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Schizophrenia-Relevant Behavioral Testing in Rodent Models: A Uniquely Human Disorder?

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Abstract

Animal models are extremely useful tools in defining pathogenesis and treatment of human disease. Creating adequate animal models of complex neuropsychiatric disorders such as schizophrenia represents a particularly difficult challenge. In the case of schizophrenia, little is certain regarding the etiology or pathophysiology of the human disease. In addition, many symptoms of the disorder are difficult to measure directly in rodents. These challenges have not daunted neuroscientists who are capitalizing on even subtle overlaps between this uniquely human disorder and rodent behavior. In this perspective, we detail the features of ideal animal models of schizophrenia, the potential utility of such models, and the rodent behaviors used to model certain aspects of schizophrenia. The development of such models will provide critical tools to understand the pathogenesis of schizophrenia and novel insights into therapeutic approaches to this complex disorder.

Keywords

Schizophrenia; animal model; psychosis; behavior; knockout; genetic

A glance at the characteristic symptoms of schizophrenia would seem to make any attempt to model schizophrenia in rodents mere folly (American Psychiatric Association 2000). Indeed some would characterize schizophrenia as a quintessentially human disease, recalcitrant to rodent modeling. Certainly, the primary difficulty in modeling schizophrenia in rodents is that they cannot self-report hallucinations, scattered thinking, and other features of the disease. This has not fazed neuroscientists keen to capitalize on even subtle overlaps between this uniquely human disorder and rodent behavior and to make use of the many advantages of studying even complex neuropsychiatric disorders with animal models.

In this brief perspective, we do not list in detail existing animal models of schizophrenia, as such reviews abound (Gainetdinov et al 2001b; Lipska and Weinberger 2000). Rather we provide a blueprint for animal models of schizophrenia, from ideal features, to utility, to behavioral methodology. We discuss potential contributions of animal models of schizophrenia and desired features and utility of an “ideal” animal model. We then detail the behavioral tests that map directly or indirectly onto certain signs and symptoms of

schizophrenia. Finally, we discuss challenges for the future of rodent models of schizophrenia.

What Constitutes an “Ideal” Animal Model?

The “ideal” animal model of schizophrenia begins with the known pathogenesis of the human disease. Unfortunately, at this point, we are far from understanding the precise etiologies of human schizophrenia, although we know that interactions between genetic susceptibility (Cardno and Gottesman 2000; Sullivan et al 2003) and environment (Hoek et al 1998; Jablensky and Kalaydjieva 2003; Koenig et al 2005; Selten et al 1999; Susser and Lin 1992; Susser et al 1996; Takei et al 1995, 1996; Thomas et al 2001) play a prominent role. Human genetic studies have identified several candidate susceptibility genes to date; however, these typically represent only an increased or decreased statistical incidence of single nucleotide polymorphisms (SNPs) associated with schizophrenia (Harrison and Owen 2003; Harrison and Weinberger 2005; Owen et al 2005) with some exceptions. Furthermore, in most cases we do not understand the functional significance of these risk alleles. How are we to make the leap from association to causality in a heterogeneous, polygenetic disorder with environmental influences like schizophrenia? Reproducing these genetic alterations along with putative environmental factors (Hornig and Lipkin 2001; Lavin et al 2005; Rubinstein 1993; Van den Buuse et al 2003) in rodents and measuring schizophrenia-related behavioral abnormalities will provide one means to understand the gene/behavior relationship and to study the underlying pathophysiology.

Just as patients with schizophrenia do not manifest every possible symptom of the disease, an “ideal” animal model of schizophrenia will not necessarily exhibit abnormalities in all schizophrenia-relevant behaviors. We expect that an animal model will recapitulate some features of the disorder, and indeed some susceptibility genes or environmental interactions might dictate a subset of symptoms or a particular “endophenotype” of schizophrenia in humans and rodents. Creating a decision tree to assess relevance of animal models would be helpful. For example, one might suggest that at least three separate schizophrenia-relevant behaviors must be abnormal for a given model to have relevance to schizophrenia. Unfortunately, it is far too early in characterization of animal models of schizophrenia for such rigid constructs.

Predictive validity for current and future therapies is one of the more desirable features of an ideal animal model of schizophrenia. However, some current “predictive models” of schizophrenia treatment measure only a single dimension of antipsychotic drug effects, often testing the effects of acute antipsychotic drug administration on dopamine or glutamate receptor-mediated behaviors (Lipska and Weinberger 2000). Improved models of schizophrenia will likely lead to unique advances in schizophrenia treatment.

Because schizophrenia is a heterogeneous disorder, no single “ideal” animal model can represent the entire population of schizophrenic patients. It is likely that with the advent of additional models, each new model might represent a subpopulation of schizophrenia or even a particular aspect or endophenotype of schizophrenia.

Why Model Schizophrenia in Animals?

An animal model affords the opportunity to understand how genetic, molecular, or environmental associations might lead to schizophrenia. To go beyond statistical genetic associations with human disease or measured molecular alterations in human brains, it is helpful to manipulate these molecules in a prospective manner. With animal models, we can examine the causal relationship between genetic and environmental alterations and behavioral abnormalities, although only in a rodent surrogate.

Improved animal models of schizophrenia will provide an excellent tool for screening therapies. Current predictive models based on acute responses to existing drugs have not been successful in identifying novel therapies. Thus a test designed to measure a drug's effect on dopamine-regulated behavior such as apomorphine-induced cage climbing (Lordi et al 1997; Riffée et al 1979; Wilcox et al 1979) might not adequately measure efficacy of a drug that has no effect on the dopaminergic system.

Finally, animal models of schizophrenia will afford a better understanding of pathogenesis. Exploring pathogenesis in an animal model requires significant faith that the model represents the actual etiology of the disorder. Animal models that faithfully recapitulate a particular etiology or risk factor for schizophrenia will allow for studies of molecular and cellular alterations in mice that might be present in human schizophrenia. In the case of neuregulin 1 (NRG1) heterozygous mice, for example, a significant reduction in N-methyl-D-aspartate (NMDA) receptors was demonstrated, linking manipulation of NRG1 to a decrease in functional NMDA receptors. Similar reductions in functional NMDA receptors have been observed in certain regions of brains from schizophrenic individuals (Stefansson et al 2002). The ability to identify downstream molecular alterations will also open new windows into targeted therapy for schizophrenia.

Even if a genetic linkage study fails to prove a significant association of a genetic variation with schizophrenia, the potential importance of this gene for pathogenesis is not excluded. For example, an unstudied mutation in this gene might be associated with schizophrenia. Variation in the gene might account for symptoms in a different sample or subgroup. Regulation of the gene of interest by mutation in another unstudied gene might be involved in schizophrenia. Finally, the gene might be part of a broader signaling pathway that is important for pathogenesis of schizophrenia.

Rodent Behaviors Relevant to Human Schizophrenia

Individual rodent behaviors are not animal models of schizophrenia. Rather, they are critical experimental protocols in the development and testing of animal models. Unfortunately, we have not yet developed strict rules for assessing the relevance of a particular behavioral paradigm to schizophrenia.

Multiple overlapping criteria are used to assess the relevance of rodent behaviors to schizophrenia. First, some measurable behavioral abnormalities in schizophrenia can be measured directly in rodents. These measures go beyond a superficial similarity to schizophrenia, because the behavioral measurement is almost exactly the same in rodents and humans. Such similarity of a behavior in rodents and humans is likely only valid because of the conservation of neural circuitry underlying the behavior across species. Thus, many have argued that a behavior is relevant to schizophrenia if it relies on brain regions implicated in human schizophrenia, such as the prefrontal cortex, cingulate cortex, hippocampus, and other areas. Unfortunately, even behaviors almost identical in humans and rodents, such as prepulse inhibition of startle (PPI, described in the following paragraphs), can be modulated by a vast array of brain regions including hippocampus, prefrontal cortex, basolateral amygdala, nucleus accumbens, striatum, ventral tegmental area, ventral pallidum, globus pallidus, substantia nigra reticulata, thalamus, pedunculopontine nucleus, superior colliculus, and inferior colliculus (Swerdlow et al 2001). The modulation by many different brain regions does not make PPI less relevant to schizophrenia, although it does underscore the difficulty in using involvement of brain regions as the only measure of relevance to schizophrenia. Were this the sole criterion, our list of schizophrenia-relevant behaviors might be overly inclusive. Indirect measures are relevant to schizophrenia in that they resemble features of the disorder. Abnormalities in a

behavioral paradigm in existing animal models of schizophrenia are also taken into account. For example, alteration of a behavior by psychotomimetic drugs, neonatal hippocampal lesion, and genetic manipulation of schizophrenia susceptibility genes is more likely relevant to the disease than those behaviors affected by none of these manipulations. Thus, identification of relevant behaviors has been unfortunately a circular process in which the more plausible models define behaviors and these behaviors define the models, and so on. Over time the convergence of multiple animal models with better identification of the molecular and pathological abnormalities in human schizophrenia will likely provide a more rigid framework. Several rodent behaviors are currently used to model various aspects of schizophrenia (Table 1).

Hyperactivity, either at baseline or in response to the mild stress of a novel environment, has been demonstrated in many different putative animal models of schizophrenia (Lipska and Weinberger 2000). A subset of schizophrenic patients exhibits “psychomotor agitation,” which includes hyperactivity or increased stereotypic movements. In a neurodevelopmental model of schizophrenia involving early postnatal lesions of the ventral hippocampus, rats are hyperactive in response to a novel environment (Sams-Dodd et al 1997). So-called “psychotomimetic” drugs such as ketamine, PCP (phencyclidine), and amphetamine increase locomotor activity, and this effect can be decreased by antipsychotic treatment in rodents (Freed et al 1984; O’Neill and Shaw 1999). Among putative genetic models of schizophrenia, dopamine transporter knockout (Gainetdinov et al 1999) or knockdown mice (Zhuang et al 2001), NMDA receptor subunit NR1 knockdown mice (Mohn et al 1999), NMDA receptor glycine binding site mutants (Ballard et al 2002), neuregulin knockout mice (Stefansson et al 2002), Calcineurin (CN) mutants (Miyakawa et al 2003), NPAS1/3 double knockout mice (Erbel-Sieler et al 2004), and others have exhibited hyper-activity at baseline or in response to novelty. Thus, a simple measure such as locomotor activity or locomotor response to a novel environment might mimic the psychomotor agitation seen in schizophrenia. Of course, increased locomotor activity can be a hallmark of several neuropsychiatric disorders, such as attention- deficit/hyperactivity disorder or bipolar disorder.

Another way to characterize locomotor activity is by the response to psychotomimetic drugs, such as MK-801, ketamine, PCP (phencyclidine), and amphetamine, that cause psychosis in human control subjects (Tamminga et al 2003) and exacerbate psychotic symptoms in schizophrenia (Lahti et al 1995, 2001). Similarly, in rodents, hyperactivity and increased stereotypic behaviors can be induced by dopaminergic drugs, amphetamine, or cocaine and by non-competitive NMDA receptor antagonists MK801, PCP, and ketamine (Gainetdinov et al 2001b). Increased sensitivity to the locomotor-activating effects of these agents in rodents loosely parallels the increased sensitivity of schizophrenic patients to these psychotomimetic drugs. Thus, sensitivity to psychotomimetic drugs is another correlate of positive symptoms. Many of the schizophrenia-relevant behavioral tests mentioned in the following sections can be altered by psychotomimetic drugs administered to control rodents, and altered responsiveness to psychotomimetics might be tested with a variety of different behavioral paradigms.

Social interaction measures in rodents are directly analogous to social interaction measures in humans. Social interaction tests for rodents are often conducted in an open-field-like arena, wherein a test rodent encounters a stranger rodent. This test was originally used for assessing anxiety-like behavior (File and Hyde 1978) and subsequently used to assess the social behavior in potential animal models of schizophrenia (Miyakawa et al 2003; Sams-Dodd 1995). Many variants exist. For example, the “stranger” rodent can be freely moving (Miyakawa et al 2003) or trapped in a small wire-cage (Moy et al 2004; Nadler et al 2004). Additionally, two connected chambers might be used to define the animal’s preference for

social novelty versus a familiar conspecific (Crawley 2004). Other social tests are more difficult to directly link to schizophrenia but measure aspects of social dominance, such as the “tube test” (Lijam et al 1997). As with any behavioral dimension, it is preferable to use multiple methods to show decreased social interaction.

Many social interaction tasks are conducted in a novel environment that invokes exploratory and anxiety-like behavior in addition to social behaviors, confounding the outcome by reaction to the novel environment. Tests conducted in the home cage solve such problems. One of the authors (TM) devised an automated observation system that can monitor social behaviors for several days in home cages (Miyakawa et al 2003). Forebrain-specific CN mutant mice showed profound abnormalities in social behavior as assessed with this automated home-cage system and with a more conventional 10-min social interaction test under novel environment (Miyakawa et al 2003). Lijam et al (1997) found that mice lacking disheveled homolog 1 (*Dvl1*) show reduced social interaction in their home cage, including reduced whisker trimming and less huddling contacts. Also, the resident-intruder test conducted in the home cage can be used to assess aggression. With this test, Mohn et al (1999) discovered that NR1 knockdown mice display social withdrawal when an intruder is introduced in their home cage and that this phenotype was rescued by clozapine treatment. Thus, several social interaction tests are used to model negative symptoms of schizophrenia in rodents.

Disruption of nesting behavior in rodents is another common index of social behavior. When a sheet of cotton is introduced into a rodent home cage, they typically build a nest by shredding the material and piling it together to form a single unit (Schneider and Chenoweth 1970). Psychotomimetic agents, such as amphetamine, mescaline, and lysergic acid diethylamide, are known to disrupt this nesting behavior in rodents (Schneider and Chenoweth 1970). In addition, nest-building is a cooperative or “social” activity for rodents and is a measure of social activity (Crawley 2004). As mentioned previously, social isolation or withdrawal is a prominent negative symptom of schizophrenia. Putative genetic models of schizophrenia such as *Dvl1* knockout mice, NMDA receptor glycine binding site mutant mice, and CN mutants have been reported to show dramatic deficits in nesting behavior (Ballard et al 2002; Lijam et al 1997; Miyakawa et al 2003).

Recently, cognitive impairment in schizophrenia has drawn attention as particularly important for the morbidity in schizophrenia (Elvevag and Goldberg 2000; Green 1993). Cognitive impairment includes information processing, abstract categorization, executive function, cognitive flexibility, attention, memory, and visual processing (Services 1999). This is in contrast to the traditional construct of “cognitive symptoms” in schizophrenia that refers to disorganization of thought and behavior (Andreasen and Olsen 1982; Andreasen et al 1990), a symptom category that might be modeled by combined deficits in several schizophrenia-relevant behaviors.

One of the more studied and reproducible cognitive impairments in schizophrenia is an impairment in working memory (Elvevag and Goldberg 2000; Goldman-Rakic and Selemon 1997). In rodents, working memory can be measured in working memory paradigms in the eight-arm radial maze (Olton and Papas 1979), delayed alternation or spontaneous alternation task in T-maze or Y-maze (Moghaddam and Adams 1998), and delayed matching to place task in Morris water maze (Steele and Morris 1999). The duration during which rodents can retain transiently valid information varies from seconds to hours among these tasks, depending on the protocol used. Working memory requires the ability to rapidly form memory traces of unique events (single trial or one-time-experience learning) and the ability to distinguish currently valid information from older and already-invalid information (suppression of interference) (Zeng et al 2001). Impairments in some working memory tasks

might also be due to reduced behavioral flexibility or enhanced perseveration (failure to switch from previously learned solution to a new solution). With these tasks, it is often difficult to ascertain the precise nature of the working memory impairment. In the 8-arm radial maze, for example, apparent deficits in working memory might also be ascribed to reduced behavioral flexibility or increased perseveration. However, reduced behavioral flexibility and enhanced perseveration (Crider 1997) are also among the features of cognitive impairments of schizophrenic patients, thus, these “working memory” tasks in rodents are quite useful in the assessment of schizophrenia-relevant cognitive impairment.

Another aspect of cognitive impairment in schizophrenia is impaired long-term explicit or declarative memory (Heinrichs and Zakzanis 1998; Saykin et al 1991, 1994). This type of memory has been the subject of numerous behavioral studies in rodents in recent decades (Kandel 2001; Powell et al 2004; Silva 2003; Squire 2004; Sweatt 2003; Tonegawa et al 2003). As a result, several excellent behavioral tests in rodents exist to measure long-term explicit/declarative memory including the Morris water maze (Morris 1984), 8-arm radial maze (Markowska et al 1983; Pick and Yanai 1983), and Barnes maze (Barnes 1979), to name a few. Newer tests are being developed that are perhaps more ethologically relevant and more directly analogous to tasks in neuropsychiatric batteries in humans. These include odorant-based tasks where animals are asked to learn the significance of different relationships between odors to achieve some reward (Alvarez et al 2001, 2002; Eichenbaum 1998; Fortin et al 2004). Given the large body of knowledge regarding the molecular basis of learning and memory, it will be of interest to examine the overlap between manipulations that affect memory and those that affect other schizophrenia-relevant behaviors.

Measures of sensorimotor gating model the pre-attentive processing deficits observed in schizophrenia. Schizophrenic patients report oversensitivity to sensory stimulation that theoretically correlates with stimulus overload and leads to cognitive fragmentation (Braff and Geyer 1990). Prepulse inhibition is a common measure of sensorimotor gating and is decreased in schizophrenic patients (Braff and Geyer 1990). To measure PPI, one must first record the baseline response to a loud, brief, white noise pulse. The animal exhibits a quantifiable startle response to this pulse. Then, the same response is measured in the presence or absence of a smaller, non-startling prepulse that precedes the startle pulse by a brief delay (100 msec). This behavioral measure can be directly measured in both humans and rodents in essentially the same manner, and measures of PPI are among the most frequently used paradigms in animal models of schizophrenia (Braff and Geyer 1990; Geyer et al 2002; Paylor and Crawley 1997). It should be noted, however, that PPI deficits are not unique to schizophrenia (Braff et al 2001).

P50 gating is an electrophysiologic measure of pre-attentive processing that can be performed in humans as well as in rodents (Swerdlow et al 2006). P50 gating refers to the reduction in amplitude of an auditory evoked potential, measured with electroencephalography (EEG), by a pre-stimulus that is identical to the test stimulus (Nagamoto et al 1991). Like PPI deficits, P50 gating deficits are not specific to schizophrenia, because both are reduced in multiple psychiatric disorders (Ambrosini et al 2001; Baker et al 1987; Clementz et al 1998a, 1998b; Freedman et al 1987; Gillette et al 1997; Jessen et al 2001; Neylan et al 1999; Siegel et al 1984). As such, P50 gating and PPI are behavioral features used to model one aspect of schizophrenia that is shared by multiple additional disorders.

Latent inhibition refers to an animal's ability to ignore or suppress biologically irrelevant stimuli. Animals live in an environment full of varied stimuli, most of which are not relevant to their life. The ability to ignore irrelevant stimuli is critical in focusing on biologically important things and in using mental resources efficiently. Human schizophrenic patients are

known to exhibit abnormalities in latent inhibition, especially when they are acutely symptomatic (Lubow 2005; Weiner 2003). In rodents, latent inhibition can be demonstrated in a variety of classical and instrumental conditioning procedures (Weiner 2003), including the one using a modified cued fear conditioning paradigm (Caldarone et al 2000). In this paradigm, animals pre-exposed to a conditioning cue are subsequently unable to learn an association of this cue with an aversive unconditioned stimulus (foot-shock). The animal essentially “ignores” the tone/shock relationship, because it has learned that the tone is “safe.” Latent inhibition is performed in an analogous manner in humans and is impaired in schizophrenia. Latent inhibition has not been extensively used in animal models yet, but CN mutant mice are reported to show deficits in latent inhibition (Miyakawa et al 2003), whereas they do not show any significant abnormalities in aversive conditioning with conventional contextual and cued fear conditioning tasks (Zeng et al 2001). Neuregulin-1 mutant mice also show deficits in latent inhibition (Rimer et al 2005).

Another promising cognitive task of relevance to schizophrenia involves attentional set-shifting paradigms. The Wisconsin Card Sorting Test (WCST) is widely used to test attentional set-shifting ability in patients (Donohoe and Robertson 2003; Goldberg and Weinberger 1994; Morice 1990; Nieuwenstein et al 2001). In the WCST, subjects are required to sort cards on the basis of three perceptual dimensions (color, shape, and number), and schizophrenic patients show poor performance in this test (Owen et al 1993). In rodents, an analogous attentional set-shifting task is used (Birrell and Brown 2000; Colacicco et al 2002). In this task, subjects are trained to dig in bowls for a food reward. The bowls are presented in pairs, only one of which is baited. The subject has to select the bowl in which to dig by either an odor or the texture that covers its surface. In a single session, subjects perform a series of discriminations, including reversals, an intra-dimensional shift, and an extra-dimensional shift. In rats, the performance of this task is improved by pharmacological inhibition of catechol-O-methyl transferase, the product of a susceptibility gene for schizophrenia (Tunbridge et al 2004), and is impaired by NMDA receptor antagonists (Egerton et al 2005; Stefani and Moghaddam 2005). This task was introduced only recently to mice, and more work will be needed to validate this promising task with existing pharmacologic or genetic rodent models of schizophrenia (Colacicco et al 2002).

An elegant measure of attention and some aspects of executive function is the five-choice serial reaction time task (5-CSRTT) developed by Trevor Robbins et al (Chudasama and Robbins 2004; Robbins 2002). This task is loosely based on a popular measure of sustained attention used in humans (Rosvold et al 1956). The 5-CSRTT requires the subject to monitor five operant response locations for a brief visual stimulus. The animal then reports the location of this stimulus with an operant response that elicits a food reward. Accuracy of responses is a measure of sustained, spatial attention. Variations on this task include measures of selective or focused attention. The task can also examine features of executive functioning such as impulsivity and perseverative behavior (Chudasama and Robbins 2004; Robbins 2002). Although originally designed for rats, the task has can be modified for mice (Humby et al 1999; Marston et al 2001). The 5-CSRTT has already begun to illuminate the basic neural circuitry and neuromodulation of prefrontal executive and cognitive functions (Dalley et al 2004) and has particular relevance to attentional deficits measured in schizophrenia (Chudasama and Robbins 2004).

No single rodent behavioral task adequately captures the full spectrum of schizophrenia, nor is any single behavioral task uniquely relevant to schizophrenia. Likewise, no single symptom in isolation is diagnostic evidence of schizophrenia in humans. Therefore, we favor a broad behavioral screen or “battery” approach to assaying the relevance of experimental manipulations to schizophrenia. The number of behavioral abnormalities to deem a particular experimental manipulation of relevance to schizophrenia remains

unresolved. Focusing on a single behavioral paradigm to validate an animal model, however, is not appropriate. Each individual behavioral task suffers important limitations that require further refinement and use of important additional control behaviors (Dalley et al 2004; Dudchenko 2004; Sarter 2004). Thus, we cannot overemphasize the importance of continuing to examine in detail the molecular and cellular basis of each individual behavior in its own right. As we develop a better understanding of each behavioral paradigm and the underlying circuitry and pharmacology, we will be in a better position to link genetic and environmental manipulations to alterations in behavior.

Genetic Approaches to Animal Models of Schizophrenia

Recent advances in human genomics and in manipulation of the mouse genome allow for unprecedented progress in modeling schizophrenia. Some 99% of mouse genes have homologues in the human genome (Austin et al 2004). Although the human brain undeniably has tremendous capabilities that are uniquely human, these unique features are based on very subtle evolutionary changes that build on the rest of the genome. Thus, it is quite likely that abnormal behaviors in schizophrenia might be based on genes that have overlapping functions in mice. With genetic mouse models, one can determine whether altering known schizophrenia-susceptibility gene candidates leads to schizophrenia-relevant behavioral abnormalities in mice. This approach has been suggested as a means to determine “biological plausibility” of a candidate gene as causative in a complex neuropsychiatric disorder (Glazier et al 2002; Mackay 2001). In addition, one can screen potential target genes and, if manipulation of these genes produces behavioral abnormalities relevant to schizophrenia, one can test for the relevance of these target genes in humans.

The concept of testing the causal relationship between a putative susceptibility gene and schizophrenia with genetic models is a modern one. A heterozygous knock in mouse in which the mouse gene is replaced by the human gene containing relevant genetic variations would provide a most accurate model.

For the most part, genetic models of schizophrenia have been limited to constitutive knockouts of the gene of interest, heterozygotes, or conditional knockouts. Theoretically, transgenic overexpression is another viable approach, especially for genes that might be upregulated in postmortem brains of schizophrenic patients. The functional effects of most of the genetic variants associated with schizophrenia are unknown (Harrison and Owen 2003), and the effects of genetic variants are not necessarily equivalent to a genetic knockdown or knockout. That said, it is important to begin to understand the potential relevance of a human genetic association to behavioral abnormalities in animal models.

One recent example is the candidate schizophrenia-susceptibility gene *NRG1* (Stefansson et al 2002). The initial report of the association of *NRG1* with schizophrenia included behavioral studies on *NRG1* and *NRG1* receptor, *ErbB4*, heterozygous mice exhibiting schizophrenia-relevant behavioral abnormalities that were partially reversible with the antipsychotic drug clozapine (Stefansson et al 2002). Specifically, these mice exhibited hyperactivity in a novel environment that was “treated” with clozapine. The *NRG1* heterozygotes also showed a significant decrease in PPI. The PPI deficit was not treated by clozapine. Thus, an animal model was used as partial “validation” of the link between *NRG1* and schizophrenia. Subsequent behavioral characterization of related mutant mice has given additional support for the role of *NRG1* in schizophrenia-relevant behavioral abnormalities in mice (Rimer et al 2005).

The *NRG1* study exemplifies quite well some of the aforementioned challenges in modeling schizophrenia in mice. First, heterozygous, haploinsufficient *NRG1* mice are hardly equivalent to the association of a cluster of SNPs in the *NRG1* gene in humans. Second,

these mice were only tested in measures of sensorimotor gating and locomotor activity, whereas other potential schizophrenia-relevant behavioral tests were not measured. These issues do not serve to lessen the potential importance of NRG1 to schizophrenia susceptibility or even the quality of the published study but rather to highlight the difficulty in modeling even reproducible genetic associations in mice.

Other studies using mouse genetic models have attempted to link candidate proteins and genes to schizophrenia-relevant behavioral abnormalities and pathology. Studies of the susceptibility gene disrupted-in-schizophrenia (DISC1-1) indicate its involvement in neuronal migration and cortical development. Specifically, overexpression of a human mutant DISC1 at embryonic day 14.5 resulted in delayed neuronal migration assayed at postnatal day 2 and a significant reduction in vertically oriented pyramidal neurons assayed at postnatal day 14 (Kamiya et al 2005; Ozeki et al 2003). Although these studies were limited to neuroanatomical rather than behavioral correlations, the results suggest that cortical neuropathology in schizophrenia could indeed be linked to mutant DISC1. Neuronal PAS domain protein-3 (NPAS3) is a candidate susceptibility gene identified in a family carrying a translocation between chromosomes 9 and 14 (Kamnasaran et al 2003). Erbel-Sieler et al (2004) revealed abnormal PPI, social interactions, and locomotor activity in NPAS3 knockout mice. Additional candidate susceptibility genes remain to be studied or have not exhibited sufficient schizophrenia-relevant behavioral abnormalities.

An initial strategy in genetic models was to mimic pharmacologic models of schizophrenia-relevant behavioral abnormalities. These studies led to both dopamine and glutamate hypothesis-based knockout studies. Dopamine transporter knockout mice exhibit locomotor hyperactivity to novelty, impaired PPI, repetitive movements, and deficits in spatial learning (Barr et al 2004; Gainetdinov and Caron 2003; Gainetdinov et al 2001a; Jamain et al 2003; Ralph et al 2001; Zhuang et al 2001). Interestingly, amphetamines tend to alleviate the hyperactivity phenotype in the dopamine transporter knockout mice, making them akin to an animal model of attention deficit/hyperactivity rather than schizophrenia in spite of the other behavioral deficits (Gainetdinov and Caron 2000). The NMDA receptor subunit 1 knockdown mice exhibit hyperactivity, social interaction deficits, and response of hyperactivity to antipsychotics, whereas NMDA receptor subunit 2 knockout mice exhibit hyperactivity responsive to antipsychotics (Kishimoto et al 2001; Miyamoto et al 2001; Mohn et al 1999). These deficits in genetic models mimic their pharmacologic counterparts for the most part.

Another approach is to identify genes involved in schizophrenia-relevant behavioral abnormalities in mice and then to prospectively look for genetic linkage to schizophrenia. In the rush to understand the behavioral and cellular functions of the genome, hundreds of knockout mice are being created and characterized. At the same time, our ability to screen the behavioral relevance of these knockouts in a high-throughput manner is improving (Tecott and Nestler 2004). The data coming out of such studies have already begun to direct association studies of particular genes.

An example of this approach involves the behavioral characterization of CN knockout mice. Initially, no prior hypothesis existed regarding the relationship between CN and psychiatric disease. Forebrain-specific CN knockout mice were created with the cre-loxP system to test the role of CN in learning and memory. Initial behavioral characterization revealed severe deficits in working/episodic-like memory but completely normal reference memory (Zeng et al 2001). The CN knockout mice exhibited increased activity in response to novel stimuli, such as experimenter handling or cage changing. A more comprehensive behavioral test battery revealed multiple behavioral abnormalities relevant to schizophrenia, including increased locomotor activity, decreased social interaction, increased anxiety-like behavior,

and impairments in PPI. Further testing revealed impaired latent inhibition, abnormal nesting behavior, and increased sensitivity to the NMDA receptor antagonist MK-801. Thus, the CN mutant mice were impaired on multiple schizophrenia-relevant behaviors (Miyakawa et al 2003).

These findings encouraged an examination of the literature that revealed that abnormalities in the CN signaling pathway are relevant to traditional theories of schizophrenia pathogenesis. Calcineurin is a major modulator of dopaminergic signaling, and its activity is regulated by activation of NMDA receptors (Nishi et al 1997). On the basis of these links to schizophrenia, human genetics studies in a large sample of affected families were conducted and a modest but significant association of the PPP3CC gene was detected. PPP3CC encodes the CN- γ catalytic subunit (Gerber et al 2003). Subsequently, decreased hippocampal expression of the susceptibility gene PPP3CC and other CN subunits were found in postmortem brains of schizophrenia patients (Eastwood et al 2005). Moreover, subchronic administration of haloperidol and risperidone increase the activity of CN (Rushlow et al 2005), raising the possibility that some part of their clinical efficacy might be via modulation of CN. In this manner, the potential relevance of CN-related genes in schizophrenia was prospectively identified using a schizophrenia-relevant behavioral screen in an existing mouse mutant model. It is likely that additional susceptibility genes might be discovered prospectively using schizophrenia-relevant behaviors in genetically modified mice.

Other approaches to animal models of schizophrenia have paved the way for genetic models. Early studies focused on pharmacologic approaches. Direct or indirect agonists of dopamine receptors and blockade of the NMDA subtype of glutamate receptors can produce symptoms relevant to schizophrenia that are partially treated by antipsychotics (Gainetdinov et al 2001b). Genetic correlates to these pharmacologic findings have been created (Gainetdinov et al 2001a; Mohn et al 1999; Zhuang et al 2001). Following the “neurodevelopmental hypothesis” of schizophrenia, altering early brain development and neurogenesis has led to behavioral changes relevant to schizophrenia (Fiore et al 1999; Jongen-Relo et al 2004; Lipska and Weinberger 2000; Talamini et al 1998, 1999). Environmental stressors such as gestational malnutrition, viral infection, and maternal separation have also been proposed as animal models of schizophrenia (Hoek et al 1998; Jablensky and Kalaydjieva 2003; Koenig et al 2005; Selten et al 1999; Susser and Lin 1992; Susser et al 1996; Takei et al 1995, 1996; Thomas et al 2001). Although the particulars of these models are outside the scope of this perspective, the potential contribution of non-genetic components and developmental components to schizophrenia should be kept in mind.

Summary and Directions for the Future

Modeling signs and symptoms of schizophrenia in rodents is a difficult but necessary task. The advent of more accurate genetic mouse models, in combination with environmental factors, will allow for well-controlled studies to compare molecular, cellular, and circuit-level pathogenesis in animals with the more difficult human studies.

To design accurate models, additional advances in human genetic studies will be critical. Animal models are required to understand the functional relevance of mutations or SNPs in non-coding regions of the genome associated with schizophrenia. Indeed, it might even be difficult to understand how mutations with obvious functional effects lead to disease symptoms without reproducing such genetic pathology in animals.

How might we prioritize genetic models in schizophrenia? First priority should be given to animal models beginning with known or reasonably suspected susceptibility genes. The emphasis should begin to shift from traditional knockout models to knock-in approaches

wherein analogous genetic variations are modeled more accurately. Almost any schizophrenia- relevant behavioral abnormality in such a model is likely to be important. These animal models should be studied further for insights into downstream molecular targets of relevance to the phenotype that would become important targets for pharmacologic therapy and for future models. We might also examine mutant mice with alterations in molecular pathways downstream of neurotransmitter receptors hypothesized to be involved in schizophrenia. Another important approach will be to combine known genetic susceptibility with relevant environmental factors. One example of such a gene/environment interaction is exemplified by the moderation of progression to psychosis in subjects with the catechol- O-methyltransferase polymorphism by adolescent cannabis use (Caspi et al 2005). The main caveat is that minor susceptibility gene mutations might not lead to behavioral abnormalities. Thus, there is still a role for heterozygous or homozygous knockout mice in understanding the function of potential susceptibility genes.

As characterization of the rodent genome using knockouts advances along with high-throughput behavioral screening, we might identify additional susceptibility genes in a “prospective” manner going from rodents to human disease. One approach would be to target molecules identified in studies of human postmortem brain. Alterations in messenger RNA or protein expression levels in human schizophrenia might lead to behavioral abnormalities, be a consequence of treatment, or be a parallel phenomenon of the disorder. Animal models can help to assess the potential relevance of such findings.

Existing knockout mice that are known to be abnormal in a few of the listed behaviors should have their behavioral characterization expanded to include additional schizophrenia-relevant tasks. In this manner, we might use mouse genetics to gather information on the many potential molecular mechanisms of schizophrenia-relevant behavioral abnormalities. This information might in turn provide additional clues to pathogenetic mechanisms.

The modeling of schizophrenia in animals is continuously evolving. We need to broaden and refine our repertoire of behaviors relevant to schizophrenia. We must continue to develop reproducible cognitive tasks in humans that have exact parallels in rodents so that more tests are directly comparable and involve similar neuronal circuitry. Of particular relevance will be the domains of attention, impulsivity, working memory, and executive function. In parallel, we need to gain a better understanding of the brain regions involved in schizophrenia, because regionally targeted genetic manipulations will help us to dissect the circuit-level changes that lead to schizophrenia-relevant behavioral abnormalities. Finally, when animal models are created, it is important to test as many aspects of behaviors relevant to schizophrenia as possible. If we are to gain insights into the molecular and cellular basis of behavioral abnormalities relevant to schizophrenia, we must gain a broader understanding of the behavioral ramifications of a given manipulation.

To bridge the gap from rodent to patients, it will be useful to have intermediate phenotypes between behavior and molecules. One area deserving further exploration is functional neuroimaging in vivo. Advances in human and, more recently, rodent imaging could potentially bridge this gap quite readily. As alterations in the activity of various brain regions are implicated in human imaging, we might find correlates in imaging of animal models as analogous neuroimaging in rodents becomes feasible (Tamminga and Holcomb 2005; Tamminga et al 2003). Neuropathological correlates of disease are also used, but the difficulties with human postmortem tissue makes neuroimaging in vivo even more attractive.

As genetics and epidemiology in schizophrenia advance and rodent behavioral testing becomes more sophisticated and integrated with human behavioral tasks, the future will hold

great promise for animal models of schizophrenia. These new models will allow us not only to validate or identify genetic associations but also to explore pathophysiology and treatment options with a level of experimental control not yet possible in humans.

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Table 1**Mouse Behaviors of Potential Relevance to Signs and Symptoms of Schizophrenia**

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- I. Positive Signs/Symptoms:**
    - A. Psychomotor agitation**
      - a.** Locomotor activity
      - b.** Locomotor activity in response to novelty
    - B. Sensitivity to psychotomimetic drugs**
      - a.** Augmented locomotor response to non-competitive NMDA receptor antagonists (MK-801, PCP, ketamine)
      - b.** Augmented locomotor response to amphetamine
      - c.** Increased sensitivity of other tests to psychotomimetic drugs (e.g., increased effect of MK-801, PCP, or ketamine on PPI test)
  - II. Negative Signs/Symptoms:**
    - A. Social withdrawal**
      - a.** Decreased interaction with a juvenile conspecific
      - b.** Decreased place preference for a caged peer conspecific
      - c.** Decreased preference for social novelty
      - d.** Altered social dominance on tube test
      - e.** Altered aggression behavior on resident intruder assay
      - f.** Decreased nesting behavior
      - g.** Home-cage social interaction
  - III. Cognitive Signs/Symptoms:**
    - A. Decreased working memory**
      - a.** Impaired alternation in T-maze working memory task
      - b.** Impaired performance in 8-arm radial maze working memory task
    - B. Deficits in attention/sensorimotor gating/executive function**
      - a.** Decreased sensorimotor gating (PPI deficits)
      - b.** Decreased latent inhibition
      - c.** 5-choice serial reaction time test (5-CSRTT)
      - d.** Decreased set-shifting ability
    - C. General cognitive deficits**
      - a.** Decreased spatial learning in Morris water maze
      - b.** Decreased spatial learning in 8-arm radial maze
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NMDA, N-methyl-D-aspartate; PCP, phencyclidine; PPI, prepulse inhibition; CSRTT, 5-choice serial reaction time task.