptoms that are observed in schizophrenia, including positive (e.g., deficits in PPI and latent inhibition), negative (e.g., deficits in social behaviors), and cognitive components (e.g., deficits in spatial learning and memory). Other behavioral changes include addiction vulnerability, increased amphetamine-induced locomotor activity, and hyperresponsiveness to stress (reviewed in 113; see also, 114–118). It is interesting to note that the disruption of PPI in this animal model could be attenuated by atypical antipsychotics as well as ORG 24598, a

selective glycine transporter 1 inhibitor (118). In addition, several important (schizophrenia-relevant) anatomical and neurophysiological alterations have been observed in the prefrontal cortex of NVHL rats, including decreased dendritic length and spine density of pyramidal neurons, alterations of plasticity, and improper maturation of interneurons during adolescence (118–120). Thus, while on first glance the construct validity of the NVHL model might appear to be questionable, after the animals reach adolescence several of the requirements of face, construct, as well as predictive, validity appear to be met.

Neonatal NOS Inhibition—It has been suggested that nitric oxide affects neurodevelopmental processes in the central nervous system. Neonatal exposure to a nitric oxidase inhibitor resulted in sex-dependent behavioral deficits that included hypersensitivity to amphetamines, deficits in PPI, and social interaction (121, 122). Behavioral deficits in latent inhibition that were reversed by glycine 1 inhibitors (GlyT1) and α-7 nicotinic receptor agonists were also observed in animals exposed to prenatal NOS inhibition, suggesting alterations in glutamatergic and cholinergic systems (123, 124).

Antimitotic Agent—Some studies have suggested that low doses of antimitotic agents given prenatally will perturb the developmental progression of neurogenesis (a process thought to be altered in schizophrenia). Prenatal exposure to the antimitotic drug, cytosine arabinoside (Ara-C), produced postpubertal deficits in PPI and disorganization in hippocampal pyramidal cell layers (125). Prenatal exposure to the mitotic inhibitor, methylazoxymethanol (MAM), produced increased amphetamine-induced locomotor activity, deficits in social interaction, impairments in set-shifting tasks, and deficits in radial arm maze performance (126–128). Prenatal MAM exposure also resulted in decreased tissue weight in the hippocampus and prefrontal cortex (127).

Genetic Models

Considerable evidence supports an important role of genetics in schizophrenia and, accordingly, a vast number of risk genes have been studied in mutant mouse models (for review, 29, 129, 130). While the most promising gene candidates for schizophrenia have failed to be replicated in multiple populations, several transgenic mouse models have been useful for studying the behavioral consequences of specific gene/molecular alterations and the mechanisms potentially underlying the pathogenesis of schizophrenia (129). For the purposes of this review, mouse models specifically designed to study the schizophrenia-related gene candidates that are also known to play an important role in neurodevelopment will be discussed. These include neuregulin 1 (NRG1), disrupted-in-schizophrenia-1 (DISC1), and dysbindin (DTNBP1) (see Table 6).

Neuregulin 1 (NRG1)—Neuregulin 1 (NRG1), part of a family of growth and differentiation factors, was first suggested as a potential candidate gene for schizophrenia in a study of the Icelandic population (131). This association of NRG1 with schizophrenia was later confirmed in Scottish (132) and Irish (133) subjects. NRG1 has been found to be essential for neurodevelopment, with key roles in synapse formation, neuronal migration, synaptic plasticity, and regulation of neurotransmitter systems (134). Homozygous null mice embryos die midgestation; however, heterozygous mutant mice are viable and can reproduce

(135). NRG1 hypomorph epidermal growth factor (EFG)-like domain models produce hyperactive mice with impaired PPI only after treatment with MK-801 (135, 136). Most NRG1 proteins are synthesized with a transmembrane (TM) domain, and NRG1 hypomorph TM models also produce hyperactivity that can be reduced by the second-generation antipsychotic, clozapine. These animals also exhibit impaired PPI (that is not reversed by clozapine), altered habituation, increased aggression, and decreased functional NMDA receptors (131, 137, 138). NRG1 immunoglobulin (Ig)-like domain mutant mice, however, do not appear to be hyperactive, although they do exhibit impairments of latent inhibition (139). A more recent model focusing on the deletion of a specific NRG1 isoform (Type III) produced mice with more pronounced PPI deficits and impaired performance on delayed alteration memory tasks, as well as enlarged lateral ventricles and decreased dendritic spine density (140).

Disrupted-in-Schizophrenia-1 (DISC1)—Disrupted-in-schizophrenia-1 (DISC1) was suggested as a possible candidate gene when it was found to be disrupted by a balanced (1;11)(q42.1; q14.3) translocation that cosegregates with schizophrenia and related psychopathologies (141, 142). DISC1 has been suggested to play important roles in neurite outgrowth, cell migration and cell signaling (143). Studies of a DISC1 mutant model of a deletion variant in mDisc1 specific to the 129S6/SvEV strain transferred onto a C57BL/6J strain revealed impairments in working memory, decreased mPFC volume, altered synaptic transmission in the hippocampus, and reduced dendritic growth in the dendate gyrus (144, 145). An inducible DISC1 C-terminal fragment (DISC1-cc) transgenic model exhibited abnormal spatial working memory and deficits in social interaction, as well as decreased hippocampal dendritic complexity (146). A model expressing the dominant negative C-terminal truncated DISC1 (DN-DISC1) exhibited enlarged lateral ventricles, hyperactivity, disrupted PPI, and depressive-like symptoms (147). Inducible expression of mutant hDISC1 also produced mice with enlarged lateral ventricles, deficits in spatial working memory, impaired social interaction, and hyperactivity (148). DISC1tr (truncated) transgenic mice are characterized by enlarged lateral ventricles, decreased cortical neurogenesis (and decreases in cerebral cortex), as well as partial agenesis of the corpus callosum. In addition, parvalbumin GABAergic neurons are reduced in the hippocampus and medial prefrontal cortex, and displaced in the dorsolateral frontal cortex. In behavioral studies, DISC1tr mice exhibit increased immobility and reduced vocalization in depression-related tests, as well as impairment in conditioning of latent inhibition (149).

It should be noted, however, that there are some ambiguities in the results of the animal and cell-based studies that need to be addressed before final conclusions can be drawn regarding the role of DISC1 in neurodevelopmental processes that are relevant to schizophrenia. For example, the cellular models based on the knockdown of DISC1 or expression of dominant negative DISC1 indicate clear disruptions in the developmental processes that are critical for normal cortical architecture. However, the aforementioned mutant mice (i.e., with the 29S6/SvEV-derived DISC1 gene transferred onto a C57BL/6J genetic background) showed relatively subtle behavioral abnormalities and no major deficits in cortical architecture. Such a finding leads to confusion, especially regarding a so-called “critical role” of DISC1 in neurodevelopment given that these mutant mice have a 25-bp deletion in a coding exon of

the DISC1 gene that would be expected to completely abolish the full-length DISC1 protein. Efforts are currently underway to resolve these questions (see 150).

Dysbindin (DTNBP1)—Several studies have described dysbindin (DTNBP1) as a candidate gene in schizophrenia (151–154). Dysbindin binds to dystrobrevins, components of the dystrophin- associated glycol-protein complex (DGC), and is thought to play a fundamental role in the regulation of synaptic structure and signaling (155, 156). In 1991, Swank and colleagues first described a mouse mutant (sandy) which arose from the DBA/2J strain and was later found to have a deletion of the DTNBP1 gene (157, 158). Behavioral studies on sandy (sdy) mutant mice showed decreased activity, increased anxiety and impaired social interaction, as well as deficits in working memory and recognition memory (159, 160). These mice also displayed an increased freezing response to a conditioned stimulus in a fear-conditioning paradigm suggestive of deficits in emotional and motivated learning and memory (161). Decreased dopamine levels, reduced steady state levels of snapin (a synaptic priming regulator), and deficiencies in neurosecretion were also observed in the sdy mutant mice (162–164). In contrast, a recent study on sdy mutant mice (DTNBP1 KO) from the C57BL/6J strain found no evidence of increased anxiety or increased activity, although the mice were impaired in spatial learning and memory (165).

Conclusions

Novel therapeutic strategies for schizophrenia are critically important in light of the inadequate treatment options currently available. Accordingly, the development of valid and reliable animal models of the illness is essential so that novel treatment-related hypotheses can be tested at the basic science level. While a number of schizophrenia-related animal models have been introduced (see references 166 and 167 for a comprehensive list), few have been rigorously examined for their translational value in the context of novel drug discovery. However, several neurodevelopmental models have met some of the requirements of face validity as evidenced by deficits/alterations in social interaction, PPI, amphetamine sensitivity, latent inhibition, and spatial learning (i.e., features commonly observed in patients with schizophrenia [16]). Some of these behavioral deficits (e.g., PPI, latent inhibition) were reversible by first- and second-generation antipsychotics, thus providing evidence of predictive validity. Furthermore, neuroanatomical alterations (e.g., cortical atrophy, enlarged ventricles, neuronal disorganization) observed in some of the neurodevelopmental models correlate with what is often observed in patients with schizophrenia, thus satisfying some requirements of construct validity (28). Another striking feature of the neurodevelopmental models is the ability to produce age-dependent behavioral and neurochemical deficits as well as strain-specific alterations (i.e., factors that support an important role of ecogenetics in schizophrenia). The age-dependent emergence of schizophrenia-related symptoms in some of the animal models could be very useful for testing hypotheses related to the contemporary (and controversial) topic of therapeutic intervention during the prodromal stages of schizophrenia. There is also an emerging interest in the development of animal models that mimic gene-environment interactions in schizophrenia (i.e., combine mutant mouse transgenics with measurable environmental insults). Such an approach (see 168 for review) may lead to more optimal models for

identifying important gene-environment interactions in schizophrenia, as well as for testing novel drug-development strategies.

It is important to note that another potential reason for the disappointing progress in the development of novel therapeutic agents for schizophrenia to date may have been the focus on designing a single compound for treating an illness with multiple dimensions. It has been suggested that a more rational approach would be to deconstruct schizophrenia into its various phenomenological components that could be targeted independently with separate molecules or specifically designed multi-target drugs (169). While it may be that no single animal model would satisfy all the requirements necessary for drug discovery purposes using this approach, several of the neurodevelopmental models discussed in this review could theoretically be used concurrently for such an approach.

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References

1. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Fourth Edition. Washington, DC: American Psychiatric Association; 2000. Text Revision.
2. Lewis DA, Lieberman JA. Catching up on schizophrenia: natural history and neurobiology. Neuron. 2000; 28(2):325–334. [PubMed: 11144342]
3. Floresco SB, Geyer MA, Gold LH, Grace AA. Developing predictive animal models and establishing a preclinical trials network for assessing treatment effects on cognition in schizophrenia. Schizophr Bull. 2005; 31(4):888–894. [PubMed: 16079387]
4. Kurtz MM. Neurocognitive impairment across the lifespan in schizophrenia: an update. Schizophr Res. 2005; 74(1):15–26. [PubMed: 15694750]
5. Lewis S, Lieberman J. CATIE and CUtLASS: can we handle the truth? Br J Psychiatry. 2008; 192(3):161–163. [PubMed: 18310570]
6. Lader M. Some adverse effects of antipsychotics: prevention and treatment. J Clin Psychiatry. 1999; 60(Suppl 12):18–21. [PubMed: 10372605]
7. Haddad PM, Sharma SG. Adverse effects of atypical antipsychotics: differential risk and clinical implications. CNS Drugs. 2007; 21(11):911–936. [PubMed: 17927296]
8. Swartz MS, Stroup TS, McEvoy JP, Davis SM, Rosenheck RA, Keefe RS, et al. What CATIE found: results from the schizophrenia trial. Psychiatr Serv. 2008; 59(5):500–506. [PubMed: 18451005]
9. Keefe RS, Bilder RM, Davis SM, Harvey PD, Palmer BW, Gold JM, et al. CATIE Investigators; Neurocognitive Working Group. Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE Trial. Arch Gen Psychiatry. 2007; 64(6):633–647. [PubMed: 17548746]
10. Jones PB, Barnes TR, Davies L, Dunn G, Lloyd H, Hayhurst KP, et al. Randomized controlled trial of the effect on quality of life of second- vs first-generation antipsychotic drugs in schizophrenia: Cost Utility of the Latest Antipsychotic Drugs in Schizophrenia Study (CUtLASS 1). Arch Gen Psychiatry. 2006; 63(10):1079–1087. [PubMed: 17015810]
11. Carpenter WT, Koenig JI. The evolution of drug development in schizophrenia: past issues and future opportunities. Neuropsychopharmacology. 2008; 33(9):2061–2079. [PubMed: 18046305]

12. Geyer, MA.; Markou, A. Animal models of psychiatric disorders. In: Bloom, FE.; Kupfer, DJ., editors. Psychopharmacology: the fourth generation of progress. New York: Raven Press, Ltd.; 1995. p. 787-798.
13. Decker, MW. Cognition models and drug discovery. In: Levin, ED.; Buccafusco, JJ., editors. Animal models of cognitive impairment. Boca Raton (FL): CRC Taylor & Francis; 2006. p. 343-352.
14. Geyer, MA.; Moghaddam, B. Animal models relevant to schizophrenia disorders. In: Davis, KL.; Charney, D.; Coyle, JT.; Nemeroff, C., editors. Neuropsychopharmacology: the fifth generation of progress. Philadelphia: Lippincott Williams & Wilkins; 2002. p. 689-701.
15. Meyer U, Feldon J, Schedlowski M, Yee BK. Towards an immuno-precipitated neurodevelopmental animal model of schizophrenia. Neurosci Biobehav Rev. 2005; 29:913–947. [PubMed: 15964075]
16. Buckley PF. Neuroimaging of schizophrenia: structural abnormalities and pathophysiological implications. Neuropsychiatr Dis Treat. 2005; 1(3):193–204. [PubMed: 18568069]
17. van Haren NE, Bakker SC, Kahn RS. Genes and structural brain imaging in schizophrenia. Curr Opin Psychiatry. 2008; 21(2):161–167. [PubMed: 18332664]
18. Young JW, Powell SB, Risbrough V, Marston HM, Geyer MA. Using the MATRICS to guide development of a preclinical cognitive test battery for research in schizophrenia. Pharmacol Ther. 2009; 122(2):150–202. [PubMed: 19269307]
19. van der Staay FJ, Arndt SS, Nordquist RE. Evaluation of animal models of neurobehavioral disorders. Behav Brain Funct. 2009; 5:11. [PubMed: 19243583]
20. Geyer MA, Ellenbroek B. Animal behavior models of the mechanisms underlying antipsychotic atypicality. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27:1071–1079. [PubMed: 14642967]
21. Kapur S, Mamo D. Half a century of antipsychotics and still a central role for dopamine D2 receptors. Prog Neuropsychopharmacol Biol Psychiatry. 2003; 27:1081–1090. [PubMed: 14642968]
22. Lipska BK, Weinberger DR. To model a psychiatric disorder in animals: schizophrenia as a reality test. Neuropsychopharmacology. 2000; 23:223–239. [PubMed: 10942847]
23. Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. Arch Gen Psychiatry. 1987; 44:660–669. [PubMed: 3606332]
24. Murray RM, O'Callaghan E, Castle DJ, Lewis SW. A neurodevelopmental approach to the classification of schizophrenia. Schizophr Bull. 1992; 18:319–332. [PubMed: 1377834]
25. Bloom FE. Advancing a neurodevelopmental origin for schizophrenia. Arch Gen Psychiatry. 1993; 50:224–227. [PubMed: 8439244]
26. Singh SM, McDonald P, Murphy B, O'Reilly R. Incidental neurodevelopmental episodes in the etiology of schizophrenia: an expanded model involving epigenetics and development. Clin Genet. 2004; 65(6):435–440. [PubMed: 15151498]
27. Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. Mol Psychiatry. 2005; 10(5):434–449. [PubMed: 15700048]
28. Pantelis C, Yücel M, Wood SJ, Velakoulis D, Sun D, Berger G, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. Schizophr Bull. 2005; 31(3):672–696. [PubMed: 16020551]
29. O'Tuathaigh CM, Babovic D, O'Meara G, Clifford JJ, Croke DT, Waddington JL. Susceptibility genes for schizophrenia: characterisation of mutant mouse models at the level of phenotypic behaviour. Neurosci Biobehav Rev. 2007; 31(1):60–78. [PubMed: 16782199]
30. Stefansson H, Steinthorsdottir V, Thorgeirsson TE, Gulcher JR, Stefansson K. Neuregulin 1 and schizophrenia. Ann Med. 2004; 36(1):62–71. [PubMed: 15000348]
31. Akbarian S, Huang HS. Molecular and cellular mechanisms of altered GAD1/GAD67 expression in schizophrenia and related disorders. Brain Res Rev. 2006; 52(2):293–304. [PubMed: 16759710]
32. Chubb JE, Bradshaw NJ, Soares DC, Porteous DJ, Millar JK. The DISC locus in psychiatric illness. Mol Psychiatry. 2008; 13(1):36–64. [PubMed: 17912248]
33. Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. Schizophr Bull. 2009; 35(3):528–548. [PubMed: 19223657]

34. van Os J, Marcelis M. The ecogenetics of schizophrenia: a review. Schizophr Res. 1998; 32(2): 127–135. [PubMed: 9713909]
35. Gottesman, II. Schizophrenia genesis: the origins of madness. New York: Freeman; 1991.
36. Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. Annu Rev Neurosci. 2002; 25:409–432. [PubMed: 12052915]
37. Brixey SN, Gallagher BJ 3rd, McFalls JA Jr, Parmelee LF. Gestational and neonatal factors in the etiology of schizophrenia. J Clin Psychol. 1993; 49(3):447–456. [PubMed: 8315050]
38. van Os J, Selten JP. Prenatal exposure to maternal stress and subsequent schizophrenia. The May 1940 invasion of The Netherlands. Br J Psychiatry. 1998; 172:324–326. [PubMed: 9715334]
39. Deminière JM, Piazza PV, Guegan G, Abrous N, Maccari S, Le Moal M, et al. Increased locomotor response to novelty and propensity to intravenous amphetamine self-administration in adult offspring of stressed mothers. Brain Res. 1992; 586(1):135–139. [PubMed: 1511342]
40. Henry C, Guegant G, Cador M, Arnauld E, Arsaut J, Le Moal M, et al. Prenatal stress in rats facilitates amphetamine-induced sensitization and induces long-lasting changes in dopamine receptors in the nucleus accumbens. Brain Res. 1995; 685(1–2):179–186. [PubMed: 7583244]
41. Lemaire V, Koehl M, Le Moal M, Abrous DN. Prenatal stress produces learning deficits associated with an inhibition of neurogenesis in the hippocampus. Proc Natl Acad Sci U S A. 2000; 97:11032–11037. [PubMed: 11005874]
42. Takahashi LK, Turner JG, Kalin NH. Prenatal stress alters brain catecholaminergic activity and potentiates stress-induced behavior in adult rats. Brain Res. 1992; 574:131–137. [PubMed: 1322219]
43. Henry C, Kabbaj M, Simon H, Le Moal M, Maccari S. Prenatal stress increases the hypothalamo-pituitary-adrenal axis response in young and adult rats. J Neuroendocrinol. 1994; 6:341–345. [PubMed: 7920600]
44. Diaz R, Ogren SO, Blum M, Fuxe K. Prenatal corticosterone increases spontaneous and d-amphetamine induced locomotor activity and brain dopamine metabolism in prepubertal male and female rats. Neuroscience. 1995; 66:467–473. [PubMed: 7477887]
45. van den Hove DL, Blanco CE, Aendekerk B, Desbonnet L, Bruschettini M, Steinbusch HP, et al. Prenatal restraint stress and long-term affective consequences. Dev Neurosci. 2005; 27:313–320. [PubMed: 16137989]
46. Koenig JI, Elmer GI, Shepard PD, Lee PR, Mayo C, Joy B, et al. Prenatal exposure to a repeated variable stress paradigm elicits behavioral and neuroendo-crinological changes in the adult offspring: potential relevance to schizophrenia. Behav Brain Res. 2005; 156:251–261. [PubMed: 15582111]
47. Kinnunen AK, Koenig JI, Bilbe G. Repeated variable prenatal stress alters pre- and postsynaptic gene expression in the rat frontal pole. J Neurochem. 2003; 86:736–748. [PubMed: 12859686]
48. Lee PR, Brady D, Shapiro RA, Dorsa DM, Koenig JI. Prenatal stress generates deficits in rat social behavior: reversal by oxytocin. Brain Res. 2007; 1156:152–167. [PubMed: 17540347]
49. Bogoch Y, Biala YN, Linial M, Weinstock M. Anxiety induced by prenatal stress is associated with suppression of hippocampal genes involved in synaptic function. J Neurochem. 2007; 101(4): 1018–1030. [PubMed: 17254015]
50. Palmer AA, Printz DJ, Butler PD, Dulawa SC, Printz MP. Prenatal protein deprivation in rats induces changes in prepulse inhibition and NMDA receptor binding. Brain Res. 2004; 996:193–201. [PubMed: 14697497]
51. Palmer AA, Brown AS, Keegan D, Siska LD, Susser E, Rotrosen J, et al. Prenatal protein deprivation alters dopamine-mediated behaviors and dopaminergic and glutamatergic receptor binding. Brain Res. 2008; 1237:62–74. [PubMed: 18703024]
52. Mokler DJ, Torres OI, Galler JR, Morgane PJ. Stress-induced changes in extracellular dopamine and serotonin in the medial prefrontal cortex and dorsal hippocampus of prenatally malnourished rats. Brain Res. 2007; 1148:226–233. [PubMed: 17368432]
53. Almeras L, Eyles D, Benech P, Laffite D, Villard C, Patatian A, et al. Developmental vitamin D deficiency alters brain protein expression in the adult rat: implications for neuropsychiatric disorders. Proteomics. 2007; 7(5):769–780. [PubMed: 17295352]

54. Eyles D, Almeras L, Benech P, Patatian A, Mackay-Sim A, McGrath J, et al. Developmental vitamin D deficiency alters the expression of genes encoding mitochondrial, cytoskeletal and synaptic proteins in the adult rat brain. J Steroid Biochem Mol Biol. 2007; 103(3–5):538–545. [PubMed: 17293106]
55. McGrath J, Iwazaki T, Eyles D, Burne T, Cui X, Ko P, et al. Protein expression in the nucleus accumbens of rats exposed to developmental vitamin D deficiency. PLoS One. 2008; 3(6):e2383. [PubMed: 18545652]
56. Féron F, Burne TH, Brown J, Smith E, McGrath JJ, Mackay-Sim A, et al. Developmental vitamin D3 deficiency alters the adult rat brain. Brain Res Bull. 2005; 65(2):141–148. [PubMed: 15763180]
57. Burne THJ, Feron F, Brown J, Eyles DW, McGrath JJ, Mackay-Sim A. Combined prenatal and chronic postnatal vitamin D deficiency in rats impairs prepulse inhibition of acoustic startle. Physiol Behav. 2004; 81(4):651–655. [PubMed: 15178159]
58. Kesby JP, Burne TH, McGrath JJ, Eyles DW. Developmental vitamin D deficiency alters MK 801-induced hyperlocomotion in the adult rat: an animal model of schizophrenia. Bio Psych. 2006; 60(6):591–596.
59. Becker A, Eyles DW, McGrath JJ, Grecksch G. Transient prenatal vitamin D deficiency is associated with subtle alterations in learning and memory functions in adult rats. Behav Brain Res. 2005; 161(2):306–312. [PubMed: 15922058]
60. Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. Arch Gen Psychiatry. 1988; 45(2):189–192. [PubMed: 3337616]
61. Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. J Neurosci. 2003; 23:297–302. [PubMed: 12514227]
62. Fatemi SH, Pearce DA, Brooks AI, Sidwell RW. Prenatal viral infection in mouse causes differential expression of genes in brains of mouse progeny: a potential animal model for schizophrenia and autism. Synapse. 2005; 57:91–99. [PubMed: 15906383]
63. Fatemi SH, Reutiman TJ, Folsom TD, Huang H, Oishi K, Mori S, et al. Maternal infection leads to abnormal gene regulation and brain atrophy in mouse offspring: implications for genesis of neurodevelopmental disorders. Schizophr Res. 2008; 99(1–3):56–70. [PubMed: 18248790]
64. Fatemi SH, Emamian ES, Kist D, Sidwell RW, Nakajima K, Akhter P, et al. Defective corticogenesis and reduction in reelin immunoreactivity in cortex and hippocampus of prenatally infected neonatal mice. Mol Psychiatry. 1999; 4:145–154. [PubMed: 10208446]
65. Eisenman LM, Brothers R, Tran MH, Kean RB, Dickson GM, Dietzschold B, et al. Neonatal Borna disease virus infection in the rat causes a loss of Purkinje cells in the cerebellum. J Neurovirology. 1999; 5(2):181–189. [PubMed: 10321982]
66. Pletnikov MV, Rubin SA, Schwartz GJ, Carbone KM, Moran TH. Effects of neonatal rat Borna disease virus (BDV) infection on the postnatal development of the brain monoaminergic systems. Dev Brain Res. 2000; 119(2):179–185. [PubMed: 10675767]
67. Hans A, Bajramovic JJ, Syan S, Perret E, Dunia I, Brahic M, et al. Persistent, noncytolytic infection of neurons by Borna disease virus interferes with ERK 1/2 signaling and abrogates BDNF-induced synaptogenesis. FASEB J. 2004; 18:863–865. [PubMed: 15033926]
68. Pletnikov MV, Rubin SA, Vogel MW, Moran TH, Carbone KM. Effects of genetic background on neonatal Borna disease virus infection-induced neuro-developmental damage. I. Brain pathology and behavioral deficits. Brain Res. 2002; 944:97–107. [PubMed: 12106670]
69. Lancaster K, Dietz DM, Moran TH, Pletnikov MV. Abnormal social behaviors in young and adult rats neonatally infected with Borna disease virus. Behav Brain Res. 2007; 176(1):141–148. [PubMed: 16860408]
70. Borrell J, Vela JM, Arevalo-Martin A, Molina-Holgado E, Guaza C. Prenatal immune challenge disrupts sensorimotor gating in adult rats: implications for the etiopathogenesis of schizophrenia. Neuropsychopharmacology. 2002; 26:204–215. [PubMed: 11790516]

71. Fortier ME, Joober R, Luheshi GN, Boksa P. Maternal exposure to bacterial endotoxin during pregnancy enhances amphetamine-induced locomotion and startle responses in adult rat offspring. J Psychiatric Res. 2004; 38(3):335–345.

72. Hava G, Vered L, Yael M, Mordechai H, Mahoud H. Alterations in behavior in adult offspring mice following maternal inflammation during pregnancy. Dev Psychobiology. 2006; 48(2):162–168.

73. Fortier ME, Luheshi GN, Boksa P. Effects of prenatal infection on prepulse inhibition in the rat depend on the nature of the infectious agent and the stage of pregnancy. Behav Brain Res. 2007; 181(2):270–277. [PubMed: 17553574]

74. Romero E, Ali C, Molina-Holgado E, Castellano B, Guaza C, Borrell J. Neurobehavioral and immunological consequences of prenatal immune activation in rats. Influence of antipsychotics. Neuropsychopharmacology. 2007; 32(8):1791–1804. [PubMed: 17180123]

75. Romero E, Guaza C, Castellano B, Borrell J. Ontogeny of sensorimotor gating and immune impairment induced by prenatal immune challenge in rats: implications for the etiopathology of schizophrenia. Mol Psychiatry. 2008; 15(4):372–383. [PubMed: 18414405]

76. Baharnoori M, Brake WG, Srivastava LK. Prenatal immune challenge induces developmental changes in the morphology of pyramidal neurons of the prefrontal cortex and hippocampus in rats. Schizophr Res. 2009; 107(1):99–109. [PubMed: 19004618]

77. Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M. Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia. Biol Psychiatry. 2006; 59(6):546–554. [PubMed: 16256957]

78. Meyer U, Nyffeler M, Schwendener S, Knuesel I, Yee BK, Feldon J. Relative prenatal and postnatal maternal contributions to schizophrenia-related neurochemical dysfunction after in utero immune challenge. Neuropsychopharmacology. 2008; 33(2):441–456. [PubMed: 17443130]

79. Ibi D, Nagai T, Kitahara Y, Mizoguchi H, Koike H, Shiraki A, et al. Neonatal polyI:C treatment in mice results in schizophrenia-like behavioral and neurochemical abnormalities in adulthood. Neurosci Res. 2009; 64(3):297–305. [PubMed: 19447299]

80. Meyer U, Schwendener S, Feldon J, Yee BK. Prenatal and postnatal maternal contributions in the infection model of schizophrenia. Exp Brain Res. 2006; 173(2):243–257. [PubMed: 16552558]

81. Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J. Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. Brain Behav Immun. 2008; 22(4):469–486. [PubMed: 18023140]

82. Nyffeler M, Meyer U, Yee BK, Feldon J, Knuesel I. Maternal immune activation during pregnancy increases limbic GABAA receptor immunoreactivity in the adult offspring: implications for schizophrenia. Neuroscience. 2006; 143(1):51–62. [PubMed: 17045750]

83. McNeil TF, Cantor-Graae E, Ismail B. Obstetric complications and congenital malformation in schizophrenia. Brain Res Rev. 2000; 31(2–3):166–178. [PubMed: 10719145]

84. Heim C, Nemeroff CB. The role of childhood trauma in the neurobiology of mood and anxiety disorders: preclinical and clinical studies. Biol Psychiatry. 2001; 49(12):1023–1039. [PubMed: 11430844]

85. Ellenbroek BA, van den Kroonenberg PT, Cools AR. The effects of an early stressful life event on sensorimotor gating in adult rats. Schizophr Res. 1998; 30:251–260. [PubMed: 9589519]

86. Ellenbroek BA, Cools AR. The long-term effects of maternal deprivation depend on the genetic background. Neuropsychopharmacology. 2000; 23:99–106. [PubMed: 10869890]

87. Lopez-Gallardo M, Llorente R, Llorente-Berzal A, Marco EM, Prada C, Di Marzo V, et al. Neuronal and glial alterations in the cerebellar cortex of maternally deprived rats: gender differences and modulatory effects of two inhibitors of endocannabinoid inactivation. Dev Neurobiol. 2008; 68(12):1429–1440. [PubMed: 18726913]

88. Suárez J, Llorente R, Romero-Zerbo SY, Mateos B, Bermudez-Silva FJ, de Fonseca FR, et al. Early maternal deprivation induces gender-dependent changes on the expression of hippocampal CB(1) and CB(2) cannabinoid receptors of neonatal rats. Hippocampus. 2009; 19(7):623–632. [PubMed: 19115376]

89. Llorente R, Llorente-Berzal A, Petrosino S, Marco EM, Guaza C, Prada C, et al. Gender-dependent cellular and biochemical effects of maternal deprivation on the hippocampus of neonatal rats: a possible role for the endocannabinoid system. Dev Neurobiol. 2008; 68(11):1334–1347. [PubMed: 18666205]

90. Geyer MA, Wilkinson LS, Humby T, Robbins TW. Isolation rearing of rats produces a deficit in prepulse inhibition of acoustic startle similar to that in schizophrenia. Biol Psych. 1993; 34:361–372.

91. Varty GB, Geyer MA. Effects of isolation rearing on startle reactivity, habituation, and prepulse inhibition in male Lewis, Sprague-Dawley, and Fischer F344 rats. Behav Neurosci. 1998; 112:1450–1457. [PubMed: 9926827]

92. Heidbreder CA, Weiss IC, Domeney AM, Pryce C, Homberg J, Hedou G, et al. Behavioral, neurochemical and endocrinological characterization of the early social isolation syndrome. Neuroscience. 2000; 100:749–768. [PubMed: 11036209]

93. Weiss IC, Di Iorio L, Feldon J, Domeney AM. Strain differences in the isolation-induced effects on prepulse inhibition of the acoustic startle response and on locomotor activity. Behav Neurosci. 2000; 114:364–373. [PubMed: 10832797]

94. Bianchi M, Fone KF, Azmi N, Heidbreder CA, Hagan JJ, Marsden CA. Isolation rearing induces recognition memory deficits accompanied by cytoskeletal alterations in rat hippocampus. Eur J Neurosci. 2006; 24(10):2894–2902. [PubMed: 17116162]

95. Day-Wilson KM, Jones DN, Southam E, Cilia J, Totterdell S. Medial prefrontal cortex volume loss in rats with isolation rearing-induced deficits in prepulse inhibition of acoustic startle. Neuroscience. 2006; 141(3):1113–1121. [PubMed: 16750891]

96. Ferdman N, Murmu RP, Bock J, Braun K, Leshem M. Weaning age, social isolation, and gender interact to determine adult explorative and social behavior, and dendritic and spine morphology in prefrontal cortex of rats. Behav Brain Res. 2007; 180(2):174–182. [PubMed: 17477981]

97. Koike H, Ibi D, Mizoguchi H, Nagai T, Nitta A, Takuma K, et al. Behavioral abnormality and pharmacologic response in social isolation-reared mice. Behav Brain Res. 2009; 202(1):114–121. [PubMed: 19447287]

98. McLean S, Grayson B, Harris M, Protheroe C, Bate S, Woolley M, et al. Isolation rearing impairs novel object recognition and attentional set shifting performance in female rats. J Psychopharmacology. 2008; 24(1):57–63.

99. Bloomfield C, French SJ, Jones DN, Reavill C, Southam E, Cilia J, et al. Chandelier cartridges in the prefrontal cortex are reduced in isolation reared rats. Synapse. 2008; 62(8):628–631. [PubMed: 18512213]

100. Fone KC, Porkess MV. Behavioural and neurochemical effects of post-weaning social isolation in rodents-relevance to developmental neuropsychiatric disorders. Neurosci Biobehav Rev. 2008; 32(6):1087–1102. [PubMed: 18423591]

101. King MV, Seeman P, Marsden CA, Fone KC. Increased dopamine D2High receptors in rats reared in social isolation. Synapse. 2009; 63(6):476–483. [PubMed: 19217027]

102. Schubert MI, Porkess MV, Dashdorj N, Fone KC, Auer DP. Effects of social isolation rearing on the limbic brain: a combined behavioral and magnetic resonance imaging volumetry study in rats. Neuroscience. 2009; 159(1):21–30. [PubMed: 19141315]

103. El-Khodor BF, Boksa P. Birth insult increases amphetamine-induced behavioral responses in the adult rat. Neuroscience. 1998; 87(4):893–904. [PubMed: 9759977]

104. Wakuda T, Matsuzaki H, Suzuki K, Iwata Y, Shinmura C, Suda S, et al. Perinatal asphyxia reduces dentate granule cells and exacerbates methamphetamine-induced hyperlocomotion in adulthood. PLoS One. 2008; 3(11):e3648. [PubMed: 18985150]

105. El-Khodor BF, Boksa P. Long-term reciprocal changes in dopamine levels in prefrontal cortex versus nucleus accumbens in rats born by Caesarean section compared to vaginal birth. Exp Neurol. 1997; 145(1):118–129. [PubMed: 9184115]

106. Hoeger H, Engelmann M, Bernert G, Seidl R, Bubna-Littitz H, Mosgoeller W, et al. Long term neurological and behavioral effects of graded perinatal asphyxia in the rat. Life Sci. 2000; 66(10):947–962. [PubMed: 10714895]

107. Juarez I, Gratton A, Flores G. Ontogeny of altered dendritic morphology in the rat prefrontal cortex, hippocampus, and nucleus accumbens following Cesarean delivery and birth anoxia. J Comp Neurol. 2008; 507(5):1734–1747. [PubMed: 18253967]
108. Broberg BV, Dias R, Glenthøj BY, Olsen CK. Evaluation of a neurodevelopmental model of schizophrenia--early postnatal PCP treatment in attentional set-shifting. Behav Brain Res. 2008; 190(1):160–163. [PubMed: 18367258]
109. Broberg BV, Glenthøj BY, Dias R, Larsen DB, Olsen CK. Reversal of cognitive deficits by an ampakine (CX516) and sertindole in two animal models of schizophrenia-sub-chronic and early postnatal PCP treatment in attentional set-shifting. Psychopharmacology (Berl). 2009; 206(4): 631–640. [PubMed: 19390843]
110. Wang CZ, Yang SF, Xia Y, Johnson KM. Postnatal phencyclidine administration selectively reduces adult cortical parvalbumin-containing interneurons. Neuropsychopharmacology. 2008; 33(10):2442–2455. [PubMed: 18059437]
111. Xia Y, Wang CZ, Liu J, Anastasio NC, Johnson KM. Lithium protection of phencyclidine-induced neurotoxicity in developing brain: the role of phosphatidylinositol-3 kinase/Akt and mitogen-activated protein kinase kinase/ extracellular signal-regulated kinase signaling pathways. J Pharmacol Exp Ther. 2008; 326(3):838–848. [PubMed: 18544676]
112. Lipska BK, Weinberger DR. A neurodevelopmental model of schizophrenia: neonatal disconnection of the hippocampus. Neurotox Res. 2002; 4(5–6):469–475. [PubMed: 12754160]
113. Tseng KY, Chambers RA, Lipska BK. The neonatal ventral hippocampal lesion as a heuristic neurodevelopmental model of schizophrenia. Behav Brain Res. 2008; 204(2):295–305. [PubMed: 19100784]
114. Sams-Dodd F, Lipska BK, Weinberger DR. Neonatal lesions of the rat ventral hippocampus result in hyperlocomotion and deficits in social behaviour in adulthood. Psychopharmacology (Berl). 1997; 132(3):303–310. [PubMed: 9292631]
115. Le Pen G, Moreau JL. Disruption of prepulse inhibition of startle reflex in a neurodevelopmental model of schizophrenia: reversal by clozapine, olanzapine and risperidone but not by haloperidol. Neuropsychopharmacology. 2002; 27(1):1–11. [PubMed: 12062902]
116. Rueter LE, Ballard ME, Gallagher KB, Basso AM, Curzon P, Kohlhaas KL. Chronic low dose risperidone and clozapine alleviate positive but not negative symptoms in the rat neonatal ventral hippocampal lesion model of schizophrenia. Psychopharmacology (Berl). 2004; 176(3–4):312–319. [PubMed: 15179541]
117. Endo K, Hori T, Abe S, Asada T. Alterations in GABA(A) receptor expression in neonatal ventral hippocampal lesioned rats: comparison of prepubertal and postpubertal periods. Synapse. 2007; 61(6):357–366. [PubMed: 17372969]
118. Le Pen G, Kew J, Alberati D, Borroni E, Heitz MP, Moreau JL. Prepulse inhibition deficits of the startle reflex in neonatal ventral hippocampal-lesioned rats: reversal by glycine and a glycine transporter inhibitor. Biol Psychiatry. 2003; 54(11):1162–1170. [PubMed: 14643083]
119. Alquicer G, Morales-Medina JC, Quirion R, Flores G. Postweaning social isolation enhances morphological changes in the neonatal ventral hippocampal lesion rat model of psychosis. J Chem Neuroanat. 2008; 35(2):179–187. [PubMed: 18061401]
120. Tseng KY, Lewis BL, Hashimoto T, Sesack SR, Kloc M, Lewis DA, et al. A neonatal ventral hippocampal lesion causes functional deficits in adult prefrontal cortical interneurons. J Neurosci. 2008; 28(48):12691–12699. [PubMed: 19036962]
121. Black MD, Selk DE, Hitchcock JM, Wettstein JG, Sorensen SM. On the effect of neonatal nitric oxide synthase inhibition in rats: a potential neurodevelopmental model of schizophrenia. Neuropharmacology. 1999; 38(9):1299–1306. [PubMed: 10471083]
122. Black MD, Simmonds J, Senyah Y, Wettstein JG. Neonatal nitric oxide synthase inhibition: social interaction deficits in adulthood and reversal by antipsychotic drugs. Neuropharmacology. 2002; 42(3):414–420. [PubMed: 11897119]
123. Black MD, Varty GB, Arad M, Barak S, De Levie A, Boulay D, et al. Procognitive and antipsychotic efficacy of glycine transport 1 inhibitors (GlyT1) in acute and neurodevelopmental models of schizophrenia: latent inhibition studies in the rat. Psychopharmacology (Berl). 2009; 202(1–3):385–396. [PubMed: 18709358]

124. Barak S, Arad M, De Levie A, Black MD, Griebel G, Weiner I. Pro-cognitive and antipsychotic efficacy of the alpha7 nicotinic partial agonist SSR180711 in pharmacological and neurodevelopmental latent inhibition models of schizophrenia. Neuropsychopharmacology. 2009; 34(7):1753–1763. [PubMed: 19158670]

125. Elmer GI, Sydnor J, Guard H, Hercher E, Vogel MW. Altered prepulse inhibition in rats treated prenatally with the antimitotic Ara-C: an animal model for sensorimotor gating deficits in schizophrenia. Psychopharmacology (Berl). 2004; 174:177–189. [PubMed: 14985933]

126. Flagstad P, Mork A, Glenthoj BY, van Beek J, Michael-Titus AT, Didriksen M. Disruption of neurogenesis on gestational day 17 in the rat causes behavioral changes relevant to positive and negative schizophrenia symptoms and alters amphetamine-induced dopamine release in nucleus accumbens. Neuropsychopharmacology. 2004; 29:2052–2064. [PubMed: 15199377]

127. Featherstone RE, Rizos Z, Nobrega JN, Kapur S, Fletcher PJ. Gestational methylazoxymethanol acetate treatment impairs select cognitive functions: parallels to schizophrenia. Neuropsychopharmacology. 2007; 32(2):483–492. [PubMed: 17035930]

128. Gourevitch R, Rocher C, Le Pen G, Krebs MO, Jay TM. Working memory deficits in adult rats after prenatal disruption of neurogenesis. Behav Pharmacol. 2004; 15:287–292. [PubMed: 15252279]

129. Kellendonk C, Simpson EH, Kandel ER. Modeling cognitive endophenotypes of schizophrenia in mice. Trends Neurosci. 2009; 32(6):347–358. [PubMed: 19409625]

130. Desbonnet L, Waddington JL, O'Tuathaigh CM. Mutant models for genes associated with schizophrenia. Biochem Soc Trans. 2009; 37(Pt 1):308–312. [PubMed: 19143653]

131. Stefansson H, Sigurdsson E, Steinthorsdottir V, Bjornsdottir S, Sigmundsson T, Ghosh S, et al. Neuregulin 1 and susceptibility to schizophrenia. Am J Hum Genet. 2002; 71(4):877–892. [PubMed: 12145742]

132. Stefansson H, Sarginson J, Kong A, Yates P, Steinthorsdottir V, Gudfinnsson E, et al. Association of neuregulin 1 with schizophrenia confirmed in a Scottish population. Am J Hum Genet. 2003; 72(1):83–87. [PubMed: 12478479]

133. Corvin AP, Morris DW, McGhee K, Schwaiger S, Scully P, Quinn J, et al. Confirmation and refinement of an 'at-risk' haplotype for schizophrenia suggests the EST cluster, Hs. 97362, as a potential susceptibility gene at the Neuregulin-1 locus. Mol Psychiatry. 2004; 9(2):208–213. [PubMed: 14966480]

134. Falls DL. Neuregulins: functions, forms, and signaling strategies. Exp Cell Res. 2003; 284(1):14–30. [PubMed: 12648463]

135. Gerlai R, Pisacane P, Erickson S. Heregulin, but not ErbB2 or ErbB3, heterozygous mutant mice exhibit hyperactivity in multiple behavioral tasks. Behav Brain Res. 2000; 109(2):219–227. [PubMed: 10762692]

136. Duffy L, Cappas E, Scimone A, Schofield PR, Karl T. Behavioral profile of a heterozygous mutant mouse model for EGF-like domain neuregulin 1. Behav Neurosci. 2008; 122(4):748–759. [PubMed: 18729627]

137. Karl T, Duffy L, Scimone A, Harvey RP, Schofield PR. Altered motor activity, exploration and anxiety in heterozygous neuregulin 1 mutant mice: implications for understanding schizophrenia. Genes Brain Behav. 2007; 6(7):677–687. [PubMed: 17309661]

138. O'Tuathaigh CM, O'Connor AM, O'Sullivan GJ, Lai D, Harvey R, Croke DT, et al. Disruption to social dyadic interactions but not emotional/anxiety-related behaviour in mice with heterozygous 'knockout' of the schizophrenia risk gene neuregulin-1. Prog Neuropsychopharmacol Biol Psychiatry. 2008; 32(2):462–466. [PubMed: 17980471]

139. Rimer M, Barrett DW, Maldonado MA, Vock VM, Gonzalez-Lima F. Neuregulin-1 immunoglobulin-like domain mutant mice: clozapine sensitivity and impaired latent inhibition. Neurorepor. 2005; 16(3):271–275.

140. Chen YJ, Johnson MA, Lieberman MD, Goodchild RE, Schobel S, Lewandowski N, et al. Type III neuregulin-1 is required for normal sensorimotor gating, memory-related behaviors, and corticostriatal circuit components. J Neurosci. 2008; 28(27):6872–6883. [PubMed: 18596162]

141. Millar JK, Wilson-Annan JC, Anderson S, Christie S, Taylor MS, Semple CA, et al. Disruption of two novel genes by a translocation co-segregating with schizophrenia. Hum Mol Genet. 2000; 9(9):1415–1423. [PubMed: 10814723]

142. Millar JK, Christie S, Anderson S, Lawson D, Hsiao-Wei Loh D, et al. Genomic structure and localisation within a linkage hotspot of Disrupted In Schizophrenia 1, a gene disrupted by a translocation segregating with schizophrenia. Mol Psychiatry. 2001; 6(2):173–178. [PubMed: 11317219]

143. Mackie S, Millar JK, Porteous DJ. Role of DISC1 in neural development and schizophrenia. Curr Opin Neurobiol. 2007; 17(1):95–102. [PubMed: 17258902]

144. Koike H, Arguello PA, Kvajo M, Karayiorgou M, Gogos JA. Disc1 is mutated in the 129S6/SvEv strain and modulates working memory in mice. Proc Natl Acad Sci U S A. 2006; 103(10):3693–3697. [PubMed: 16484369]

145. Kvajo M, McKellar H, Arguello PA, Drew LJ, Moore H, MacDermott AB, et al. A mutation in mouse Disc1 that models a schizophrenia risk allele leads to specific alterations in neuronal architecture and cognition. Proc Natl Acad Sci U S A. 2008; 105(19):7076–7081. [PubMed: 18458327]

146. Li W, Zhou Y, Jentsch JD, Brown RA, Tian X, Ehninger D, et al. Specific developmental disruption of disrupted-in-schizophrenia-1 function results in schizophrenia-related phenotypes in mice. Proc Natl Acad Sci U S A. 2007; 104(46):18280–18285. [PubMed: 17984054]

147. Hikida T, Jaaro-Peled H, Seshadri S, Oishi K, Hookway C, Kong S, et al. Dominant-negative DISC1 transgenic mice display schizophrenia-associated phenotypes detected by measures translatable to humans. Proc Natl Acad Sci USA. 2007; 104(36):14501–14506. [PubMed: 17675407]

148. Pletnikov MV, Ayhan Y, Nikolskaia O, Xu Y, Ovanesov MV, Huang H, et al. Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. Mol Psychiatry. 2008; 13(2):173–186. [PubMed: 17848917]

149. Shen S, Lang B, Nakamoto C, Zhang F, Pu J, Kuan SL, et al. Schizophrenia-related neural and behavioral phenotypes in transgenic mice expressing truncated Disc1. J Neurosci. 2008; 28(43): 10893–10904. [PubMed: 18945897]

150. Ishizuka K, Chen J, Taya S, Li W, Millar JK, Xu Y, et al. Evidence that many of the DISC1 isoforms in C57BL/6J mice are also expressed in 129S6/SvEv mice. Mol Psychiatry. 2007; 12:897–899. [PubMed: 17895924]

151. Straub RE, Jiang Y, MacLean CJ, Ma Y, Webb BT, Myakishev MV, et al. Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. Am J Hum Genet. 2002; 71(2):337–348. [PubMed: 12098102]

152. Tang JX, Zhou J, Fan JB, Li XW, Shi YY, Gu NF, et al. Family-based association study of DTNBP1 in 6p22.3 and schizophrenia. Mol Psychiatry. 2003; 8(8):717–718. [PubMed: 12888799]

153. Schwab SG, Knapp M, Mondabon S, Hallmayer J, Borrmann-Hassenbach M, Albus M, et al. Support for association of schizophrenia with genetic variation in the 6p22.3 gene, dysbindin, in sib-pair families with linkage and in an additional sample of triad families. Am J Hum Genet. 2003; 72(1):185–190. [PubMed: 12474144]

154. Kirov G, Ivanov D, Williams NM, Preece A, Nikolov I, Milev R, et al. Strong evidence for association between the dystrobrevin binding protein 1 gene (DTNBP1) and schizophrenia in 488 parent-offspring trios from Bulgaria. Biol Psychiatry. 2004; 55(10):971–975. [PubMed: 15121479]

155. Benson MA, Newey SE, Martin-Rendon E, Hawkes R, Blake DJ. Dysbindin, a novel coiled-coil-containing protein that interacts with the dystrobrevins in muscle and brain. J Biol Chem. 2001; 276(26):24232–24241. [PubMed: 11316798]

156. Benson MA, Sillitoe RV, Blake DJ. Schizophrenia genetics: dysbindin under the microscope. Trends Neurosci. 2004; 27(9):516–519. [PubMed: 15331232]

157. Swank RT, Sweet HO, Davisson MT, Reddington M, Novak EK. Sandy: a new mouse model for platelet storage pool deficiency. Genet Res. 1991; 58(1):51–62. [PubMed: 1936982]

158. Li W, Zhang Q, Oiso N, Novak EK, Gautam R, O'Brien EP, et al. Hermansky-Pudlak syndrome type 7 (HPS-7) results from mutant dysbindin, a member of the biogenesis of lysome-related organelles complex 1 (BLOC-1). Nat Genet. 2003; 35(1):84–89. [PubMed: 12923531]

159. Hattori S, Murotani T, Matsuzaki S, Ishizuka T, Kumamoto N, Takeda M, et al. Behavioral abnormalities and dopamine reductions in sdy mutant mice with a deletion in Dtnbp1, a susceptibility gene for schizophrenia. Biochem Biophys Res Commun. 2008; 373(2):298–302. [PubMed: 18555792]

160. Takao K, Toyama K, Nakanishi K, Hattori S, Takamura H, Takeda M, et al. Impaired long-term memory retention and working memory in sdy mutant mice with a deletion in Dtnbp1, a susceptibility gene for schizophrenia. Mol Brain. 2008; 1(1):11. [PubMed: 18945333]

161. Bhardwaj SK, Baharnoori M, Sharif-Askari B, Kamath A, Williams S, Srivastava LK. Behavioral characterization of dysbindin-1 deficient sandy mice. Behav Brain Res. 2009; 197(2):435–441. [PubMed: 18984010]

162. Murotani T, Ishizuka T, Hattori S, Hashimoto R, Matsuzaki S, Yamatodani A. High dopamine turnover in the brains of Sandy mice. Neurosci Lett. 2007; 421(1):47–51. [PubMed: 17548156]

163. Chen XW, Feng YQ, Hao CJ, Guo XL, He X, Zhou ZY, et al. DTNBP1, a schizophrenia susceptibility gene, affects kinetics of transmitter release. J Cell Biol. 2008; 181(5):791–801. [PubMed: 18504299]

164. Feng YQ, Zhou ZY, He X, Wang H, Guo XL, Hao CJ, et al. Dysbindin deficiency in sandy mice causes reduction of snapin and displays behaviors related to schizophrenia. Schizophr Res. 2008; 106(2–3):218–228. [PubMed: 18774265]

165. Cox MM, Tucker AM, Tang J, Talbot K, Richer DC, Yeh L, et al. Neurobehavioral abnormalities in the dysbindin-1 mutant, sandy, on a C57BL/6J genetic background. Genes Brain Behav. 2009; 8(4):390–397. [PubMed: 19220483]

166. Schizophrenia Research Forum: Research Database Animal Models of Schizophrenia. Available from: URL: http://www.schizophreniaforum.org/res/models/default.asp.

167. Carpenter WT, Koenig JI. The evolution of drug development in schizophrenia: past issues and future opportunities. Neuropsychopharmacology. 2008; 33(9):2061–2079. [PubMed: 18046305]

168. Ayhan Y, Sawa A, Ross CA, Pletnikov MV. Animal models of gene-environment interactions in schizophrenia. Behav Brain Res. 2009; 204(2):274–281. [PubMed: 19379776]

169. Gründer G, Hippius H, Carlsson A. The 'atypicality' of antipsychotics: a concept re-examined and re-defined. Nat Rev Drug Discov. 2009; 8(3):197–202. [PubMed: 19214197]

Table 1

Desirable Characteristics of a Schizophrenia-Related Animal Model

Behavioral Features
Elevated Locomotor and Stereotypic Activity - Increased sensitivity to dopaminergic psychostimulants - Increased sensitivity to NMDA antagonists
Abnormal Gating - Decreased Prepulse Inhibition (PPI) - Deficits in P20 (analogous to human P50 component of ERP)
Deficits in Habituation
Deficits in Latent Inhibition
Social Behavior - Social withdrawal - Deficits in social recognition
Cognitive Dysfunction - Deficits in attention - Deficits in speed of processing - Deficits in visual learning and memory - Deficits in working memory - Deficits in reason and problem solving
Structural and Molecular Features
Abnormalities in the Neuronal Organization of Prefrontal Cortex - Reduction in cortical volume - Reduced neuropil - Elevated neuronal density - Altered laminar distribution of neurons
Abnormalities in Cortical Neurotransmitter Function - Alterations in GABA neurons - Decreased tyrosine hydroxylase immunoreactive axons - Changes in gene expression of subunits of NMDA receptor
Other Changes in Neuroanatomy - Enlarged third and lateral ventricles - Decreased gray matter in frontal and temporal cortices - Enlarged caudate nucleus

Table 2

Behavioral, Structural, and Neurochemical Phenotypes of Prenatal Stress Models

Prenatal Stress Models	Structural and Neurochemical Phenotype	Behavioral Phenotype	References
Restraint Stress	Changes in dopamine sensitivity in nucleus accumbens; increased HPA axis response; inhibition of neurogenesis in hippocampus	Anxiety- and depressive-like behaviors; learning deficits in Morris water maze; locomotor activity and sensitivity to amphetamine	39, 40, 41, 42, 43, 44, 45
Variable Stress	Dysregulation of genes involved in NMDA, GABAergic, and synaptic function in the frontal pole and hippocampus	Increased response to amphetamine; impaired social interaction; disrupted PPI (sensory gating) and N40	46, 47, 48, 49
Maternal Protein Malnutrition	Altered DA and 5-HT response to stress; increased NMDA and DA receptor binding in striatum and hippocampus of female rats	Increased stereotypic response to apomorphine; increased locomotor response to amphetamine; disrupted PPI; (behaviors only in females)	50, 51, 52
Vitamin D Deficiency	Dysregulation of proteins involved in mitochondrial function and synaptic plasticity; enlarged lateral ventricles; reduced cortical thickness	Impaired habituation; altered PPI with additional chronic postnatal vitamin D deficiency; impairment of latent inhibition	53, 54, 55, 56, 57, 58, 59

Table 3

Behavioral, Structural, and Neurochemical Phenotypes of Prenatal and Neonatal Immune Challenge Models

Prenatal/Neonatal Immune Challenge Models	Structural and Neurochemical Phenotype	Behavioral Phenotype	References
Human Influenza Virus	Dysregulation of genes involved in cell structure and function; significant brain atrophy	Impaired PPI; deficits in exploratory behavior in both open field and novel object test; impaired social interaction	61, 62, 63, 64
Borna Disease Virus	Impaired hippocampal synaptogenesis; increased cortical and cerebellum levels of NE and 5-HT; loss of Purkinje cells in cerebellum	Impaired social behaviors; increased locomotor activity; impaired habituation and PPI (rat strain dependent)	65, 66, 67, 68, 69
LPS	Age-specific changes in accumbal DA levels and striatal DOPAC; dendritic changes in mPFC and hippocampus	Disrupted PPI; increased amphetamine-induced locomotor activity; deficits in social interaction	70, 71, 72, 73, 74, 75, 76
Poly I:C	DA-related pharmacological abnormalities; increase in GABAA receptor subunit α2 in ventral dentate gyrus and basolateral amygdala	Learning deficits in Morris water maze; postpubertal latent inhibition and PPI deficits; impaired object recognition; impaired social behavior	77, 78, 79, 80, 81, 82

Table 4

Behavioral, Structural, and Neurochemical Phenotypes of Perinatal and Neonatal Stress Models

Perinatal/Neonatal Stress Models	Structural and Neurochemical Phenotype	Behavioral Phenotype	References
24-Hour Maternal Deprivation	Cerebellum neuronal degeneration; increased astrocytes in cerebellum and hippocampus (sex dependent)	Impaired PPI; increased susceptibility to apomorphine (rat strain dependent)	85, 86, 87, 89
Isolation Rearing	Decreased cortical and hippocampal synaptic plasticity; increased striatal dopamine receptors in the functional high state	Increased locomotor activity; impaired set-shifting and object recognition; increased social interaction; deficits in PPI (rat strain dependent)	90, 91, 92, 93, 94, 95, 96, 97, 98, 99, 100,101, 102
Birth Insults	Decreased dentate granule cells; increased DA release in nucleus accumbens and striatum; decreased DA release in PFC	Increased amphetamine-induce locomotor activity (age dependent)	103, 104, 105, 106, 107

Table 5

Behavioral, Structural, and Neurochemical Phenotypes of Neonatal Pharmacological and Lesion Models

Pharmacologic/Lesion Models	Structural and Neurochemical Phenotype	Behavioral Phenotype	References
Neonatal PCP	Apoptosis of GABAergic interneurons in primary somatosensory, motor, and retrosplenial cortices	Deficits in attention set-shifting	108, 109, 110, 111
Neonatal Ventral Hippocampal Lesion	Decreased dedritic density of pyramidal neurons; alterations in GABAA receptor expression; improper interneuron maturation	Increased amphetamine-induced locomotor activity; PPI deficits; decreased social interaction; hyperresponsive to stress	112, 113, 114, 115, 116, 117, 118, 119, 120
Neonatal NOS Inhibition	Possible changes in NMDA function	Hypersensitivity to amphetamine; deficits in social interaction; PPI deficits (all sex dependent)	121, 122, 123, 124
Antimitotic Agent: MAM or AraC	Decreased tissue weight in hippocampus and PFC; disorganization of pyramidal cell layers in hippocampus	PPI deficits (postpubertal); deficits in radial arm maze; impaired social interaction; increased amphetamine-induced locomotor	125, 126, 127, 128

Table 6

Behavioral, Structural, and Neurochemical Phenotypes of Genetic Models

Genetic Models	Structural and Neurochemical Phenotype	Behavioral Phenotype	References
NRG1 (phenotypes dependent on domain mutations)	Decreased NMDA receptor function; enlarged lateral ventricles; decreased dendritic spine density	Increased locomotor activity; PPI deficits; impaired social interaction; deficits in latent inhibition; impaired delayed alteration memory task performance	131, 134, 135, 136, 137, 138 139, 140
DISC1	Decreased mPFC volume; decreased hippocampal dendritic complexity; enlarged lateral ventricles; reduced parvalbumin GABAergic neurons in the hippocampus and mPFC	Impaired working memory; disrupted PPI; altered latent inhibition; hyperactivity; depressive-like symptoms; abnormal spatial working memory	144, 145, 146, 147, 148, 149
DTNBP1	Decreased DA levels; decreased steady-state snapin; deficiencies in neurosecretion and vesicular morphology	Increased anxiety; decreased activity; impaired social interaction; working memory deficits; recognition memory deficits; emotional learning and memory deficits	159, 160, 161, 162, 163, 164, 165