Review Paper

Contribution of nonprimate animal models in understanding the etiology of schizophrenia

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Schizophrenia is a severe psychiatric disorder that is characterized by positive and negative symptoms and cognitive impairments. The etiology of the disorder is complex, and it is thought to follow a multifactorial threshold model of inheritance with genetic and neurodevelopmental contributions to risk. Human studies are particularly useful in capturing the richness of the phenotype, but they are often limited to the use of correlational approaches. By assessing behavioural abnormalities in both humans and rodents, nonprimate animal models of schizophrenia provide unique insight into the etiology and mechanisms of the disorder. This review discusses the phenomenology and etiology of schizophrenia and the contribution of current nonprimate animal models with an emphasis on how research with models of neurotransmitter dysregulation, environmental risk factors, neurodevelopmental disruption and genetic risk factors can complement the literature on schizophrenia in humans.

Introduction

Schizophrenia is a devastating psychiatric disorder that disrupts cognition, emotion, language and thought, and it typically affects 0.5%–1.5% of the population.[1] The onset of the disorder usually occurs during adolescence or early adulthood, although a prodromal phase usually precedes its onset.[1] The etiology of the disorder is complex and is thought to be largely genetic in nature. Association and linkage studies with humans, although useful in determining genes that increase the risk for schizophrenia, have produced inconsistent results. Animal models may be particularly useful for assessing the impact of genetic and environmental risk factors in the development of schizophrenia by providing evidence of a causal relation between risk factors and the development of schizophrenia-related behavioural abnormalities and endophenotypes.

Many animal models have been focused on rodents, using mice and rats, whereas others have used nonhuman primates. Given the homology between the human and nonhuman primate brain, the latter models promise to be an important area of research.[2,3] However, examination of the genetic mechanisms implicated in schizophrenia is difficult in nonhuman primate models, whereas genetic knockouts can be designed in mouse models with relative ease. In addition, neurodevelopmental processes can also easily be examined in rats. Hence, this review focuses on nonprimate (i.e., rodent) models of schizophrenia, and for the purposes of this review we refer to such models as animal models. Whereas the homology between human and rodent brains is less than that between human and nonhuman primate brains, important endophenotypes and behaviours related to schizophrenia can be examined effectively in rodent models. Descriptions of the homology between human and rodent brains, however, are beyond the scope of this review.

After discussions of the behavioural and biologic features of schizophrenia and the etiology of the disorder, this review discusses the concept of endophenotypes, which serve as a behavioural link between animal behaviour and human symptomatology. This serves as background for a discussion on animal models in schizophrenia research that focuses on animal models of disrupted neurotransmission, environmental risk factors, disrupted neurodevelopment and genetic risk factors. We focus on the behavioural endophenotypes of animal models that are created by particular experimental manipulations (i.e., gene mutations, lesions or drug injections)

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as a method of understanding etiologic and mechanistic hypotheses of schizophrenia. We argue that animal model research can complement the literature on schizophrenia in humans by using experimental paradigms to test causative and mechanistic hypotheses of schizophrenia in ways that would not be feasible in human participants.

Behavioural and biologic features of schizophrenia

Symptomatology and course

The symptomatology of schizophrenia is generally grouped into positive, negative and cognitive symptoms. Positive symptoms reflect an excess or a distortion in normal functioning and include conceptual disorganization, hallucinations and unusual thought content.[1,4] Negative symptoms reflect a loss or diminution of normal functioning and include restricted affect, alogia, anhedonia, decreased sense of purpose, diminished social drive and motor abnormalities.[1,4,5] Cognitive symptoms, considered by some to be the most important features of schizophrenia, include impairments in attention and information processing speed, visual and verbal learning, working memory, social learning and executive function.[6,7]

The active phase of the disorder is generally marked by the emergence of positive symptoms and typically occurs during adolescence, possibly coinciding with the maturation of and axonal pruning in certain brain areas.[8] A prodromal phase usually precedes the active phase and presents as a nonspecific behavioural change, although the lack of specificity and predictive validity of the associated symptoms do not permit their use in early diagnosis or treatment.[1,8] A premorbid stage may also precede the prodromal stage and may manifest as motor, cognitive and social abnormalities in children in whom schizophrenia later develops.[8,9] Should the positive symptoms remit, either spontaneously or as a result of treatment, the individual is said to be in the residual stage, which is primarily characterized by negative and cognitive symptoms.[1,7,8]

Neurotransmitter system abnormalities

Abnormalities of the major neurotransmitter systems have been reported in the brains of individuals with schizophrenia. Dopaminergic hyperactivity has been reported in the striatum and may be the result of a greater number of D_2 receptors that have a higher affinity for dopamine (DA) or an enhanced presynaptic accumulation of DA in the striatum.[10–12] In addition, dopaminergic hypoactivity has been reported in the prefrontal cortex (PFC).[13,14]

Glutamatergic hypoactivity has been reported in the brains of patients with schizophrenia. Depletion of glutamate and its synthesizing enzyme, as well as *N*-methyl-D-aspartate (NMDA) receptors for glutamate, may be responsible for the hypoactivity of the glutamatergic system.[15–17] Consistent with this, glutamatergic antagonists have been shown to induce acute psychotic reactions, including thought disorder, social withdrawal and catatonia in unaffected volunteers.[18]

Hypoactivity of the GABAergic system has also been reported in the brains of patients with schizophrenia. This dysregulation is thought to be the result of reductions in key γ-aminobutyric acid (GABA)–related compounds, including glutamic acid decarboxylase (GAD), an enzyme required for the synthesis of GABA, and GABA transporter 1 (GAT-1) synthesis, a presynaptic GABA reuptake transporter.[19–21]

Neuroanatomic brain abnormalities

There are also gross neuroanatomic abnormalities in the brains of patients with schizophrenia, affecting most of the brain's major structures. Ventricular enlargement, particularly in the lateral and third ventricles, as well as a reduction of cerebral volume have been reported in the brains of patients with schizophrenia compared with controls.[22–24]

Abnormalities of the PFC have also been reported in schizophrenia. These abnormalities include reductions in cortical grey matter, a decrease in the size of pyramidal neurons and a reduction in the total volume of dendrites and axons.[25,26] Developmental errors in neuronal migratory patterns have also been observed in postmortem tissue taken from the PFCs of patients with schizophrenia.[27,28]

Abnormalities of the temporal lobe include reduced grey and white matter volume in patients with schizophrenia.[29,30] Volumetric decreases in the superior temporal gyrus, the parahippocampal gyrus, the hippocampus and the amygdala have also been identified.[31–33] Volumetric decreases of both the hippocampus and amygdala have also been found in patients with schizophrenia, although with some inconsistency.[34–36] Decreased neuronal size and density, as well as a disorganization of hippocampal neurons, have been reported in the hippocampus.[37,38]

Volumetric reductions of the thalamus and structures of the basal ganglia in the brains of patients with schizophrenia have also been reported.[22,39,40]

Etiology of schizophrenia

Evidence of behavioural and cognitive disturbances before the onset of schizophrenia is important because it suggests that the causes of the disorder precede the development of schizophrenia by many years. These causes are thought to include genetic factors, as well as a number of prenatal and perinatal developmental insults. The neurodevelopmental hypothesis of schizophrenia posits that schizophrenia may result from subtle abnormalities affecting critical circuits in the brain during early development, with full-blown consequences becoming evident during early adulthood when the damaged structures become fully functional.[9] According to Weinberger,[41] if some form of damage affects a structure or region that has not fully matured, the effects of the damage would remain clinically silent until the structure fully develops. However, it is possible that some manifestations of the damage that do not reach clinical significance might be evident in childhood.[9] Although Weinberger's hypothesis suggests that the brain damage results from prenatal and perinatal developmental events, it does not preclude the possibility that the damage might be

caused by disrupted genes that begin to exert their effect early in life. In fact, studies have shown a substantial genetic component to schizophrenia, with a heritability (i.e., the proportion of variance in the phenotype that can be attributed to genetic variance) of the disorder of about 80%.[6,42]

Family, twin and adoption studies

Family studies, in which prevalence data are gathered on parents, offspring, siblings and extended family members, have shown that schizophrenia occurs in about 10%–12% of first-degree relatives and 3%–4% of second-degree relatives of patients with the disorder (i.e., probands), compared with a 1% incidence rate in the general population.[43–45] However, genetic and environmental effects cannot be well distinguished, as family members often share a similar environment.

Twin studies can be used to address this confound as monozygotic (MZ) twins share 100% of their genes, whereas dizygotic (DZ) twins share on average 50% of their genes. A greater similarity or concordance between MZ twins than between DZ twins suggests a genetic variation underlying the disorder, which has been confirmed by several studies.[42,46,47] However, interpretation of these results requires an assumption of the equality of the prenatal, perinatal and postnatal environments, which may not always be the case.[46]

To address the limitations of twin studies, adoption studies have been used. In such studies, the development of schizophrenia in the adoptee is correlated with the development of the disorder in biologic and adoptive parents and relatives. Adoption studies have consistently shown that the biologic relatives of adoptees with schizophrenia have higher rates of schizophrenia and schizophrenia-spectrum disorders than the adoptive relatives.[43,48,49] Although these results provide the best evidence for a genetic component to the disorder, adoption studies do not separate in utero or perinatal environmental effects from genetic effects.

Despite some limitations, family, twin and adoption studies have successfully demonstrated that schizophrenia is not a single-gene disorder, nor is it a collection of single-gene disorders.[50] In such models, the penetrance of the disorder (i.e., the probability of the expression of the phenotype given the presence of a particular gene), based on concordance rates between MZ twins, would be 50%, and a linear decrease in risk would be predicted as relatives become more distant, which, as previously mentioned, is not the case.[44] Hence, it has been suggested that the mode of inheritance must follow a polygenic (i.e., a large number of genes, each of a small effect) model of inheritance.[50]

Multifactorial threshold model of inheritance

Most current etiologic theories posit a multifactorial threshold model of inheritance.[51,52] In this model, a large number of polygenes and nonshared environmental experiences have interchangeable and additive effects on the risk for schizophrenia.[44,51] In addition, the model posits an arbitrary categorical threshold on the dimension of risk, beyond which schizophrenia would develop in an individual.[44,51]

Multifactorial models posit a greater number of possible risk factors than the number necessary to cross the threshold.[44] Hence, individuals in whom schizophrenia develops need only be exposed to a subset of possible risk factors to cross the threshold, which allows for genetic and phenotypic variation among patients with schizophrenia and is consistent with the presentation of the disorder. For example, it has been suggested that paranoid schizophrenia, a less severe form of the disorder, may develop in individuals with fewer polygenes, whereas nonparanoid schizophrenia, a more severe form, may develop in individuals with a greater number of polygenes.[53] Multifactorial models also predict a curvilinear decrease in risk as relatives become more distant, which is consistent with family studies.[44]

Endophenotypes

Clearly, the etiology and symptom presentation of schizophrenia is complex. As this complexity is difficult to replicate in animal models of schizophrenia, particularly in terms of the direct assessment of symptoms, other behavioural markers or biomarkers are necessary to assess for schizophrenia-related symptoms in animals. The concept of a biomarker is used across multiple scientific disciplines. In this context, it is considered to be endogenous and measurable characteristics that indicate the risk for or presence of a psychiatric illness.[54] One subtype of biomarkers is the endophenotype, which is more restrictive in its definition.[54] Endophenotypes serve as the "bridge" between animal models of schizophrenia and the human disorder. Since actual schizophrenia symptoms generally cannot be directly assessed in animal models, endophenotypes can be used to measure more "upstream" behavioural disturbances that are related to schizophrenia symptoms. Endophenotypes are defined as measurable phenotypes that are unseen by the unaided eye and lie along the pathway between the genotype and the disease.[55] In essence, each genetic abnormality would be reflected in a specific protein change, which would be reflected in a discrete functional abnormality, such that an endophenotype can be viewed as the direct phenotype of the abnormal gene.[56] It should be noted that abnormal genes can be influenced by multiple factors, including environmental, epigenetic and genetic interactions.[55,56] It is also possible that each gene or genetic interaction could give rise to 1 or more endophenotypes, and that the endophenotypes resulting from an abnormal gene may be similar or distinct, depending on where these genes are expressed in the brain.[56,57] Endophenotypes can be diverse and may include behavioural, biochemical, neuroanatomic, cognitive or endocrinologic measures.[55] To gain further understanding of the etiology and underlying mechanisms of the symptomatology of schizophrenia, we mainly discuss behavioural endophenotypes as they relate to particular animal models. We also discuss neuroanatomic and neurotransmitter abnormalities as appropriate.

There are several guidelines used to identify endophenotypes, which render them more specific than general biomarkers:[55,56]

- the endophenotype is associated with the illness;

- the endophenotype is heritable, thereby implying a genetic basis;
- the endophenotype is state-independent, such that state-related changes in the individual's status (i.e., remission) should not affect the expression of the endophenotype;
- endophenotypes cosegregate with the illness within families; and
- the proband's endophenotype is found at a higher frequency in the proband's relatives than in the general population.

Consistent with the last point, since schizophrenia consists of multifactorial traits and each individual trait segregates independently in family members, some unaffected relatives will express some endophenotypes linked with the disorder, but others will not.[56]

According to this approach, schizophrenia symptoms are thought to result from the combination of multiple endophenotypes. Thus, defective genes do not code for the disease directly, but rather for physiologic processes that culminate "downstream" in the development of the disease.[57,58] Different combinations of risk factors could therefore give rise to different combinations of endophenotypes. Consistent with the heterogeneity of schizophrenia, these differential endophenotype combinations may also result in differential symptom presentation. For example, different genetic risk factors may distinguish between paranoid and nonparanoid schizophrenia subtypes.[53]

One major advantage of using endophenotypes as behavioural markers is that they are particularly useful when the imprecision of psychiatric diagnoses can impede genetic investigations.[59] Specifically, the relation between the endophenotypes and particular genes should show a stronger association than that between risk genes and the symptoms of schizophrenia.[56] It should be noted that the standard definition of an endophenotype requires that it be heritable or genetically based. However, in many animal models, environmental manipulations are used to mimic some form of brain damage, and the behavioural features of endophenotypes associated with schizophrenia are examined. In addition, in most genetically based animal model studies, many of the criteria required to meet the definition of an endophenotype are not met or remain untested. For example, in some studies the heritability or the state independence of the genetic manipulation are not measured. Although the results of certain assays are often referred to as "endophenotypes" in the literature, they are more correctly defined as biomarkers if all the criteria of an endophenotype are not met or tested. Hence, when presenting results of animal model studies, we either refer to the observed behavioural abnormalities as such, or as biomarkers.

Multiple endophenotypes have been associated with schizophrenia, and similar biomarkers have been assessed in animal models of the disorder. Only those that are commonly measured in rodents will be discussed in detail in subsequent sections. However, it is worth briefly mentioning several endophenotypes that are based on research with human patients because they could theoretically be assessed in animal models, more likely in primate than in rodent models. It should be noted that many of the endophenotypes and biomarkers that we discuss are not exclusive to schizophrenia and are associated with other psychiatric disorders.

Deficits in smooth pursuit eye movements have been among the most reliable biologic findings in schizophrenia research and may be representative of frontal lobe dysfunction and deficient stimulus encoding processes.[60,61] Several studies have reported abnormalities of smooth pursuit eye movements in both patients and their relatives.[62,63] A second human-related endophenotype is impairment in the P300 response, which is an event-related potential that is thought to represent brain activity resulting from tasks that require information to be maintained in working memory.[64] Several meta-analyses have implicated the P300 response as an endophenotype of schizophrenia, and studies have shown that unaffected family members of probands exhibit deficits in the P300 response.[65,66] Deficits in P50 suppression, which is operationalized as a decrease in the amplitude of the P50 wave (i.e., a positive-going wave at 50 ms latency) to the second of 2 paired auditory stimuli, is thought to reflect a sensory gating mechanism.[65] Abnormalities in P50 suppression have been described in both patients with schizophrenia and their unaffected relatives.[65,67] Finally, episodic memory retrieval, which is defined as the conscious recollection of an event by reliving it mentally, appears to be disrupted in patients with schizophrenia, irrespective of medication status, and in unaffected relatives of schizophrenia probands.[68,69]

Sensorimotor gating deficits

Sensorimotor gating is a process whereby excess or trivial information is screened out of awareness (i.e., gated out), permitting the individual to focus on the more important stimuli in the environment.[70] Deficits in the ability to filter irrelevant internal and external stimuli may result in misperceptions, a sense of sensory flooding and disorganized thinking and distractibility, which are all reminiscent of the positive symptoms of schizophrenia.[71] In fact, studies of precategorical processing have suggested that patients with schizophrenia have deficits in selective attention or a "filtering deficit."[72]

Prepulse inhibition (PPI) of startle is a commonly used measure to test sensorimotor gating in humans and animals.[73] The procedure is based on the fact that a brief, startling stimulus will produce a startle response. If a weaker, nonstartling prepulse precedes the startling stimulus by a short time interval (i.e., 30–300 ms), the startle response will be reduced.[74] This reduction is thought to result from a momentary inhibitory sensorimotor gating process that is caused by the nonstartling prepulse, which serves to protect its ability to be processed.[74]

Several studies have reported that patients with first-episode schizophrenia and medicated patients with acute psychosis have deficits in acoustic PPI, especially when strong prepulses are used.[71,75,76] Using an eye-blink PPI paradigm, it has been shown that patients with schizophrenia, their unaffected relatives, and individuals with schizotypal personality disorder had deficits in right-eyeblink PPI compared with controls.[77] Studies have also indicated that deficits in PPI often correlate with both positive and negative symptoms.[74,75,78] However, despite being one of the most replicable

findings in schizophrenia, it is important to note that a deficit in PPI is not exclusive to schizophrenia and has been observed in many other psychiatric disorders.[79]

Deficits in sensorimotor gating can be observed in animal models of schizophrenia using the PPI test with mice or rats. The animal is first placed in a small restraining device to minimize movement and is then placed in an apparatus that can deliver acoustic startle pulses and prepulses. A sensor records startle responses to startle-alone trials and to prepulse + startle trials. The relative difference between the 2 startle responses constitutes PPI. Rats treated with pharmacologic agents and environmental insults, as well as genetic mutant mice, have all shown deficits in PPI.[79,80]

Working memory deficits

Working memory is conceptualized as a "limited capacity storage system, which temporarily maintains and stores information [and] supports human thought processes by providing an interface between perception, long-term memory and action."[81] Many studies have found impairments in working memory in patients with schizophrenia and their unaffected siblings. Studies have suggested that patients with schizophrenia may have deficiencies in active rehearsal processes, whereas passive stimulus maintenance processes and long-term memory networks may remain unaffected.[72]

More specifically, spatial working memory may be one possible endophenotype of schizophrenia. Some studies have shown that patients with schizophrenia and their unaffected relatives performed worse than controls on spatial working memory tasks, but that only patients performed significantly below controls on working memory tasks across other domains (i.e., verbal and object).[82–84] However, another study has suggested that spatial working memory deficits were only present in family members with diagnosable schizophrenia-spectrum personality disorders.[85] Other studies have also suggested that patients with schizophrenia may have a reduced memory span across modalities.[86,87] Two meta-analyses that examined working memory in patients with schizophrenia have suggested that the latter showed a substantial effect size for working memory deficits, regardless of modality, although there may be more consistent impairments in visual working memory.[88,89] However, it also has been suggested that working memory deficits may be the result of a general encoding deficit, particularly stimulus encoding (i.e., the transformation and preparation of presenting stimuli into a format facilitating collateral functions, including those of "working memory").[90–92] In addition, it has been suggested that impairments in working memory may be the result of deficits in processing speed.[93] Moreover, developments in mathematical modelling of schizophrenia cognition have formally integrated memory-trace impairment and encoding elongation.[92]

Spatial working memory is easily assessed in animal models of schizophrenia using spatial memory tasks. The Morris water maze is the most commonly used task in behavioural neuroscience research and can easily be configured to test spatial working memory with rats.[94] In this procedure, rats are placed in a pool of opaque water where there is a hidden platform located slightly below the water's surface. The rat is then released into the water at various points around the periphery of the pool and must navigate to the platform on the basis of the spatial cues in the room.[94] Although the water maze protocol can be used to test working memory in mice, this species tends to float and does not remain on the platform once it is reached, making interpretation of its behaviour uncertain.[95] Hence, the paddle pool task was developed to remove these confounds.[95] In this task, the mouse is placed in a circular pool that contains water to a depth of 2 cm. This motivates the mouse to escape but does not require it to swim. There are 12 exit holes on the wall of the pool, only 1 of which leads to an actual exit, which is connected to the mouse's home cage. The mouse is released near the centre of the pool and must learn to find the exit hole based on the spatial cues in the room.[95]

Although these tasks require the acquisition of a spatial working memory, simple versions of the tasks do not unambiguously measure working memory. Therefore, special versions of the tasks have been used to assess spatial working memory. These typically include a period of initial acclimation and training in a conventional version of the task, followed by frequent reversals of the hidden platform or exit location or new matching-to-place tasks on successive days.[96,97] These versions engage frontal cortex mechanisms by using retention intervals in the working memory time-frame and also allow for intertrial proactive interference.[98] Other tests of working memory include tests of continuous delayed alternation, discrete paired trial variable-delay alternation tasks and the radial arm maze.[99] Many animal models, including pharmacologic, neurodevelopmental and genetic models, have shown impairments in these working memory tasks.[99]

Stereotypy and perseverative behaviour

Stereotypy and perseverative behaviour are also considered to be viable endophenotypes, as well as symptoms, of schizophrenia, and are related to working memory performance. For example, the ability to set-shift is necessary for successful performance of the modified versions of the Morris water maze. In fact, studies have shown that patients with schizophrenia are often impaired on both reversal learning and extra-dimensional set-shifting.[100,101] Studies have shown that patients engage in perseverative behaviour on the Wisconsin Card Sorting Test (WCST), which is considered to be a measure of prefrontal cortical activity, as well as on a measure designed specifically to assess stereotypy, the Stereotypy Test Apparatus.[102,103] Studies have also shown that first-degree relatives of schizophrenia probands demonstrate perseverative behaviour on the WCST, further suggesting its relevance as a measureable endophenotype.[104,105]

Assessing perseverative behaviour is relatively simple in animal models. Rats given psychostimulants often exhibit locomotor hyperactivity, and at higher doses they exhibit stereotyped or perseverative behaviour.[106] Although people with schizophrenia generally do not exhibit hyperlocomotion, they do often engage in stereotyped or perseverative behaviour, which is thought to be modelled by stereotyped

behaviour in rats.[106] Hyperlocomotion and stereotyped behaviour are often seen in pharmacologic animal models and are thought to model the positive symptoms of schizophrenia.[107,108]

Deficits in latent inhibition

Latent inhibition (LI) is a process whereby an unreinforced stimulus interferes with the conditioning of a new contingency to the same previously unreinforced stimulus.[109] In such studies, the conditioned stimulus (CS) is presented alone (i.e., the CS-nothing contingency). Later, the CS is paired with an unconditioned stimulus (US), usually an aversive stimulus (i.e., the CS–US contingency). The CS-nothing pairing is thought to proactively interfere with the learning of the CS–US pairing, such that the conditioned response (CR) to the CS is reduced.[109] This reduction in the CR to the CS is known as LI. The interference in learning the CS–US contingency is thought to result from a decline in attentional processing of the CS when it was presented alone, such that the absence of LI is interpreted as an inability to discern relevant from irrelevant stimuli.[110]

Several studies have shown that LI is disrupted in patients with acute schizophrenia, but not those with chronic schizophrenia, although 1 study has found LI to be disrupted and persistent in the latter population.[110–112] These differences noted between patients with acute and chronic schizophrenia do not appear to be the result of stabilization due to medication, but rather the result of an evolution of the intrinsic factors of schizophrenia.[112] Impairments in LI have been found in first-degree relatives of schizophrenia probands, regardless of whether these relatives displayed schizotypal features.[113,114] One study, however, has not found an association between LI and schizophrenia.[115] Latent inhibition is thought to correlate with both positive and negative symptoms, depending on the methodology used.[109]

Latent inhibition tasks are easily conducted with rats and mice. Generally the CS is a tone, the US is a footshock, and the CR is a freezing response (i.e., conditioned fear). The differential response between the presentation of the CS–US contingency without the prior presentation of the CS alone and the presentation of the CS–US contingency with the prior presentation of the CS alone is an index of LI. Abnormal LI has been observed in pharmacologic, neurodevelopmental and genetic animal models of schizophrenia.[109]

Social withdrawal

Although not strictly considered to be an endophenotype, but rather a negative symptom of schizophrenia, social withdrawal is often assessed in animal models of schizophrenia. Studies have shown that adult patients with schizophrenia have a reduced social network and deficits in social competence, social skills and social cognition, including the misperception of affective information.[116–119] Social anhedonia has also been observed in the relatives of schizophrenia probands.[120,121]

Rodents are typically social animals and tend to approach unfamiliar conspecifics. As such, the social interaction test in animal models of schizophrenia is designed to measure social impairments similar to those in human patients. Recent developments in automated, digitized equipment and software have allowed the efficient collection of data on the social behaviour of pairs of animals on a time scale of seconds to weeks.[107,122] Tests can include observations of animal dyads in their home cages[122] or in a novel arena[107] or while 1 animal's movements are limited by placing it under a wire cup.[123] Regardless of the test used when studying social behaviour, the basic expectation is a reduction in social behaviour. Pharmacologic, genetic and neurodevelopmental animal models of schizophrenia have consistently found a reduction in social behaviour.[107,122,124,125]

Animal models in schizophrenia research

Animal models of schizophrenia can be developed in several different ways. Pharmacologic animal models are often used to test hypotheses related to glutamatergic and dopaminergic dysfunction. Neurodevelopmental models are used to either mimic certain neurodevelopmental risk factors of schizophrenia or to heuristically approximate damage that might occur by other means in schizophrenia. Gene knockout mouse models of schizophrenia target and disrupt specific genes that are thought to be risk factors in schizophrenia.

Ideally, an animal model should begin with the known pathogenesis of the disease, such that modelling schizophrenia risk factors in rodents would increase the value of these models.[126,127] Given that the etiology and symptomatology of schizophrenia is complex, no animal model will be able to capture its full complexity, particularly since the full complexity of human etiologic interactions and most symptoms cannot be modelled in rodents. Delusions, hallucinations, disorganized thinking, affective flattening, alogia and avolition are virtually impossible to model in animals, although it has recently been suggested that impaired reality testing may be modelled in rodents using certain Pavlovian conditioning procedures.[128,129] Given that schizophrenia is often characterized as a higher-order cognitive disorder, the ability to faithfully model symptoms in less cognitively developed animals can be difficult.[130] As a result, researchers have had to rely on the assessment of biomarkers and endophenotypes. However, despite being present in patients with schizophrenia, the relation between these biomarkers and the symptoms is not always clear, and many biomarkers are also observable in other disorders.[128] For example, social interaction deficits are observable in animal models of schizophrenia and autism.[107,131] However, the necessity of using endophenotypes and biomarkers in animal models of schizophrenia might also be an advantage of such studies, given the closer relation between risk factors and endophenotypes compared with the more distant relations between risk factors and symptoms. As previously mentioned, human association studies may also benefit from the use of endophenotypes as phenotypic markers. In addition, the lack of complete homology between the rodent and human central nervous systems (CNS) and the unknown specifics of how a particular endophenotype is expressed in each species mean that animal model data must be related back to schizophrenia with caution. It should also

be noted that there is a great deal of behavioural variability in different mouse strains used to generate animal models, thereby requiring additional caution in interpreting behavioural biomarkers.[132]

Despite these shortcomings, animal models are not meant to serve as complete equivalents to the disorder. Rather, animal models are useful in testing causative or mechanistic hypotheses of schizophrenia.[130] Animal models, while not providing a complete account of schizophrenia, complement the literature on schizophrenia in humans, which is largely correlational, by their ability to experimentally manipulate and control factors that could not otherwise be manipulated or controlled in humans. This permits a causal determination of the relation between the manipulation, whether it be pharmacologic, neurodevelopmental or genetic, and the presence of behavioural biomarkers.

Animal models can also be useful in understanding the mechanisms underlying the development of schizophrenia. In both genetic and neurodevelopmental models, brain tissue can be examined at different points throughout the lifespan to determine how the disease progresses and what factors may be involved in its progression. For example, the dysregulation of subcortical DA may permit a determination of specific brain changes that result from chronic dopaminergic dysregulation and of how those changes might impact other areas of the brain.

The fact that animal models often involve 1 particular gene knockout or environmental insult allow behavioural abnormalities associated with particular risk factors to be assessed without confounds from other risk factors that would be expected given the multifactorial nature of schizophrenia. This may also provide a better understanding of the etiology and underlying mechanisms of schizophrenia as they relate to a particular risk factor. In a sense, each model may provide 1 piece of the puzzle in understanding the causal relations between the etiology and mechanisms of schizophrenia and the development of the disorder. Although gene–environment interaction models can be created and would be extremely useful in advancing the field, such models are rare.[133] Hence, a single animal model cannot represent the entire population of patients with schizophrenia, but rather only a subset of patients with a particular risk factor.[126] When taken together, the resulting information can provide a more complete understanding of schizophrenia in a way that would not be feasible in studies on schizophrenia in humans.

Animal models of neurotransmitter dysregulation

As previously mentioned, studies in schizophrenia in humans show a dysregulation in several neurotransmitter systems, including those involving DA, glutamate and GABA. Animal model studies have typically focused on dopaminergic, glutamatergic and, to a lesser extent, GABAergic transmission, either through pharmacologic or genetic manipulations.

Pharmacologic animal models

Pharmacologic animal models typically involve the injection of amphetamine, a dopaminergic agonist, or phencyclidine (PCP), ketamine or MK-801, which are glutamatergic antagonists, into a rat or mouse.

As previously mentioned, patients with schizophrenia show dopaminergic hyperactivity in the striatum and dopaminergic hypoactivity in the PFC.[10,13] In animal models, administration of chronic amphetamine by implantation of slow-release silicone pellets is thought to model paranoid schizophrenia.[134] As time progresses, rats show increased locomotion (0–6 h), motor stereotypies (6 h to 3 d), reclusion to their burrows (4 d) and aggressive social interaction (5–7 d).[134] Amphetamine administration has been shown to disrupt PPI, spatial learning and social interaction.[135–137] Interestingly, other studies have found no effect of amphetamine on social interaction, but noted an increase in stereotypy and locomotor activity.[107,108] Dopaminergic antagonists applied to the PFC have been shown to disrupt PPI but not LI.[138]

As previously described, patients with schizophrenia show glutamatergic hypoactivity, such that the administration of glutamatergic antagonists induce acute psychotic reactions, including thought disorder, social withdrawal and catatonia in normal volunteers.[18] In animal models, gultamatergic antagonists, such as PCP, disrupt PPI, spatial learning and social interaction.[135,137,139–141] Increased locomotion and stereotyped behaviour were also evident in rats treated with single and repeated doses of PCP.[107,142,143] The social interaction deficits and stereotypy caused by PCP administration were reversed by conventional and novel antipsychotic medications.[144,145] The administration of ketamine or MK-801 also disrupts LI, spatial learning and social behaviour.[135,146,147] In fact, early repeated blockade of NMDA receptors using MK-801, where injections were administered from postnatal days 6–21, showed behavioural deficits, including decreased locomotion and exploratory behaviour, in adulthood.[148] This latter study better approximates glutamatergic dysfunction in schizophrenia, as the disruptions were made both repeatedly and early, whereas other studies merely used 1 acute injection. Consistent with the neurodevelopmental hypothesis, any disruption should occur early in life. Hence, the acute versus perinatal administration of glutamatergic antagonists may be responsible for the behavioural differences observed among studies.

As previously mentioned, the brains of patients with schizophrenia also show hypoactivity of the GABAergic system. The administration of picrotoxin, an antagonist of $GABA_A$ receptors, in the medial PFC but not in the lateral PFC or the hippocampus, has been shown to reduce PPI in rats.[149] Furthermore, it has been shown that blockade of $GABA_A$ receptors in the rat amygdala leads to abnormal GABAergic transmission in the hippocampus in a manner that is consistent with patients with schizophrenia.[150–152]

Taken together, the results show that pharmacologic animal models are useful in understanding the behavioural features associated with widespread neurotransmitter dysfunction, although the specific mechanisms are not fully known.[153,154] However, these models have limited use in assessing the developmental nature of the disorder. It has been suggested that the predictive and explanatory capabilities of pharmacologic models have, in fact, reached their limit.[130]

One point of interest is that many of these pharmacologic

manipulations can be conducted in humans with and without schizophrenia. Hence, their use in complementing the literature on schizophrenia in humans is limited. However, they are useful in demonstrating that similar biomarkers are observable in both humans and rodents when specific pharmacologic agents are administered. The identification and the expression of these biomarkers can then be assessed in other animal models.

Another shortcoming of pharmacologic models is that the transient nature of the drug effects does not follow an etiologically relevant course, as no permanent changes in the brain are expected. In addition, given the neurodevelopmental nature of schizophrenia, early-life neurotransmitter dysfunction would be expected to have an impact on brain development. Such an impact would not be expected in this type of animal model, as the animals will have undergone normal development before drug administration. Even when chronic drug administration occurs, prenatal and early perinatal neurotransmission function is normal. However, downstream effects of this neurotransmitter dysregulation can be examined in these models, without any confounds from morphologic brain abnormalities or other dysregulated neurotransmitter systems, both of which could be expected in patients with schizophrenia.

Genes involved in neurotransmission

Genetic animal models based on neurotransmitter abnormalities have focused on the disruption of the dopaminergic and glutamatergic systems. Dopamine transporter (*Dat*) knockout mice are unable to reuptake released DA, resulting in a hyperactivity of the dopaminergic system.[155] Similar to the findings in rats treated with amphetamine, *Dat* knockout mice display hyperactivity, perseverative locomotion and deficits in PPI and spatial learning but no deficits in social behaviour.[155–157]

The NMDA receptor is one of the receptors for glutamate, and mutations have been made in the NR1 subunit of the receptor such that the receptor's functionality was lowered.[155] Similar to the findings of PCP administration in rats, mice with NMDA receptor NR1 subunit hypofunction display deficits in PPI, hyperactivity, decreased anxiety-related behaviours and deficits in social interaction.[158–160] Calcineurin may be involved in the glutamatergic system and in the neurodevelopment of the brain.[161] Conditional calcineurin knockout mice displayed hyperactivity, deficits in PPI and LI, as well as abnormal social behaviour over a 3-day period.[122]

Taken together, these genetic animal models tend to show similar results to their pharmacologic counterparts. However, given the persistent developmental disruption of these genes, genetic models provide a greater consistency with the etiology of schizophrenia. As a result, they appear to be more informative than the aforementioned pharmacologic models in terms of etiology and underlying developmental mechanisms.

Animal models of environmental risk factors

Environmental risk factors in the multifactorial threshold model are generally considered to be those occurring prenatally or perinatally, although postnatal environmental stressors may also contribute to risk.

Viral exposure

In utero viral infections are examples of prenatal factors that may increase the risk of schizophrenia. In utero exposure to maternal influenza has been implicated in increased risk for schizophrenia.[162,163] In addition, prenatal exposure to rubella, toxoplasmosis and herpes simplex virus type 2 have all been linked with the development of schizophrenia.[164]

In animal model studies, maternal exposure to influenza was found to upregulate several genes and downregulate others that are involved in signal transduction, transport, protein metabolism and cell growth, as well as some genes that have been implicated in schizophrenia.[165,166] Studies have also shown that maternal influenza infection results in deficits in PPI, social interaction and exploratory behaviour.[167–169] Exposure to the herpes simplex virus and the Borna disease virus also impaired PPI.[170,171] However, it has been suggested that it is not fetal exposure to the virus itself that confers risk but rather exposure to the maternal immune response that may lead to altered brain development.[166,167,172,173] In fact, maternal exposure to a viral mimic, polyinosinic:polycytidylic acid (Poly I:C) or lipopolysaccharide (LPS) leads to deficits in LI, working memory, avoidance learning and PPI.[167,174,175] Although the precise effects of the maternal immune response on the developing brain are unknown, several hypotheses have been advanced:

- the maternal immune response elevates cytokines in the placenta, amniotic fluid and in the fetal brain, resulting in an inflammatory reaction that may impact neurodevelopment, fetal growth and placental function;
- fever, as a consequence of cytokine release, can result in abnormalities of the CNS and apoptosis in the cerebral cortex; and
- antibodies resulting from the infection may react and injure fetal brain structures.[168,176]

Obstetric complications

Perinatal obstetric complications have been found to increase the risk of schizophrenia developing later in life.[9] It has been shown that children born with obstetric complications at delivery, including preeclampsia, gestational age of less than 33 weeks, inertia of labour, vacuum extraction and respiratory illness, have about twice the risk for schizophrenia than those without such complications.[177,178] Whereas these obstetric complications are not specific to increasing risk for schizophrenia, they have been hypothesized to be etiologically relevant in the presence of schizophrenia risk genes.[179] Since the expression of many genes typically changes throughout development, a genetic predisposition involving the lack or early expression of susceptibility genes may cause an individual to be more susceptible to perinatal insults.[9,180] In fact, it has been shown that several schizophrenia risk genes that are regulated by hypoxia or involved in vascular function in the brain showed a significant gene × obstetric complications interaction.[181] This suggests that mutations in susceptibility genes may render schizophrenia more likely to develop in the presence of an obstetric complication. Similarly, it has also been suggested that in the presence of genetic vulnerability, postnatal stressors can result in the onset of or an increase in schizophrenia symptomatology.[182]

Several animal models of obstetric complications have been

assessed for schizophrenia-related biomarkers. Fetal hypoxia has been shown to lead to schizophrenia-related abnormalities in rats.[183] Rats exposed to neonatal asphyxia by being placed in a chamber of nitrogen gas for 30 minutes, showed amphetamine-induced hyperactivity, stereotypy, decreased social interaction and decreased brain-derived neurotrophic factor, the latter a finding in some patients with schizophrenia.[184–186] Another study has shown that 3 months after neonatal asphyxia, rats had an increase of vesicular monoamine transporter, which is involved in DA transport, in the striatum and an increase of glutamate transporter in the frontal cortex.[187]

Prenatal stress has also been used in the development of animal models of schizophrenia. In 1 study using maternal restraint stress, DA and glutamate receptors in the offspring were increased in the dorsal frontal cortex, the medial frontal cortex and the hippocampus.[188,189] Early maternal deprivation effects on offspring have included retarded motor development, reduced locomotion in an open field, increased amphetamine-induced locomotion and impairments in PPI and spatial memory.[190,191]

The aforementioned animal models replicate actual neurodevelopmental insults that are correlationally related to the development of schizophrenia and are useful in understanding the direct impact of prenatal and perinatal insults in the development of schizophrenia. Since these models replicate actual risk factors associated with schizophrenia, they would be most useful in assessing the neurodevelopmental nature of the disorder. Whereas the literature on schizophrenia in humans has provided correlational evidence between these insults and the development of schizophrenia, these animal models can address the question of a causal link between the risk factor and the development of specific schizophrenia-related biomarkers. These models are also useful in characterizing the mechanisms by which these insults exert their effects. For example, given the nature of human prenatal viral exposure research, it would be difficult to determine that it is the immune response, rather than the virus itself, that confers risk for the development of schizophrenia. Clearly, given the extreme manipulations described above, no such experiments could ever be conducted on human participants. Hence, the specific relations between the neurodevelopmental insults and schizophrenia-associated behavioural abnormalities can be elucidated mainly through animal model research. This kind of research exemplifies the relation between the human and animal literature. It is unfortunate that a full behavioural characterization of many of these models has not yet been conducted. However, given their strong etiologic relevance, future research into these models holds promise for further understanding the etiology of schizophrenia.

Animal models of neurodevelopmental disruption

Given the neurodevelopmental nature of the disorder, several animal models have attempted to heurisically replicate in animals brain damage that may occur by other means in human patients. Such models permit an understanding of the developmental sequellae that result from particular forms of neurodevelopmental disruptions.

Neonatal ventral hippocampal lesions

Neonatal excitotoxic damage to the ventral hippocampus (VH) is thought to disrupt the development of both the subcortical dopaminergic system and widespread cortical and subcortical circuitry in which the hippocampus participates, including projections to the PFC.[130,192] Similarly, inactivation of the VH is thought to disrupt normal maturation of the PFC.[192]

The appearance of abnormalities in this model follows the neurodevelopmental hypothesis in that they emerge postpubertally.[125,193] Studies involving neonatal ibotinic acid lesions to the VH have reported the postpubertal emergence of hyperlocomotion and deficits in PPI, LI, working memory and social interaction.[125,193–197] Interestingly, these deficits were not evident in rats that received postpubertal lesions of the VH.[194,197]

Rats neonatally lesioned in the VH showed a postpubertal downregulation of D_1 and D_2 receptor binding in the striatum, as well as an enhancement of glutamate binding in the PFC, which suggested hyperactivity of the dopaminergic system and hypoactivity of the glutamatergic system.[198] In addition, dopaminergic modulation of interneurons in the PFC has been shown to be disrupted.[199] It has also been shown that neonatal ventral hippocampal lesions result in a decrease in GAD–producing neurons and a decrease of GABA–related inhibitory interneurons in the hippocampus, enthorinal cortex and PFC.[200] Given the presence of multiple behavioural, neurochemical and neuroanatomic abnormalities that are consistent with schizophrenia, this animal model is useful in understanding the effects of suspected dysregulation of neurotransmitter systems in a developmental manner. However, although the resulting abnormalities are thought to arise from prefrontal cortical and dopaminergic disruptions, it is also possible that they may instead arise from indirect results of the lesion or the lesion itself.

The purpose of the VH lesion model is thought to serve as a heuristic to replicate both morphologic abnormalities in the PFC, as well as the dysregulation of neurotransmitter systems in a developmental manner. For example, it has been suggested that, as a direct result of the lesion, maturation of interneurons in the PFC is abnormal, which is consistent with human studies of schizophrenia.[199,201] This model is beneficial, as these abnormalities will be present during perinatal stages of brain development in the model, increasing the etiologic relevance. However, it should be noted that, although there are morphologic abnormalities observed in the hippocampus of patients with schizophrenia, the particular damage involved in the animal model (i.e., the complete destruction of the VH) is not observed in human patients. Hence, although the lesioning of the VH may replicate some of the downstream effects of schizophrenia, in terms of behavioural and brain abnormalities, such effects likely arise for different reasons in humans. However, resulting behavioural, neurochemical and neuroanatomic changes are reminiscent of schizophrenia and appear to model appropriate schizophrenia-related biomarkers.

Neonatal medial prefrontal cortex lesion

Given the importance of the PFC in the etiology of schizophrenia, some studies have attempted to lesion the medial PFC (mPFC). The PFC is connected with multiple cortical areas and

structures and also modulates some neurotransmitter function, notably the dopaminergic system.[202] Studies have shown no effect of the lesion on PPI or locomotor activity; however, there was increased sensitivity to a dopaminergic agonist on PPI in adult animals.[202] In addition, it has been found that the lesion, in conjunction with chronic pubertal treatment with a cannabinoid agent, reduces social behaviour and impairs object recognition memory.[203,204] Nonbehavioural abnormalities include enlarged ventricles, failure of myelinization of projections from the mPFC to the thalamus, hippocampus, nucleus accumbens and amygdala, as well as an increase in the sensitivity of the mesoaccumbal dopaminergic system.[202,205]

This model is quite beneficial in that it models developmental deficits in the PFC that are etiologically relevant to the development of schizophrenia. However, as with the VH lesion model, frank lesions of the mPFC are not observed in humans. Given the limited number of studies that have examined this lesion, more work is needed to clarify the nature of resulting biomarkers and the mechanisms underlying the behavioural disturbances. Nevertheless, this model appears to be a promising avenue for further research.

Neurogenesis disruption

One model that involves neurogenesis disruption is the methylazoxymethanol acetate (MAM) model of schizophrenia. In this model, a pregnant dam is treated with MAM, an antimitotic compound that leads to the methylation of nucleic acids and the death of cells that are actively replicating DNA.[206] This disrupts brain development in the offspring, particularly neuronal proliferation in the entorhinal cortex.[206–208] Offspring of MAM–treated dams display hyperlocomotion and rearing; a hyperreactive stress response; dopaminergic hyperresponsivity; and deficits in PPI and LI, passive avoidance learning, object recognition, social interaction and reversal learning.[207–211] In contrast, some studies have found no deficits in social interaction or spatial and working memory.[207,208] Brain changes include abnormalities of the entorhinal, frontal and occipital cortices, the thalamus, the parahippocampal region, the hippocampus and the amygdalohippocampal complex.[206,211]

Other studies have perturbed epidermal growth factor (EGF) signalling in the brain by administering early postnatal injections of exogenous EGF. In the CNS, EGF enhances the survival and promotes the differentiation of neurons, particularly the dopaminergic neurons of the midbrain.[212] Studies have shown that exogenous postnatal injections of EGF lead to hyperlocomotion and increased DA synthesis, and deficits in PPI and social interaction.[212,213]

Other studies have attempted to perturb neurotrophic signalling. One study infused p75 antibodies conjugated to saporin into the developing PFC, causing loss of the cells in the subplate and the marginal zone.[214] The results were the postpubertal emergence of amphetamine-induced locomotion and rearing, and a deficit in PPI. A subsequent study that used postnatal infusions of exogenous nerve growth factor (NGF) into the developing PFC, which caused similar damage as in the p75 model,[214,215] also reported similar brain abnormalities consistent with those observed in schizophrenia, as well as hyperactivity at 6 weeks of age and deficits in social interaction in adulthood.[216]

Taken together, the results of these models are useful in that they permit an understanding of behavioural and brain abnormalities resulting from a disruption of neuronal development and migration in a manner that is consistent with the etiology of schizophrenia. Again, this permits a more specific assessment of mechanisms, behavioural abnormalities and downstream neuroanatomic and neurochemical disruptions, independent of additional genetic or neurodevelopmental risk factors. The results of these models indicate that disruptions in neurodevelopment and cellular migration are causally linked to the development of many schizophrenia-related biomarkers. However, as in the VH lesion model, the causative neurodevelopmental disruption is not etiologically relevant. For example, patients with schizophrenia have not been perinatally injected with EGF or NGF.

A potential problem with these models is that the injection of an exogenous compound may result in nonspecific effects in the brain or other organs. For example, although it has been shown that MAM–exposed offspring display dopaminergic dysregulation and cortical impairments consistent with the neurodevelopmental hypothesis of schizophrenia, the administration of an antimitotic compound could also disrupt functioning in many other organs.[217] Despite these shortcomings, such models complement the literature on schizophrenia in humans by providing a more direct assessment of the effects of abnormal neuronal development and cell migration on the development of schizophrenia in a manner that could not be carried out with human participants.

Animal models of genetic risk factors

Given the evidence for a genetic component to schizophrenia, many studies have been undertaken to identify the genes that confer risk for the disorder. As one might expect, based on the brain abnormalities of patients with schizophrenia, many of the implicated genes are those involved in regulating neurodevelopment or neurotransmitter systems. As studies on schizophrenia in humans can only provide correlational analyses, genetic animal models are important in establishing a causative association between a biomarker and a particular risk gene. To describe the complementary nature of both human and animal approaches, We briefly review the methodology and results of both human linkage and association studies and genetic animal model studies. A more detailed discussion of specific genes that have been associated with schizophrenia follows, from both human and animal model perspectives. Since genes specifically related to neurotransmitter dysfunction have already been discussed, we discuss only the other major schizophrenia risk genes here.

Human genetic studies

A linkage analysis is a method for mapping the loci of genes related to a particular disease. The details of the linkage analysis method have been reviewed elsewhere.[218] Briefly, the demonstration of nonindependent segregation between schizophrenia and a genetic marker (i.e., another gene or

nucleotide sequence) indicates the presence of a disease allele on the chromosome containing that marker.[218]

Several meta-analyses have been conducted on linkage studies, confirming that schizophrenia is not linked to a single gene locus, but may be linked to multiple genes on multiple chromosomes, as hypothesized by the multifactorial threshold model of inheritance.[180,219] Badner and Gershon[220] examined all published genome scans for bipolar disorder and schizophrenia in which the location of the marker was provided and significant *p* values were reported. They found that the strongest linkage with schizophrenia was located on chromosomes 8q, 13q and 22q.[220] They also determined that there was some evidence for significant linkage on chromosomes 1q, 2q, 6q and 16q, but that these results were likely owing to the results of single studies.[220] Another meta-analysis of 20 genome scans suggested that chromosome 2p12–2q22.1 was significantly linked with schizophrenia when using stringent statistical criteria, whereas when using less stringent statistical criteria, the results showed linkage on chromosomes 5p, 3p, 11q, 6p, 2q, 1p, 22q, 8p, 20p and 14q.[221] Another recent linkage analysis study that employed a full genome scan found similar results with linkage on chromosomes 8p, 9q, 8q and 2q.[222] One point of interest is that the linkage results are somewhat inconsistent, possibly arising from differences in study selection criteria in the case of the meta-analyses and study methodology, although there are some chromosomal locations that are implicated in multiple studies.

Deletions of one noteworthy chromosomal area, 22q11, are often implicated in the development of schizophrenia. The 22q11 deletion syndrome involves a deletion of the chromosome at 22q11.2 during meiosis.[223] Children with this deletion show physical abnormalities, including congenital heart disease, facial deformities and immune system deficiencies, and neuropsychologic deficits, including impairments in visual memory, visual attention, working memory and motor function.[224] In addition, children with the 22q11 deletion syndrome are at about 25 times greater risk for schizophrenia developing later in life.[225,226] Several studies have also shown that children with the 22q11 deletion syndrome show decreases in PPI.[223]

Although linkage studies are powerful methods for determining the location of specific risk genes and their locations, they are limited by the fact that they provide only the chromosomal location of risk genes without providing any indication as to which gene is disrupted. To better understand the etiology of schizophrenia, it is crucial to identify specific risk (i.e., disease) genes to elucidate the disruption of biologic pathways.

Human association studies allow for the determination of correlations between particular genes and the development of schizophrenia. The methodology for these studies has been described elsewhere;[218] briefly, a particular allele may be considered to confer risk for the development of schizophrenia if the correlation between them is higher than would be expected by chance.[218] However, correlation does not necessarily mean causation. In fact, there are several noncausal explanations, such as linkage disequilibrium (i.e., the disease allele is near a gene that has been associated with the disease) or population stratification (i.e., the existence of several subgroups in the population with higher frequencies of both the disease and a particular gene), for finding an association between a particular gene and the disease.[218] Hence, an association may be found where no true causal relation exists.

Animal model genetic studies

There are several approaches to assessing the effects of particular gene knockouts in mouse models of schizophrenia. The first begins from the genetic manipulation approach. In this approach, specific genes of interest are mutated (e.g., loss of functionality, referred to as a gene knockout; reduced functionality, referred to as a gene knockdown; increased functionality; or new functionality), such that any observed schizophrenia impairments can be attributed to the gene product's effect.[227] The second approach uses behavioural assessment of the offspring of mice that have undergone random mutagenesis, where random point mutations are induced throughout the genome. Once a behavioural impairment of interest has been identified, genetic analyses can localize the gene responsible for the impairment.[227]

Mouse models can be derived from a variety of different hypotheses regarding the etiology of schizophrenia. Some knockout models have focused genes that are implicated in neurotransmission, and others on specific schizophrenia risk factors that have been identified in human patients. Several specific genes have been implicated in schizophrenia on the basis of human linkage and association studies. These genes have been selected for discussion based on the strength of their association with schizophrenia, as reported in the literature.

Proline dehydrogenase (*PRODH*)

Proline dehydrogenase is a gene encoding the mitochondrial enzyme proline oxidase, which is involved in the metabolism of L-proline and in the transfer of redox potential across the mitochondrial membrane.[228] This gene may also have an indirect influence on glutamate-mediated transmission, which was previously mentioned to be disrupted in schizophrenia.[228] This gene is located on chromosome 22q11, an area that has been implicated in several linkage studies; if deleted, this dramatically increases the risk of schizophrenia.[225] Studies have shown that polymorphisms in *PRODH* are associated with a reduction in bilateral frontal white matter density, decreased striatal volume and increased striatal–frontal functional connectivity, which are all consistent with neuroanatomic findings of schizophrenia.[229,230]

Several human association studies have implicated polymorphisms in *PRODH* with the development of schizophrenia. The first study to implicate *PRODH* examined a 1.5-Mb region of chromosome 22q11 to address the individual role of the genes in this area and their contribution to the development of schizophrenia.[231] After *PRODH* had been implicated in this initial study, the authors sought to identify further mutations in this gene. They found that in children with early-onset schizophrenia there were missense mutations in the *PRODH* gene that may have lead to a reduced functionality of the gene.[231] A missense mutation is a point mutation (i.e., alteration of a single nucleotide) resulting in the substitution of one amino acid by another during translation. The

resulting protein can be nonfunctional, isomorphic, neomorphic, hypomorphic or hypermorphic. Another study implicated nonsense or missense mutations in *PRODH* in a subset of patients with schizophrenia, along with a condition of hyperprolinemia.[232] A nonsense mutation is a point mutation resulting in the replacement of an amino-acid coding codon by a stop codon, thereby terminating the translation of the protein prematurely. The resulting protein is therefore truncated and often nonfunctional. Other studies have also implicated this gene in the development of schizophrenia in a Chinese family[233] and in individuals affected with schizoaffective disorder.[234] However, other studies have not found such an association.[235–237] Despite some inconsistency in the results, taken together, the evidence seems to suggest that mutations in *PRODH* are implicated in the etiology of schizophrenia.

Mutations in *PRODH* have also been associated with the development of particular schizophrenia-related endophenotypes in humans. An at-risk polymorphism in *PRODH* has been shown to attenuate PPI in healthy controls, as well as reduce performance verbal working memory tasks.[238]

In animal models, this gene, when overexpressed, also appears to modulate PPI in mice, but has no effect on locomotor activity.[239] Proline dehydrogenase knockout mice show highly increased levels of proline in the plasma, decreased levels of glutamate, aspartate and GABA in the hypothalamus, and reduced levels of GABA and aspartate in the frontal cortex.[240] These mice have been shown to have deficits in PPI and nonspatial hippocampus-dependent learning and memory, but are not hyperactive and do not display stereotyped behaviour or deficits in spatial working memory or have any particular gross morphologic brain abnormalities.[240,241] In sum, these animal models replicate similar endophenotypic findings as the human studies and suggest the possibility that several additional biomarkers may be linked to this gene.

Catechol-O-methyltransferase (*COMT*)

Catechol-O-methyltransferase is another gene located on chromosome 22q11. It encodes a protein that degrades catecholamines, such as DA, in the neuronal synapses.[242] In fact, patients with schizophrenia have increased expression of COMT glial cells in the PFC, possibly disrupting dopaminergic transmission in that area.[243] Several studies have implicated mutations of this gene in the development of schizophrenia. It has been suggested that a Val/Met substitution at codon 108 and/or 158 increases the activity of the enzyme by destabilizing the active site structure of the enzyme, thereby reducing dopaminergic transmission in the dorsolateral PFC.[244] Polymorphisms in *COMT* have also been associated with an increase in the grey matter of the right superior temporal gyrus and decreases in the volume of the hippocampus and parahippocampal gyrus.[230,245]

Though a promising candidate gene, the results of *COMT* human association studies are inconsistent. Several studies using different populations, as well as several meta-analyses, have shown that polymorphisms in *COMT* were highly associated with the development of schizophrenia, although not necessarily the Val/Met substitution, which may have no effect or only a modest effect, or may be itself highly associated with another polymorphism that has a causative effect.[246–250] Whereas the above-mentioned studies found associations between polymorphisms of *COMT* and schizophrenia, it is noteworthy that the studies are rather inconsistent in their results. Each association study generally investigates more than 1 polymorphism and reports significant findings on 1 or more of these, but any given polymorphism is not necessarily associated across studies. Nevertheless, despite these inconsistent results, *COMT* appears to be an important gene in the development of schizophrenia, although the Val/Met polymorphism may not confer as much risk as originally believed.[242]

Mutations in *COMT* have also been associated with several schizophrenia endophenotypes. Consistent with increased dopaminergic function in individuals with the Val/Met polymorphism in *COMT*, healthy volunteers and patients with schizophrenia show increased PPI.[73,251] Furthermore, this polymorphism has frequently been associated with WSCT performance, although recent studies and a meta-analysis have found that the association may only be small, although significant.[252,253] Finally, mutations in *COMT* have also been associated with social anhedonia.[254]

In animal model studies, male homozygous *Comt* knockout mice showed a 2- to 3-fold increase in DA levels, although female mice did not.[255,256] These knockout mice also exhibit decreased social behaviour, consistent with human studies, but no hyperactivity, stereotypy (i.e., perseverative behaviour) or deficits in PPI.[256] The lack of a disruption in the latter 2 biomarkers appears to be inconsistent with the aforementioned human studies.

Neuregulin-1 (*NRG1*)

Neuregulin-1 is a gene located on chromosome 8p that has a role in the expression and activation of glutamate, GABA and other neurotransmitters, as well as additional roles in neurodevelopment, specifically cellular differentiation and neuronal development and migration.[257] A variant in the *NRG1* promoter region has been associated with decreased frontal and temporal lobe activation, the development of psychotic symptoms, cognitive deficits and increased volume of the lateral ventricles.[258,259]

Human association studies have suggested that mutations in *NRG1* are highly implicated in the development of schizophrenia. The main haplotypes that have been associated with schizophrenia have been localized to both the 3′ and 5′ ends of the gene.[260] Studies of various races have shown a significant association between schizophrenia, as well as psychotic features related to other disorders, and haplotypes of *NRG1*.[261–263] However, some studies have failed to find an association between mutations in *NRG1* and schizophrenia.[264,265] A recent meta-analysis of 13 human association studies of *NRG1* found that 6 polymorphisms in *NRG1*, as well as at-risk haplotypes, showed a strong and consistent positive association with schizophrenia.[266] Another recent meta-analysis also found several polymorphisms of *NRG1* that were significantly associated with the development of schizophrenia.[267] Interestingly, some haplotypes have been associated with the deficit form of schizophrenia, whereas others have been associated with the nondeficit form of schizophrenia.[261] Again, as with the results

of *COMT*, the various haplotypes associated with schizophrenia are not always consistent across studies, and no endophenotypes have been associated with this gene as of yet. Nevertheless, taken together, the results suggest a significant role for *NRG1* in the development of schizophrenia.

Although results have been inconsistent across studies, in animal model studies *Nrg1* hypomorphic mice have shown modest baseline locomotor hyperactivity, but normal amphetamine-, PCP– and MK-801–induced hyperactivity. They also showed PPI and LI disruptions, as well as increased drug-dependent disruption of PPI, but no spatial memory deficits.[263,268,269] No differences were reported in terms of DA or serotonin receptor numbers.[269] These mouse models are consistent with the literature on schizophrenia in humans and elucidate some possible schizophrenia-related biomarkers that can now be specifically examined in human patients.

Disrupted in schizophrenia 1 (*DISC1*)

Disrupted in schizophrenia 1 was originally discovered from a balanced translocation between chromosome 1 and 11, in which parts of chromosome 1 and 11 were interchanged.[242,270] The 1q breakpoint was found to involve 2 genes: *DISC1* and *DISC2*; the latter is thought to be a non–protein coding regulatory gene.[270] Given the minimal number of genes at the breakpoint location on chromosome 11, it is not thought that any genes on this chromosome confer risk for the development of schizophrenia.[270] The protein DISC1 appears to interact with a number of proteins that are important in neurite growth and neuronal migration and may also impact granule cell migration in the dentate gyrus.[271,272] The neurodevelopmental roles of *DISC1* render it of potential importance for understanding hypothesized brain development abnormalities in schizophrenia. Studies have suggested that polymorphisms in *DISC1* may lead to a volumetric reduction of the supramarginal gyrus, a part of the posterior parietal cortex, a reduction in grey matter in the PFC, specifically in the superior frontal gyrus and anterior cingulate gyrus, impairments in PFC function and increased severity of positive symptoms.[273–275]

The *DISC1* translocation was first identified in a Scottish family and was associated with schizophrenia, bipolar disorder, major depression and other psychiatric disorders.[270,276] These results may indicate that disruptions in *DISC1* may not be unique to schizophrenia, but they may nonetheless confer risk for the development of the disorder. Polymorphisms of *DISC1* have also been associated with schizophrenia and schizoaffective disorder in multiple populations of various races.[277–279] A recent meta-analysis and association study found a significant association between polymorphisms in *DISC1* and schizophrenia in a European sample, and the meta-analysis revealed evidence for a common risk interval extending from intron 4 to 6, although several other polymorphisms were found to be significantly associated with schizophrenia across studies.[280] Interestingly, it has been reported that the genes showing the strongest association were in the area of the breakpoint previously described.[270,277] Polymorphisms of the *DISC1* gene have only been associated with 1 endophenotype: social anhedonia.[281]

In animal model studies, working memory has been shown to be disrupted in a mouse strain that contains a natural mutation in *Disc1*.[98] Behaviourally, studies have shown that mutations in *Disc1* result in impairments in PPI, LI, social interaction and impairments in spatial and working memory.[282–285] A 22-hour locomotor test has also suggested that *Disc1* knockout mice are hyperactive in the dark phase of the light-dark cycle.[284] Disrupted in schizophrenia 1 knockout mice have also been shown to have enlarged lateral ventricles, reduced cerebral cortical volume, reduced neuronal proliferation, reduced GABAergic interneurons in the hippocampus and cortex and attenuated neurite outgrowth in primary cortical neurons.[284,285] The behavioural and brain abnormalities are all reminiscent of those found in patients with schizophrenia. Therefore, these results suggest that mutations in *DISC1* have a significant role in the development of schizophrenia-related biomarkers.

D-amino acid oxidase activator (*DAOA*)

D-amino acid oxidase activator, also known as *G72*, which is located on chromosome 13q, has also been associated with the development of schizophrenia.[242] The protein, DAOA, is thought to be indirectly involved in glutamatergic transmission.[242] Given that DAOA interacts with a protein called D-amino acid oxidase (DAO), which metabolizes a modulator of NMDA receptors (i.e., receptors for the glutamatergic system), it is thought that DAOA is involved in schizophrenia by influencing these receptors.[286]

Several studies have found significant associations between polymorphisms in *DAOA* and multiple racial groups.[286–288] Other studies have been more inconsistent in their results. One study was unable to replicate associations for previously reported polymorphisms but discovered positive associations with 2 new polymorphisms, which the authors potentially attributed to chance.[289] A recently conducted meta-analysis found significant associations between polymorphisms in *DAOA* and schizophrenia in Chinese populations, but the associations lost significance when Korean populations were incorporated into the analysis.[290] Other studies have altogether failed to find an association between polymorphisms in *DAOA* and schizophrenia.[264,265,291] A large meta-analysis of 49 studies found a weak association between schizophrenia and mutations in *DAOA*, and there was a great deal of heterogeneity among the associated risk alleles.[292] Taken together, the results suggest that *DAOA* may play only a minor role in the development of schizophrenia.

It has also been suggested that mutations in *DAOA* may also be involved in modulating the endophenotype of working memory. Interestingly, healthy individuals who carried the high-risk allele of *DAOA* had better memory performance than those who did not.[293]

From an animal model perspective, there has been little work done to characterize the behavioural abnormalities resulting from disruptions of this gene. In the human genome, there are 2 overlapping genes, *G72* (*DAOA*) and *G30*, the former of which is only expressed in primates.[294] Therefore, the human *G72/G30* genomic region was spliced into mouse DNA to create the model. This transgenic mouse showed impairments in PPI, uncoordinated locomotor activity and increased sensitivity to PCP administration.[294] It is unclear how

and why behavioural deficits would appear in these mice if the spliced gene region did not contain schizophrenia-related polymorphisms. Nevertheless, this study suggests that the *DAOA* gene may be important in the development of schizophrenia-related biomarkers.

Dystrobrevin binding protein I (*DTNBP1*)

Dystobrevin binding protein I, also known as dysbindin, is located on chromosome 6p and is thought to influence glutamatergic transmission, although its exact function is not well understood.[242] It has been suggested that reduced expression of *DTNBP1* mRNA in the PFC and the glutamatergic terminals of the hippocampal formation are associated with schizophrenia, although the exact mechanisms are not well understood.[295,296]

A strong association has been found between polymorphisms in *DTNBP1* and schizophrenia in multiple racial cohorts, some particularly at the 3′ end of the gene.[265,297–299] However, several studies have failed to confirm this association.[300–302] Again, as with many of the previously discussed genes, there were multiple inconsistencies in and failures to replicate the positively associated polymorphisms across studies. A recent meta-analysis of 12 studies suggested that there is only a weak association of 1 single nucleotide polymorphism (SNP) in *DTNBP1* and schizophrenia and that associations of additional SNPs with the disorder may be the direct result of only 1 study.[303] These results suggest that some form of association may exist between mutations in *DTNBP1* and schizophrenia, although the exact extent to which mutations of *DTNBP1* are involved in the development of schizophrenia is still unclear.

In terms of endophenotypes, *DTNBP1* seems to be involved in memory performance. Patients with an at-risk haplotype of *DTNBP1* performed more poorly than patients who were noncarriers on a spatial memory task.[304] Similarly, a protective haplotype of *DTNBP1* was found to increase memory performance in healthy controls, although it had no performance effect in patients with schizophrenia.[305]

Recently, there has been a proliferation of animal model studies that have examined *Dtnbp1* in the sandy mouse, which does not express the *Dtnbp1* gene.[306] Studies have shown that *Dtnbp1* knockout mice display reduced social interaction, impairments in long-term memory retention, spatial memory and working memory, as well as hyperactivity.[306–309] These mice also have a reduction in the steady state levels of synapsin in the hippocampal formation, a reduction in DA, but normal glutamate levels.[308,309] Given the findings from both animal model and human association studies, it would appear that *DTNBP1* is an influential gene in the development of schizophrenia-related biomarkers and schizophrenia, respectively.

Reticulon-4 and the reticulon-4 receptor (*RTN4* and *RTN4R*)

Reticulon-4 is also located on chromosome 22q11 and is a glycosylphosphatidilinositol-linked protein, which contains multiple leucine-rich repeats that bind to the Nogo-66 protein.[310] Nogo-66 is a myelin-associated protein that inhibits the outgrowth of neurites and nerve terminals.[310] In addition, 2 other proteins thought to be involved in the inhibitory components of myelin also bind to the reticulon-4 receptor.[310] Investigations of these genes are currently in their infancy. Several studies have shown that polymorphisms in the Nogo-66 gene itself (*RTN4*), located on chromosome 2p, particularly a CAA insert in the 3′ region of the gene, confers risk for the development of schizophrenia.[311,312] However, 3 other studies failed to replicate this result.[313,314]

When *RTN4R* has been examined, the results have been mixed. Several studies have found associations between polymorphisms of *RTN4R* and schizophrenia in multiple populations, ranging in strength of positive associations.[310,315,316] One of these studies also found that some mutant alleles resulting from missense mutations were found in patients who were strongly resistant to neuroleptic treatment.[310] However, another study did not find such an association in a Chinese population.[317] Although *RTN4R* is a positional candidate gene, it has not been associated with any particular endophenotypes, and, therefore, further work on this gene is necessary to determine more conclusively whether it is a risk factor for the development of schizophrenia.

There are few studies that have assessed behavioural abnormalities in *Rtn4r* knockout mice. One study has shown that *Rtn4r* knockout mice have locomotor deficits but no impairments in PPI or working memory.[316] However, another study has suggested that *Rtn4r* knockout mice have impairments in spatial working memory.[315] These results seem promising, but given the inconsistent results of human association and animal model studies, the involvement of *RTN4R* in the development of schizophrenia-related biomarkers and schizophrenia is still in question.

The regulator of G-protein signalling 4 (*RGS4*)

The regulator of G-protein signalling 4 is a gene located on chromosome 1q and mediates postsynaptic transduction in dopaminergic, glutamatergic and serotonergic signalling pathways.[318] One study has suggested that allelic variations in *RGS4* are associated with changes in the functional pathways involved in working memory, grey matter structural connectivity and white matter volume.[318]

Several studies, including a meta-analysis, have reported associations between polymorphisms in *RGS4* and schizophrenia.[319–321] However, other studies, including a subsequent meta-analysis, have found no such associations.[265,322,323] Whereas *RGS4* is a positional and functional candidate for the development of schizophrenia, it has not been associated with specific endophenotypes, and the results, when taken together, render it difficult to determine the extent to which *RGS4* is a risk factor for the development of schizophrenia.

In terms of animal model research, 1 study has reported that *Rgs4* knockout mice did not show impairments in PPI or working memory.[324] Given these findings, as well as the inconsistency in the human literature, *RGS4* may not be as promising a candidate gene as first expected.

Zinc finger DHHC-type containing 8 (*ZDHHC8*)

Zinc finger DHHC-type containing 8 is located on chromosome 22q11 and is a putative palmitoyltransferase protein expressed in the brain, particularly in the cortex and the hippocampus, that may be involved in synaptic transmission and

post-translational modification of neurotransmitter systems.[325]

An initial scan of the 22q11 locus revealed 3 polymorphisms in *ZDHHC8* that were associated with schizophrenia.[326] Subsequent studies have confirmed positive associations between mutations in *ZDHHC8* and schizophrenia across a number of racial groups, as well as a sex-related heterogeneity of allele transmission, whereby female patients showed a stronger association between mutations in *ZDHHC8* and schizophrenia.[325,327] However, multiple studies have been unable to replicate these findings across various racial groups, although modest evidence of a sex-related heterogeneity of allele transmission has been confirmed.[328,329] Whereas *ZDHHC8* is a positional candidate gene, no endophenotypes have been associated with it and, given the inconsistent results, it is difficult to make a conclusive determination about its role in the development of schizophrenia.

In animal model research, a mouse model where both *Comt* and *Zdhhc8* were overexpressed showed decreased locomotor activity but no differences in PPI.[239] Given that *Comt* knockout mice have shown locomotor impairments, one might hypothesize that *Zdhhc8*, or the interaction of the 2 genes, is responsible for the modulation of locomotor activity in these mice. A *Zdhhc8* knockout mouse has shown deficits in PPI, decreased locomotor activity and decreased sensitivity to MK-801 administration, but no gross morphologic brain abnormalities.[325] It has also been demonstrated that these mice have a decreased density of dendritic spines and glutamatergic dendrites, as well as impairments in dendritic growth.[330]

Conclusions of genetic animal model research

Taken together, the results from these animal models suggest that mutations in *PRODH*, *NRG1*, *DISC1* and *DTNBP1* may confer greater risk for the development of schizophrenia, as they have been shown to be causally related to many schizophrenia-related abnormalities. It is important to note that these are the same genes that tend to be consistently associated with the development of schizophrenia in humans. In addition to these genes, mutations in *COMT* have strong human but not animal model support. Conversely, animal models with weaker schizophrenia-related endophenotypic presentation tend to involve mutations in genes (i.e., *DAOA, RTN4R*, *RGS4* and *ZDHHC8*) that are not as consistently associated with the development of schizophrenia. This may suggest several possible conclusions. First, these genes may only be involved in conferring a small degree of risk, resulting in the presence of fewer schizophrenia-related abnormalities in animal studies and greater inconsistency in human association studies. Second, the gene or the specific gene mutation may not be involved in the development of schizophrenia, and the presence of biomarkers and associations may be artifactual. Third, some of these genes may require an interaction with other risk genes to confer risk. For example, *RGS4*, *DAOA* and *DISC1* all show evidence of epistatis with *COMT*, suggesting that there may be an increased risk for schizophrenia based on an interaction between the genes.[331] Single gene knockout animal models would be unable to detect these interactions.

Genetic knockout models of schizophrenia, particularly those based on genes that are known risk factors, are useful in that they can show strong etiologic relevance to schizophrenia. These studies enable a determination of the causal link between the disruption of specific genes and schizophrenia-related biomarkers independent of other genetic or neurodevelopmental risk factors. In addition, they also permit an assessment of underlying mechanisms and downstream effects of the gene, including how these effects relate to the presence of biomarkers. For example, studies on the *Dat* knockout mouse have shown that both D_1 and D_2 receptors may underlie the expression of hyperactivity, whereas D_1 may regulate stereotypy, and D_2 may regulate sensorimotor gating.[156] Interestingly, results show that not all schizophrenia-related abnormalities are observed in a particular knockout model, which suggests that the disruption of a particular gene may modulate some, but not all, endophenotypes. Genetic animal models, therefore, can help determine which genes may modulate particular biomarkers and endophenotypes, but by no means approximate the complexity of the etiology of schizophrenia.

The complementary nature of human and animal genetic studies

Human genetic studies are indispensible in understanding the genetic basis of schizophrenia. Linkage studies are necessary to determine chromosomal locations of risk genes, and association studies are important to determine the relation between specific genes and schizophrenia. However, human association studies only provide correlational results and have typically yielded inconsistent results. These inconsistencies may result from a previously associated gene that may not be associated in a new study. Additionally, studies that examine different polymorphisms of a given gene may find, quite correctly, different results. Although some human association studies do not show an association between these genes and the development of schizophrenia, the results of animal models have suggested that there may be causal relations in some cases. Hence, null results obtained in human association studies could be explained by alternative reasons, rather than the lack of an association.

The failure to obtain an association does not mean that one does not exist in some human populations. The polygenic multifactorial threshold model suggests that there are a greater number of risk-increasing polygenes than the number of genes necessary to cross the threshold.[44] Hence, in one family or population, genes A, B and C may increase the risk for schizophrenia, whereas in another population genes B, C and D may increase the risk. A negative association for gene A in the second population does not mean that gene A is not a risk factor for schizophrenia. Rather, it may mean that gene A is not a risk factor in that particular population. In fact, it was noted in a previous meta-analysis of *DAOA* that a significant association in a Chinese population was rendered nonsignificant after the addition of a Korean population.[290] This exemplifies the fact that the failure to find an association may be population-specific and that a particular gene may be associated in some populations but not others. Regardless, the gene would still likely be an important risk factor.

Another reason for inconsistent results is the heterogeneity of the polymorphisms (i.e., SNPs) that are examined. It can easily happen that one study finds an association with a particular polymorphism, but another study does not find an association with a different polymorphism in the same gene. This does not imply that the gene itself is not a risk factor but rather that a particular polymorphism of that gene is not a risk factor. Hence, the failure to replicate a positive association might be the result of using an SNP that was designed to find a polymorphism in a different part of the gene.

Finally, there may be statistical reasons why an association may not be found. Many recent studies have assessed multiple SNPs simultaneously. Often, results are presented individually for each polymorphism, where 1 or more SNPs may be significant. However, owing to the large number of SNPs simultaneously assessed, the possibility exists that some of the significant associations occurred by chance. Hence, a statistical correction must be made to the α level, rendering it more difficult to find significant associations. Only associations that are highly significant remain so after the correction, whereas those that are less significant become nonsignificant.

Clearly, there are a number of methodologic issues inherent in genetic research in humans with schizophrenia. It is in this domain where the contribution of animal models is most evident. Human association studies provide the means for identifying relevant risk genes, but these studies have their limitations. By experimentally manipulating a gene in a mouse, one can ensure that all animals in the experimental group contain the particular risk gene with a particular polymorphism. This avoids the problem of examining populations that may not have polymorphisms in a particular gene of interest. Furthermore, environmental and developmental factors can be controlled across the lifespan of the mouse, thereby removing such factors as experimental confounds. Animal models avoid the correlational nature of human linkage and association studies by using an experimental paradigm. Therefore, the effect of a particular gene can be causally related to the development of a particular endophenotype. Multiple lines of knockout mice can also be used, such that different lines each have a different mutation in the same gene, thereby permitting a controlled and more thorough investigation of the particular regions of the gene that might confer risk.

However, genetic animal models are not without their limitations. Generally, animal models have involved the study of 1 gene at a time; this is a rather artificial way to study schizophrenia, given the polygenic nature of the disorder. The reliance on the use of endophenotypes, while beneficial in some ways, is also a limitation, as the same endophenotype can be found across a number of disorders. Animal models of autism, for example, show deficits in social interaction.[131] Therefore, if a particular gene knockout mouse only shows impairments in 1 biomarker, it is difficult to conclude that that the model is one of schizophrenia as opposed to another psychiatric disorder for which the biomarker might be relevant. It is, therefore, the complementary nature of the human and animal literature that can provide the clearest picture. A causal link between a particular gene and a schizophrenia-related biomarker in an animal model is most appropriate in the context of a plausible association between that gene and schizophrenia in humans.

Evaluation of animal models of schizophrenia

The previous sections have discussed schizophrenia-related abnormalities that are associated with many different kinds of animal models, including pharmacologic, neurodevelopmental and genetic animal models. The etiologic validity of these models depends largely on how closely they can approximate known schizophrenia risk factors. The resulting abnormalities can then be causally linked with each specific experimental manipulation. As we have noted throughout this review, many of these abnormalities are present in other psychiatric disorders, and the presence of multiple schizophrenia-related abnormalities does not necessarily imply that there is a relation to the development of schizophrenia as opposed to other disorders. However, this relation becomes more valid in the context of more etiologically valid models.

In such models, one can assess the impact of each individual manipulation, whether it is a genetic knockout or a replication of an obstetric complication, on behavioural, morphologic and neurochemical levels among others. Given the heterogeneity of schizophrenia symptom presentation, this understanding is crucial in delineating possible subsets of the population that may differ in terms of phenomenology or treatment outcome depending on the presence of certain risk factors and their associated biomarkers. Interestingly, many of the aforementioned animal models seem to share similar, although sometimes distinct, schizophrenia-related abnormalities. For example, deficits in PPI, LI and working memory are among some of the more consistent behavioural changes that are observed in these models. It is noteworthy that many of these animal models have distinct etiologic origin. This may suggest a number of possibilities.

First, these animal models may highlight the multifactorial nature of the disorder, such that presence of multiple risk factors is required for schizophrenia to develop.[44] From a behavioural perspective, each gene should result in particular abnormalities, such that the additive effect would lead to the development of schizophrenia symptoms.[55] Thus, one could hypothesize that a combination of risk factors would result in greater impairments. Some biomarkers are common among risk factors, such that the combination of the risk factors could result in a more severe impairment. Alternatively, some biomarkers are distinctive to each risk factor, such that the combination of risk factors could result in a greater array of abnormalities. We discuss the necessity of multiple risk factor models in the subsequent section. However, based on the convergence and divergence of schizophrenia-related endophenotypes in etiologically distinct animal models, this may indicate that as risk factors accumulate, the severity and number of abnormalities should increase, thereby leading to the development of actual schizophrenia symptomatology.

A second possibility is that many of these risk factors could combine in a neural common pathway that ultimately leads to the development of schizophrenia. Some authors have hypothesized that many of the risk factors culminate in a disruption

of neurotransmitter function, thereby affecting multiple brain areas and leading to the development of schizophrenia.[153,154] Such hypotheses would be difficult to test in animal models, as they cannot model the full complexity of the etiology or phenomenology of schizophrenia. Animal models can never provide a surrogate for schizophrenia as they can only model the effects of 1 or potentially a few risk factors at a time. Unfortunately, animal models cannot model complex genetic and neurodevelopmental interactions or epigenetic effects, which may be crucial in the development of the disorder. In fact, this limitation may underlie some of the discrepancies between human and animal studies of a particular risk factor. For example, our earlier discussion indicated that *COMT* had more support as a schizophrenia risk factor in human studies than in animal model studies. Conversely, the discussion indicated that *DTNBP1* appeared to have more support in the animal model studies than in human association studies. Although this may be owing to the lack of homology between human and rodent neurobiology, it may also reflect both protective and nonprotective interactions that are not modelled by single-gene knockout animal models.

The main use of animal models of schizophrenia risk factors is that they can permit an understanding of the mechanism of each risk factor in isolation. However, to test the aforementioned hypotheses, animal models that replicate multiple risk factors must be created. However, such models are currently rare, despite being crucial for schizophrenia research (see the following section). Most research has focused on the level of behavioural, morphologic or neurotransmitter abnormality, but an in-depth understanding of the mechanism of action of each risk factor would be important. This becomes particularly evident in the area of treatment. As many of the animal model studies have highlighted, schizophrenia-related biomarkers have been associated with a number of different etiologies, including neurotransmitter disruption, abnormalities in brain circuitry, neurogenesis disruption and genetic effects that lead to both neurodevelopmental and neurotransmitter disruptions. This suggests that the etiology of schizophrenia is diverse and complex, and this notion can impact treatment. When one examines the etiology of a variety of animal models, current dopaminergic treatment options for schizophrenia may be largely incomplete and ineffective at targeting the underlying pathology of schizophrenia.[332] This suggests that more disease-centred treatments, as opposed to drug-centred treatments, may be required to successfully treat schizophrenia.[332] For example, it has been suggested that novel treatments involving viral-vector gene transfer into the brain could be used to ameliorate psychotic symptoms or modify the course of the illness.[333] Animal models are not only well-suited to understand the mechanisms of schizophrenia, but could be particularly useful in testing the effects of more specialized treatment.

Animal models are clearly important in understanding the mechanisms underlying particular risk factors and related biomarkers. However, animal model research must still take place to more effectively complement research on schizophrenia in humans, and allow for a further unveiling of the etiology and pathogenesis of the disorder.

Future directions for animal models of schizophrenia

Animal models are useful in complementing the understanding of research on schizophrenia in humans, although they are not without disadvantages. Several important areas for further improvement have been highlighted in this review.

First, as previously discussed, background strain effects can alter the expression of certain behavioural abnormalities. Certain background strains may inadvertently contain mutations that can render the findings of a study ineffectual. For example, previous research has determined that mutations in *Prodh* resulted in deficits in PPI.[240] However, more recent research showed that the background strain used in this study had a mutation in another schizophrenia risk gene (i.e., *Disc1*) that led to PPI disruptions.[334] Therefore, there is a genetic confound making it unclear whether it is mutation of the *Disc1* gene or mutation of both the *Prodh* and *Disc1* genes that resulted in PPI deficits. In addition, there is a large accumulation of evidence indicating that different mouse strains display different baseline behaviours.[132,335] Similarly, some strains may have sensory impairments. For example, several strains contain mutations that cause retinal degeneration or impaired vision, rendering them unsuitable in a behavioural assay that involves visual information.[336,337] To remove genetic, sensory or behavioural confounds, and to ensure consistency in endophenotype expression and comparability across studies, a standard background strain, such as C57Bl/6J, should be used in mouse models of schizophrenia.

Second, the results of human association studies are often inconsistent owing to the diversity of polymorphisms studied. Similarly, this issue can also apply to genetic knockout research. The general model of knockout research is to inactivate the gene, based on the supposition that such an inactivation would have the largest effect on behaviour. However, such drastic genetic manipulations are not necessarily etiologically valid, as many human risk genes are associated with polymorphisms rather than complete gene deactivation. Similarly, different mutations within the same gene have been shown to lead to different behavioural profiles.[282] This suggests that small and distinct changes in the gene, which could result in altered protein folding, may cause different behavioural effects. Therefore, it is important to create animal models that reflect the polymorphisms or physiologic effects of identified risk genes. Thus, although it is important to determine the general effect of the gene on the development of schizophrenia by deactivating it, it is also important to target specific polymorphisms identified in the literature on schizophrenia in humans.

Another weakness of current genetic models is that they often only target 1 gene at a time. Although this permits an understanding of the gene's effects without additional confounds, the polygenic nature of the disorder is not modelled. This review has illustrated that mutations in different genes can lead to distinct or similar biomarkers, and the possible combination of these genes could lead to a greater number or degree of behavioural impairments. To assess the contribution of multiple polygenes, as is suspected in schizophrenia

in humans, it would be important to create multiple-gene knockout mice. Although this would be a complex and laborious undertaking, it would allow for an analysis of the relative contribution, as well as the interaction and additive effects, of each gene to the development of schizophrenia. It would certainly be interesting to knock out a combination of genes of relatively strong effect, such as *Prodh*, *Nrg1*, *Disc1* and *Dtnbp1*, to determine the number or severity of the resulting abnormalities. It would also be interesting to combine knockouts of the aforementioned genes with those of more modest effect, such as *Daoa, Rtn4r*, *Rgs4* and *Zdhhc8*, to detect interactions that might exist between these different classes of genes. Another avenue for modelling the multifactorial nature of the disorder would be to combine genetic knockout with environmental risk models. As previously noted, obstetric complications take on relevance to the development of schizophrenia within the context of a genetic predisposition.[179] Therefore, single or multiple knockout mice could be combined with single or multiple environmental risk factors. These animal models would permit a more complete understanding of the contribution and interaction of all possible risk factors and would, therefore, more completely model the etiology of the disorder.

Another important factor is the use of a battery of behavioural tests when assessing the effect of a particular gene on the development of schizophrenia. This provides a more complete behavioural characterization and permits a comparison between the behavioural abnormalities observed across models. Since a specific abnormality can be observed across multiple psychiatric disorders, it is important to obtain a convergence of schizophrenia-related abnormalities to determine that a particular gene is involved in the development of the disorder. Certainly, other tests could be added to many of the aforementioned studies to assess for additional schizophrenia-related behaviours, and provide a more complete behavioural characterization. Therefore, the greater the number of tests used, the greater the amount of convergence, and the greater the validity of the animal model. It may also be important to assess for behaviours that are not related to schizophrenia (i.e., depression and anxiety) to determine whether certain abnormalities are modulated through the pathways of other psychiatric disorders and whether there is a common genetic basis between different disorders.

Conclusion

Research on schizophrenia in humans is indispensible in understanding the relation between risk factors and the development of the disorder. However, taken by itself, research in human patients has limitations. Animal models of schizophrenia can complement research in humans by employing experimental paradigms, leading to possible conclusions regarding causation, which cannot be obtained from correlational data. In addition, such models can eliminate many confounds expected in schizophrenia research in humans by studying only 1 risk factor at a time. Such studies can, therefore, elucidate the etiology of schizophrenia by examining the causal pathways involved in the development of the disorder. Nevertheless, animal models cannot provide a complete picture of schizophrenia. One cannot obtain the complete clinical picture in a rodent owing to the lack of symptom presentation and the less than perfect homology in the CNS of both species. Hence, extrapolations to schizophrenia, on the basis of findings from animal model research, must be done cautiously.

In general, animal model research, although important and often well founded in the literature, is still incomplete. Many animal models have not been fully characterized on a phenotypic level using a large battery of tests and similar background strains. In addition, research using different knockout models of the same gene, resulting from mutations in different locations, is still in its infancy. Perhaps more importantly, multiple knockout and gene–environment interaction models are lacking and must be developed. Given the polygenic nature of the disorder, such models would be useful in better approximating the etiology of schizophrenia.

Nevertheless, the convergent evidence from human and animal studies can further elucidate the etiology, the mechanisms and the phenotype of the disorder. In addition, the complementary nature of these 2 types of studies can help circumscribe the boundaries of knowledge in each case. By applying the knowledge gained in both human and animal research on schizophrenia, advances in understanding the etiology, mechanisms and neurobiology of the disorder can be achieved and refinements in treatment procedures in both clinical and research settings can be implemented.

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