Behavioral Animal Models of Antipsychotic Drug Actions

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Abstract Basic research in animals represents a fruitful approach to study the neurobiological basis of brain and behavioral disturbances relevant to neuropsychiatric disease and to establish and evaluate novel pharmacological therapies for their treatment. In the context of schizophrenia, there are models employing specific experimental manipulations developed according to specific pathophysiological or etiological hypotheses. The use of selective lesions in adult animals and

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G. Gross and M.A. Geyer (eds.), *Current Antipsychotics*, Handbook of Experimental Pharmacology 212, DOI 10.1007/978-3-642-25761-2_14,

the acute administration of psychotomimetic agents are indispensable tools in the elucidation of the contribution of specific brain regions or neurotransmitters to the genesis of a specific symptom or collection of symptoms and enjoy some degrees of predictive validity. However, they may be inaccurate, if not inadequate, in capturing the etiological mechanisms or ontology of the disease needed for a complete understanding of the disease and may be limited in the discovery of novel compounds for the treatment of negative and cognitive symptoms of schizophrenia. Under the prevailing consensus of schizophrenia as a disease of neurodevelopmental origin, we have seen the establishment of neurodevelopmental animal models which aim to identify the etiological processes whereby the brain, following specific triggering events, develops into a "schizophrenia-like brain" over time. Many neurodevelopmental models such as the neonatal ventral hippocampus (vHPC) lesion, methylazoxymethanol (MAM), and prenatal immune activation models can mimic a broad spectrum of behavioral, cognitive, and pharmacological abnormalities directly implicated in schizophrenic disease. These models allow pharmacological screens against multiple and coexisting schizophrenia-related dysfunctions while incorporating the disease-relevant concept of abnormal brain development. The multiplicity of existing models is testimonial to the multifactorial nature of schizophrenia, and there are ample opportunities for their integration. Indeed, one ultimate goal must be to incorporate the successes of distinct models into one unitary account of the complex disorder of schizophrenia and to use such unitary approaches in the further development and evaluation of novel antipsychotic treatment strategies.

Keywords Animal model • Antipsychotic drugs • Cognition • Negative symptoms • Positive symptoms • Psychosis • Schizophrenia

1 Introduction

Despite the growing consensus that schizophrenia is a brain disorder, a comprehensive neurobiological account of the disease (including the etiology, neuropathology, pathophysiology, psychopharmacology, and genetics) remains a considerable challenge to clinicians and scientists alike. Besides a direct exploration of these issues in human subjects, basic research in animals represents a fruitful approach to study the neurobiological basis of brain and behavioral disturbances relevant to schizophrenia and to establish and evaluate novel pharmacological therapies for their treatment. Indeed, the use of animal models allows a stringent experimental control of subjects in genetically homogeneous populations and facilitates the identification of neurobiological factors contributing to distinct forms of schizophrenia-related brain and behavioral abnormalities. Animal models also provide indispensable tools to test hypotheses which cannot be directly addressed in human subjects for technical and ethical reasons, including the verification of causal relationships in epidemiological studies.

One main goal of modeling a disease is to achieve a more profound understanding of its biology and thereby to identify possible targets for its treatment. It still appears that one of the major difficulties in the pharmacotherapy of schizophrenia is the limited clinical efficacy of antipsychotic drugs (APDs). Treatment with currently available APDs can only partially normalize psychopathological symptoms and are particularly poor in mitigating negative and cognitive symptoms (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010). Discovery strategies for novel APDs for the past 30 years have been dominated by efforts to reproduce the advantages of the reference atypical APD clozapine, while at the same time circumventing the drugs' numerous side effects such as agranulocytosis, hypotension, weight gain, and diabetes (Tandon et al. 2010; Rummel-Kluge et al. 2012). Even though several second-generation APDs such as olanzapine, risperidone, amisulpride, or sertindole have been labeled as "atypical antipsychotics," none of these drugs has yet approached clozapine with respect to its clinical efficacy (Hill et al. 2010). Given this, it appears that there is still a strong need for the development and evaluation of novel compounds with antipsychotic properties, which are effective in normalizing especially the negative and cognitive aspects of the disorder, and which are accompanied by minimal side effects. Preclinical research in animals is an indispensable step towards this goal because it allows a direct evaluation of possible beneficial versus harmful side effects of novel compounds with potential antipsychotic properties.

In this chapter, we discuss current attempts to model schizophrenia-relevant abnormalities in animals. Thereby, we focus on the two most widely used species, namely rats and mice. We would like to point out that in addition to these rodent species, several other species have been proven highly valuable in the experimental study of schizophrenia-relevant dysfunctions. One example is the use of (nonhuman) primate models, which may enjoy some essential advantages over rodent models in the study of cognitive processes pertinent to schizophrenic disease. An excellent discussion of this issue can be found in several recent reviews (Castner et al. 2004; Nelson and Winslow 2009; Simen et al. 2009).

In the present chapter, we first summarize the general validity criteria of animal models and outline distinct behavioral read-outs that can be used to experimentally approximate distinct symptom classes of the disorders. We then go on to describe the principal experimental methods, by which schizophrenia-relevant behaviors can be induced in animals. We attempt to provide a synthesis of different experimental approaches, thereby discussing the advantages and limitations of existing behavioral procedures and models in preclinical schizophrenia research.

2 Modeling Schizophrenia in Animals

The attempt to model any human psychiatric condition in animals has always been met with some skepticism, and schizophrenia is a particularly illustrative case (Boksa 2007; Low and Hardy 2007). The obvious reason for this is that the

clinical manifestation of schizophrenia in humans includes symptoms such as hallucinations, delusions, major thought disorders, and alogia, which are specific to humans and impossible to ascertain without structured interviews (Ellenbroek and Cools 2000a). Hence, it seems impossible to utterly mimic a complex human brain disorder such as schizophrenia in animals. Over the last three decades, however, there have been tremendous efforts to develop animal procedures that allow translations of the symptomatology observed under clinical conditions (Arguello and Gogos 2006; Lipska and Weinberger 2000; Meyer and Feldon 2010; Tarantino and Bucan 2000). These efforts are aimed at increasing the relevance of animal procedures for predicting the therapeutic efficacy of a novel substance (Markou et al. 2009; Nestler and Hyman 2010). The requirement for such efforts has also been highlighted by three recent research initiatives, namely the National Institute of Mental Health (NIMH)-funded (Measurement and Treatment Research to Improve Cognition in Schizophrenia) (Green et al. 2004; Marder 2006; Young et al. 2009), the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia (CNTRICS) (Barch et al. 2009a, b; Nuechterlein et al. 2009), and the European Commission initiative NEWMEDS (Novel Methods Leading to New Medications in Depression and Schizophrenia) (Hughes 2009). As exemplified by the latter, these initiatives aim to "... generate translational technology that could help provide early indicators of efficacy [...] and [...] to develop tools to improve patient stratification to focus on the complexity and heterogeneity of the disease." One consensus of these research initiatives is that in the view of the complexity and "human nature" of schizophrenia, one fruitful experimental approach is to focus on individual behavioral, physiological, and neuroanatomical phenotypes of the disorder rather than to model the entire syndrome (Arguello and Gogos 2006; Barch et al. 2009a, b; Floresco et al. 2005; Geyer 2008; Hughes 2009; Lipska and Weinberger 2000; Meyer and Feldon 2010; Tarantino and Bucan 2000). In parallel with similar efforts in humans, behavioral neuroscience and related research fields have established a wide variety of behavioral paradigms pertinent to the assessment of schizophrenia-related traits in experimental models. Such cross-species translational paradigms have been developed for the identification and characterization of neuropsychological, cognitive, and psychopharmacological core dysfunctions implicated in human psychotic disorders. Table 1 provides a sample of the most commonly used paradigms for the phenotypic characterization of schizophrenia-related neuropsychological, cognitive, and psychopharmacological core dysfunctions in rats and mice. These paradigms have been proven valuable and informative experimental tools to assess psychosis-like traits in a variety of lesion-based, genetic, neurodevelopmental, or psychopharmacological rodent models (Arguello and Gogos 2006; Barak and Weiner 2011; Castner et al. 2004; Meyer and Feldon 2010; Meyer et al. 2005; Moser et al. 2000; Swerdlow and Geyer 1998; Weiner 2003). It should be emphasized that the collection of the paradigms summarized in Table 1 is far from exhaustive. Theoretically, they are also not mutually exclusive of each other, even though they have been developed as tests of schizophrenia-related dysfunction largely independently of each other. Conversely, the neural substrate underlying

Table 1 A sample of experimental tests used for evaluating schizophrenia-related behavioral, cognitive, and pharmacological abnormalities in rodents

Neuropsychological, cognitive, and chemical domains	Experimental paradigm	Symptoms in schizophrenia	References
Sensorimotor gating[a]	Prepulse inhibition of the acoustic startle reflex	Impaired	Braff et al. (2001), Swerdlow and Geyer (1998), Yee and Feldon (2009)
Attentional control of selective associative learning[b]	Latent inhibition	Impaired in patients with acute positive symptoms; abnormally enhanced in patients with marked negative symptoms	Feldon and Weiner (1992), Lubow (2005), Moser et al. (2000), Weiner (2003)
	Kamin blocking	Reduced especially in acutely ill patients	Jones et al. (1992), Moran et al. (2003, 2008)
Sustained attention and vigilance[c]	5-choice serial reaction time test	Impaired in patients with schizophrenia and their nonpsychotic first-degree relatives	Birkett et al. (2007), Elvevag et al. (2000), Laurent et al. (2000, 1999)
Working memory[d]	Delayed non-match to sample/position Radial arm maze Morris water maze Y-maze	Impaired	Castner et al. (2004), Goldman-Rakic (1994), Kellendonk et al. (2009)
Executive functions[e]	Intradimensional/extradimensional shift	Impaired at impaired set-shifting and concept formation	Barch et al. (2009a, b, Brown and Bowman (2002), Ceaser et al. (2008), Dalley et al. (2004), Garner et al. (2006)
	Discrimination reversal learning	Abnormally enhanced behavioral/cognitive flexibility in patients with marked positive symptoms (switching behavior); behavioral and/or cognitive inflexibility in patients with marked negative symptoms	Brown and Bowman (2002), Crider (1997), Murray et al. (2008), Yogev et al. (2003)
Social behavior[f]	Social interaction and recognition tests	Reduced especially in patients with negative symptoms	Crawley (2008), McGlashan and Fenton (1992)
Stereotypy[g]	Open field exploration test Holeboard exploration test	Presence of stereotypic behavior	Crawley (2008), Morrens et al. (2006), Ridley (1994)

(continued)

Table 1 (continued)

Neuropsychological, cognitive, and chemical domains	Experimental paradigm	Symptoms in schizophrenia	References
Dopamine-associated neurotransmission[h]	Behavioral reaction to amphetamine In vivo microdialysis following systemic amphetamine challenge to assess the (striatal) release of dopamine and other neurotransmitters	Increased sensitivity to dopamine-stimulating drugs; enhanced striatal dopamine release	Laruelle et al. (1996, 2003), Lieberman et al. (1987)
Glutamate-associated neurotransmission[i]	Behavioral reaction to ketamine, dizocilpine and phencyclidine In vivo microdialysis following systemic treatment with ketamine, dizocilpine and phencyclidine to assess the (striatal) release of dopamine and other neurotransmitters	Increased sensitivity to NMDA-receptor-blocking drugs; reduced glutamatergic signaling at NMDA receptors	Carlsson et al. (2001), Laruelle et al. (2003)

The table summarizes the most commonly used cross-species translational experimental paradigms used to assess schizophrenia-related functional brain abnormalities and outlines the corresponding psychopathological symptoms in the human clinical condition

[a]Prepulse inhibition (PPI) of the acoustic startle reflex refers to the reduction of startle reaction to a startle-eliciting stimulus (pulse) when it is shortly preceded by a weak stimulus (prepulse). It is an operational measure of sensorimotor gating which reflects the ability to filter or gate intrusive sensorimotor information

[b]Latent inhibition (LI) and Kamin blocking (KB) are forms of selective associative learning considered to indicate an organism's capacity to ignore irrelevant stimuli. LI is usually described as the retardation in learning about the significance of a stimulus as a result of its prior non-reinforced (nonconsequential) repeated pre-exposures. In associative conditioning, pre-exposure of the to-be-conditioned stimulus (CS) impedes the subsequent development of the conditioned response (CR) following pairings between the same CS and a significant event, the unconditioned stimulus (US). KB refers to the impediment of the development and/or expression of a CR when a target conditioned stimulus (CS2) is presented as part of a compound that includes another CS (CS1) that had been used previously to establish a CR

[c]Sustained attention and vigilance can be assessed using the 5-choice serial reaction time test (5-CSRTT), which tests the ability of a subject to sustain spatial attention divided among a number of locations over a large number of trials. This capacity is measured by the subject's accuracy of reporting the correct stimuli

[d]Working memory is a special short-term memory buffer with a limited temporal capacity and is used to hold relevant information active in order to guide ongoing behavior, including comprehension, reasoning, and problem solving. Numerous experimental paradigms can be used for the assessment of working memory in experimental animals, including the delayed non-match to sample/position (DNMTS/P) task, the radial arm maze, the Morris watermaze, and the

Y-maze. An important component of working memory as assessed in these paradigms is the short-term storage of trial-unique information, whereby unique information about specific stimuli (e.g., spatial location and object information) is retained briefly in a short-term memory buffer and discarded after an appropriate response is executed

[e]Executive functions are commonly referred to as a collection of brain processes which are crucial for planning, problem solving, maintenance of goal-directed behavior, and behavioral/cognitive flexibility. Two effective experimental procedures to study executive functions in rodents are the paradigms of intradimensional/extradimensional shifts and discrimination reversal learning. An intradimensional shift occurs when the subject is required to cease responding to one feature of a particular perceptual dimension (e.g., "red" for the dimension color) and begins responding to a new feature of the same dimension (e.g., "blue"). On the other hand, an extradimensional shift occurs when the subject is required to switch responding to a novel feature of a previously irrelevant perceptual dimension (e.g., from the color "blue" to "circles" from the dimension "shape"). In reversal learning, subjects first learn to respond differentially (typically approaching or avoiding) to two stimuli of opposing valence (S1+ vs. S2−), and are then confronted with the same two stimuli but with the reversed valence (S1− vs. S2+). The ability to recognize an unexpected consequence from a previously established associative learning rule and then to switch the response contingency accordingly is crucial to reversal learning

[f]Social behavior is commonly referred to behavior that takes place in a social context and results from the interaction between and among individuals (of the same species). Since most of the commonly used experimental animals, including rats and mice, are highly social animals, social interaction and recognition tests can be efficiently used to study social behavior under experimental conditions

[g]Stereotypy is defined as uniform, repetitive, and compulsive actions within a restricted pattern which often have no obvious goals or end-points. Stereotype behavior can be assessed using open field or holeboard exploration tests, in which persistent repetitions of particular actions can be measured by observing the animal's behavior over a certain period of time

[h,i]One effective and informative way to assess the functional consequences of altered dopamine- and/or glutamate-associated neurotransmission is to measure a subject's behavioral sensitivity to acute treatment with dopamine receptor agonists such as amphetamine or NMDA-receptor antagonists such as ketamine, dizocilpine (MK-801), and phencyclidine (PCP). This can be coupled with in vivo microdialysis in order to have a parallel measure of extracellular neurotransmitter release before, during, and after the drug challenge. Adapted from Meyer and Feldon (2010)

performances on each of these behavioral, cognitive, and psychopharmacological tests share considerable common elements, and their identification is particularly crucial to the disease process of schizophrenia. Hence, the power of validation is magnified many folds when these tests are applied as a battery of tests for the phenotypic characterization of functional abnormalities relevant to complex neuropsychiatric disorders such as schizophrenia, especially when the experimental model system does not rely on any specific presumption of the disorder's neuronal substrates.

2.1 General Validity Criteria of Animal Models

The extent to which it is possible to extrapolate from animal model systems to the clinical condition in humans, and consequently the value of the information that may be derived from animal models depends on several validity criteria of the model. In general, there are three main criteria which ascertain the validity of an animal model, namely face, construct, and predictive validity (van der Staay et al. 2009; Willner 1984, 1986). It should be emphasized that no animal model is likely to fulfill all validity criteria at the same time. In fact, validity criteria are often restricted to the specific purpose of the model, and there is no general consensus about how to weigh the different categories of validity in the model evaluation process [for a detailed discussion, see van der Staay et al. (2009)]. Besides the distinct validity criteria, another major requirement of an animal model is reliability, i.e., the readiness with which the model or animal procedure data can be reproduced satisfactorily (Floresco et al. 2005).

2.1.1 Face Validity

This refers to phenomenological and symptomatological similarities between the features of the model and the clinical condition. For example, face validity reflects the degree of descriptive similarity between the behavioral abnormalities seen in the model system and the human psychopathological condition. Face validity also includes the etiological and/or epidemiological significance of the experimental manipulation used for the induction of a particular phenotype which aims at mimicking the human condition.

2.1.2 Construct Validity

According to early definitions by Cronbach and Meehl (1955), "construct validity is involved whenever a test is to be interpreted as a measure of some attribute or quality which is not operationally defined." A narrower concept of construct validity is used to describe the degree of similarity between the mechanisms

underlying the particular phenotype in the model and that underlying the phenotype in the condition which is being modeled (van der Staay et al. 2009; Willner 1984, 1986). Construct validity thus accounts for mechanistic similarities between the model and the clinical condition. In the context of animal models of human brain disorders, construct validity is a theory-driven, experimental substantiation of the behavioral, pathophysiological, and/or neuronal elements of the model. Hence, it reflects the degree of fitting of the theoretical rationale and of modeling the true nature of the symptoms to be mimicked by the animal model.

2.1.3 Predictive Validity

Predictive validity of an animal model implies that the model allows extrapolation of the effect of a particular experimental manipulation from one species to another (e.g., from rodents to humans), and from one condition to another (e.g., from the preclinical model in animals to the clinical condition in humans). A narrower concept of predictive validity is used in psychopharmacological contexts. Here, predictive validity usually implies that pharmacological compounds that are known to influence a clinical state in humans should have a similar effect in the animal model. Hence, this validity criterion refers to the sensitivity of the model system to clinically effective drugs. As a consequence, pharmacological treatments that precipitate or exacerbate a human pathological condition should exert a similar effect on the model, whereas those pharmacological treatments relieving the human pathological condition should have a similar beneficial effect on behavioral and/or cognitive abnormalities modeled in animals.

2.2 Behavioral Read-Outs in Relation to Distinct Symptom Classes

Schizophrenia is a multisymptomatic disorder that includes distinct but often coexisting symptom classes. These are commonly referred to as positive, negative, and cognitive symptoms (Tandon et al. 2009). Positive symptoms are features that are normally not present in healthy individuals but appear as a result of the disease. These include visual and/or auditory hallucinations, delusions, paranoia, major thought disorders, and psychomotor agitation. Negative symptoms refer to features that are normally present but are reduced or absent as a result of the disease process, including social withdrawal, apathy, anhedonia, alogia, and behavioral perseveration. Cognitive symptoms of schizophrenia typically involve disturbances in executive functions, working memory impairment, and inability to sustain attention. Taken together, schizophrenia is characterized by a wide spectrum of behavioral and cognitive dysfunctions that can readily undermine basic human processes of perception and judgment.

There is increasing recognition of the importance of negative and cognitive symptoms in schizophrenia, partly because currently available APDs show a limited clinical efficacy in improving these dysfunctions (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010). Negative symptoms are typically classified as primary or secondary, with primary negative symptoms representing a core feature intrinsic to the disorder, whilst secondary negative symptoms are temporary and often attributable to effects imposed by acute psychotic episodes and/or APD treatment (Möller 2004). Similar to the primary negative symptoms, cognitive symptoms of schizophrenia appear to be a core feature of the disorder and represent a major contributor to functional disability (Bowie and Harvey 2006; Elvevag et al. 2000). Both primary negative as well as cognitive symptoms often precede the onset of full-blown psychotic episodes and persist subsequent to the pharmacologically controlled resolution of acute psychotic phases (Möller 2004; Reichenberg 2005).

Given the heterogeneous nature of symptoms in schizophrenia, basic researchers who aim to develop heuristic animal models of the disorder are left with the challenge to establish and implement a set of behavioral procedures that can be used to indicate clinical features of the positive, negative, and cognitive symptoms. As reviewed in detail elsewhere [(Castagne et al. 2009; Ellenbroek and Cools 2000a; van den Buuse 2010); Table 1], the most commonly used and likely also the most reliable behavioral indices of positive symptoms in animal models are hyperlocomotor activity and behavioral stereotypies, which are taken to indicate psychomotor agitation and presence of stereotyped behavior in acutely psychotic patients. The rationale of using tests for locomotor hyperactivity and behavioral stereotypies as indices for positive symptoms is based upon the principle that enhanced dopaminergic activity in mesolimbic and nigrostriatal dopamine systems leads to enhanced locomotor activity and (in the event of pronounced hyperdopaminergia) stereotyped behaviors (Castagne et al. 2009; Ellenbroek and Cools 2000a; van den Buuse 2010). This fits well with the clinical condition showing that enhanced subcortical dopamine activity is essential in precipitating positive symptoms of schizophrenia (Laruelle 2000), but on the other hand, contrasts somewhat with the empirical evidence showing that schizophrenic patients do not display locomotor hyperactivity (Perry et al. 2009). Related to this, enhanced behavioral and/or neurochemical sensitivity to acute dopaminergic and/or glutamatergic drug challenge such as amphetamine or phencyclidine (PCP) exposure is another widely acknowledged index for approximating positive symptoms in animal models (Jentsch and Roth 1999; Robinson and Becker 1986; Steinpreis 1996). Besides spontaneous and drug-induced changes in locomotor activity and stereotyped behaviors, loss of selective associative learning in the form of disruption of latent inhibition (LI) is another cross-species translational index relevant to positive symptoms of schizophrenia (Feldon and Weiner 1992; Weiner 2003; Weiner and Arad 2009; Table 1). Indeed, consistent with the aforementioned contribution of enhanced subcritical dopaminergic activity to positive symptoms of schizophrenia, LI is readily disrupted by experimental manipulations that induce subcortical hyperdopaminergia, and attenuated LI is also found in acutely ill schizophrenic patients with marked positive symptoms (Weiner 2003; Weiner and

Arad 2009). Some researchers further suggest that disruption of prepulse inhibition (PPI) may be relevant for probing positive symptoms in animal models (van den Buuse 2010), even though it should not be considered as a straightforward model of positive symptoms as such but is more likely to represent the "interface of psychosis and cognition" (Desbonnet et al. 2009; van den Buuse 2010). In fact, since sensorimotor gating in the form of PPI involves pre-attentional/-cognitive processes preventing sensory overload and cognitive fragmentation, it may be used as a predictive index of cognitive dysfunctions relevant to schizophrenia (Geyer 2006).

Even though several cardinal aspects of the negative symptoms of schizophrenia are only hardly amenable to direct investigations in animal models, including poverty of speech and affective flattening, several behavioral procedures can readily serve to experimentally study behavioral abnormalities relevant for negative symptoms. For example, since rodents are highly social animals, social interaction can be efficiently studied under experimental conditions (Crawley 2007) and can therefore be used to probe deficient social interaction as one of the hallmark negative symptoms in schizophrenia (Foussias and Remington 2010; Table 1). Likewise, anhedonia is another hallmark of negative symptoms in schizophrenia, and anhedonic behavior can be assessed relatively easily in rodents using specific tests such as the sucrose preference test (Table 1). There are also several behavioral/cognitive tests that can be used to approximate the presence of behavioral/cognitive perseveration, which is commonly observed in schizophrenia patients with marked negative/cognitive symptoms (Crider 1997; Murray et al. 2008; Yogev et al. 2003). As outlined in Table 1, such tests include spatial and nonspatial forms of reversal learning as well as tests allowing the assessment of LI perseveration.

Within recent years, translational approaches have largely concentrated on the cognitive aspects of schizophrenia, primarily because of two reason: Firstly, cognitive symptoms of schizophrenia appear to be a core feature of the disorder and a major contributor to functional disability (Bowie and Harvey 2006; Elvevag et al. 2000). Secondly, cognitive aspects of schizophrenia may be more amendable to experimental investigations compared to the more florid psychotic manifestations, and therefore, they can be investigated in a relatively correspondent manner both in humans and in animals. The recent MATRICS and CNTRICS initiatives have identified separate core domains of cognition, all of which are (to a certain extent) affected in schizophrenia and which have to be treated to meet therapeutic needs (Green et al. 2004; Marder 2006; Young et al. 2009). These include working memory, attention/vigilance, reasoning and problem solving, processing speed, visual learning and memory, verbal learning and memory and social cognition (Green et al. 2004; Marder 2006; Young et al. 2009). As shown in Table 1, most of these cognitive domains can be experimentally addressed in animal models by the use of specific test batteries that characterize these domains. Hence, implementation of tests in existing or prospective animal models (see Sect. 3) is expected to significantly advance our understanding of the nature and possibly also the treatment of cognitive symptoms of schizophrenia.

3 Experimental Manipulations to Induce Schizophrenia-Relevant Brain Disease

In principal, most of the available rodent models of schizophrenia fit into four different induction categories, namely (1) pharmacological, (2) genetic, (3) lesion, and (4) neurodevelopmental manipulations. Notably, some of the currently used models fit into more than one category, and different induction methods can be combined so as to take into account multiple pathophysiological and/or genetic aspect of the disorder. The four cardinal induction categories are discussed in the succeeding sections.

3.1 Pharmacological Models

Pharmacological models of schizophrenia are driven by known or presumed neurochemical imbalances pertinent to the disorder's pathophysiology. Alterations in the central dopamine (DA) system have been discussed for decades, originally based on evidence that the therapeutically effective APDs act, at least in part, by blocking DA receptors, especially the DA D_2 receptor subclass (Seeman 1987) and that DA-stimulating drugs can induce psychosis-like behavior in nonpsychotic human subjects and exacerbate (positive) symptoms in schizophrenic patients (Carlsson et al. 2001; Howes and Kapur 2009). Subsequently, the putative impact of a hypofunctioning cortical DA system has been incorporated into the theories of altered DA functions in schizophrenia (Carlsson et al. 2001; Howes and Kapur 2009). In addition to these cortical-subcortical DA imbalances, functional changes in serotonergic and glutamatergic transmission seem highly relevant for the disorder (Abi-Dargham et al. 1997; Carlsson et al. 2001; Coyle et al. 2003; Javitt 2007). The current consensus is that alterations of these neurotransmitter systems either lead to a functional imbalance of DA transmission via interaction with the DA system, and/or contribute pathophysiologically to schizophrenia by direct non-dopaminergic actions. Finally, alterations in the central γ-aminobutyric acid (GABA) (Benes and Berretta 2001; Lewis et al. 2005) and cholinergic (Martin and Freedman 2007) systems have also been in the focus of attention by virtue of their modulatory functions at the relevant synapses and their impact on cognitive functions known to be impaired in schizophrenia.

Pharmacological models using acute and/or chronic administration of dopamine-releasing agents such as amphetamine or preferential dopamine receptor agonists such as apomorphine were among the first manipulations used to experimentally induce psychosis-related abnormalities in both animal models and humans [for a historical account, see Baumeister and Francis (2002)]. Indeed, behavioral changes induced by dopamine-stimulating drugs have been widely employed as screening procedures for the detection of compounds with potential antipsychotic properties (Table 2). However, even though such models may be relevant to

Table 2 Summary of schizophrenia-relevant abnormalities as identified in various pharmacological models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
Acute amphetamine treatment	$\downarrow^{a,b}$	$\downarrow^{a,b}$	ND	ND	ND	$\uparrow^{a,b}$	Mansbach et al. (1988), Swerdlow et al. (1986), Warburton et al. (1994), Weiner et al. (1997a, b)
Chronic amphetamine treatment						$\uparrow$	Kokkinidis and Anisman (1981), Robinson and Becker (1986)
Withdrawal from amphetamine	$\downarrow^{a,b}$	$\downarrow$	$\downarrow/=$	$\downarrow$	ND	$\uparrow$	Featherstone et al. (2007a, b), Featherstone et al. (2008), Fletcher et al. (2005, 2007), Murphy et al. (2001), Peleg-Raibstein et al. (2008, 2006a, b, c, 2009), Russig et al. (2002, 2005), Tenn et al. (2005a, b)
Acute NMDA antagonists	$\downarrow^{b}$	$\downarrow^{b}$	$\downarrow^{b}$	$\downarrow^{a,b}$	$\downarrow^{b}$	$\uparrow^{b}$	Amitai et al. (2007), Chatterjee et al. (2011), Egerton et al. (2005), Geyer et al. (2001), Jentsch and Roth (1999), Mansbach and Geyer (1989), Mouri et al. (2007), Nabeshima et al. (1986), Paine and Carlezon (2009), Sams-Dodd (1995, 1996)
Chronic NMDA receptor antagonist	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow$	$\downarrow^{b}$	$\uparrow^{a,b}$	Amitai et al. (2007, Becker and Grecksch (2004), Becker et al. (2003), Enomoto and Floresco (2009), Jentsch and Roth (1999), Lee et al. (2005), Mouri et al. (2007), Sams-Dodd (1999)
Withdrawal from NMDA antagonists	$\downarrow/=$	$=$	$\downarrow$	$\downarrow^{a,b\ NR}$	$\downarrow$	$\uparrow$	Amitai and Markou (2010), Becker and Grecksch (2004), Becker et al. (2003), Chatterjee et al. (2011), Paine and Carlezon (2009), Seillier and Giuffrida (2009), Tenn et al. (2005b)

(continued)

Table 2 (continued)

Experimental manipulation	Behavioral, cognitive, and pharmacological functions						References
	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	
Postnatal PCP treatment	ND	↓	↓	ND	ND	↑	Andersen and Pouzet (2004), Depoortere et al. (2005), Mouri et al. (2007), Sircar (2003), Tenn et al. (2005a), Wang and Johnson (2007)
Postnatal blockade of NMDA receptors	ND	↓[b]	↓	ND	ND	↑	Wedzony et al. (2008a, b)
Pretnatal MK-801 treatment						↑	Abekawa et al. (2007)
Postnatal MK-801 treatment	ND	↓	↓	ND	ND	ND	Baier et al. (2009), Stefani and Moghaddam (2005), Uehara et al. (2009)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control manipulation (vehicle treatment)

ND not determined, *NR* no response to: APD treatment

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

the study of neurochemical processes underlying the precipitation of positive symptoms, they readily fall short in capturing cardinal aspects of negative and cognitive symptoms of schizophrenia (Table 2). A clear refinement of acute and/or chronic administration of dopamine-stimulating drugs is the amphetamine withdrawal model (Featherstone et al. 2007a, b; Peleg-Raibstein et al. 2008, 2006a, b; Russig et al. 2002), which has been developed in the context of the endogenous dopamine sensitization theory of schizophrenia (Laurent et al. 2000; Lieberman et al. 1997). In contrast to acute amphetamine administration models, amphetamine withdrawal models have been shown to mimic at least certain aspects of cognitive dysfunctions relevant for schizophrenia (Featherstone et al. 2008; Fletcher et al. 2007).

The initial observation that administration of NMDA receptor antagonists such as ketamine or phencyclidine (PCP) disrupt various cognitive process and induce psychosis-like states in humans have led to the establishment of glutamatergic pharmacological models of schizophrenia (Kantrowitz and Javitt 2010). In essence, these models are based on acute or chronic treatment with NMDA receptor antagonists, including ketamine, PCP, and dizocilpine (MK-801), and more recently, such pharmacological agents have also been used to study the effects of withdrawal from NMDA antagonist exposure (Castner et al. 2004; Mouri et al. 2007; Nabeshima et al. 2006). Compared to dopamine-related pharmacological models, it appears that pharmacological NMDA receptor blockade models can capture a broader spectrum of schizophrenia-related dysfunctions, and notably, they may be more adequate in capturing positive, negative, and cognitive symptoms of schizophrenia (Table 2).

Hallucinogens acting on serotonin (5-HT) receptors, including lysergic acid diethylamide (LSD), psilocybin and mescaline, induce visual hallucinations in humans and cause characteristic behavioral signs in animals (Vollenweider and Kometer 2010). In rodents, acute or chronic treatments with such hallucinogenic drugs induce a set of measurable behavioral abnormalities such as paroxysmic scratching, forepaw treading, head twitches, and lower lip retraction (Cook et al. 1992; Vanover et al. 2006). Antagonism of the behavioral effects of serotonergic hallucinogens in animals would thus appear to provide a possible behavioral model for assessing antipsychotic activity, especially in relation to the suggested role of 5-HT receptor abnormalities in schizophrenia (Abi-Dargham et al. 1997). Similarly, based on the suggested role of cholinergic changes in the pathophysiology of schizophrenia (Barak 2009; Martin and Freedman 2007) acute or chronic administration of a cholinergic receptor antagonist, including scopolamine, dihydro-β-erythroidine (DHBE), or trihexyphenidyl, have been shown to robustly disrupt schizophrenia-relevant cognitive functions and to further induce other hallmark behavioral abnormalities such as disruption of LI and PPI (reviewed in Barak 2009; Barak and Weiner 2011). However, the full potential of cholinergic manipulations in preclinical research of schizophrenia still awaits further validation (Barak 2009).

3.2 Genetic Models

It has long been recognized that schizophrenia is a heritable disorder that probably involves multiple genetic abnormalities with relatively modest effects across large populations (Sullivan 2005). There have been tremendous efforts to identify potential schizophrenia susceptibility genes using single nucleotide polymorphisms (SNPs) approaches, and such investigations have put forward a number of genes that may be relevant for the genetic etiology of this disorder, including neuregulin-1 (NRG-1), catechol-*O*-methyltransferase (COMT), and disrupted in schizophrenia-1 (DISC-1) (Gogos and Gerber 2006; Harrison and Weinberger 2005). However, many of these genes have been identified and portrayed in relatively small populations, and recent research suggests that several of the presumed candidate genetic factors do not reach significance in association studies conducted in larger populations (Nieratschker et al. 2010; Sanders et al. 2008). Yet, discrete genetic abnormalities may contribute to distinct forms of behavior and cognition, so that individual schizophrenia susceptibility genes may be closely linked to a particular endophenotype of the disorder (Gottesman and Gould 2003; Gould and Gottesman 2006). For example, sensorimotor-gating deficiency in the form of PPI disruption appears to be a relatively robust endophenotype of schizophrenia which has a clear genetic contribution (Quednow et al. 2011, 2009; Roussos et al. 2011). Therefore, it may not be surprising that significant alterations in PPI are also reported in numerous genetic models which have been designed in relation to specific schizophrenia susceptibility genes (Table 3).

As a manipulative tool, the genetic approach to neuropsychiatric research has been a relatively recent event (Tarantino and Bucan 2000). Despite this, there is a rapidly increasing number of genetic mouse models that report behavioral, cognitive, and/or pharmacological alterations reminiscent of schizophrenic disease, so that the collection of genetic models presented in Table 3 is far from exhaustive. Further refinement based on temporal, regional, and cell-type specific transgenic technology will add considerable power to current genetic approaches (Abazyan et al. 2010; Ayhan et al. 2011; Kellendonk et al. 2009), and in overcoming interpretative issues concerning developmental compensation. It is expected that the genetic approach will be instrumental in the identification of the roles of specific candidate genes in the disease process of schizophrenia, and the interaction between genetic and environmental factors associated with the etiopathology of schizophrenia (Abazyan et al. 2010; Ayhan et al. 2011; Laviola et al. 2009), perhaps even paving the way to possible genetic interventions in the future (Lesch 1999).

3.3 Lesion Models

Although it has been known since Bleuler's and Kraepelin's early investigations (Bleuler 1911; Kraepelin 1919) that schizophrenia is not associated with gross brain degeneration or lesions, postmortem and imaging studies have been consistent in

Table 3 Summary of schizophrenia-relevant abnormalities as identified in various genetic models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
$NR1^{-/-}$	ND	$\downarrow^{a,b}$	ND	ND	$\downarrow^{b}$	$\uparrow$	Duncan et al. (2006), Mohn et al. (1999), Moy et al. (2006)
mGluR5 KO	$\downarrow$	$\downarrow^{b}$	$\downarrow^{b,NR}$	ND	ND	$\uparrow^{b}$	Brody et al. (2004), Gray et al. (2009), Lipina et al. (2007)
$AKT1^{-/-}$	ND	ND	$\downarrow$	ND	ND	$\uparrow$	Eastwood et al. (2007)
$Nurr1^{+/-}$	ND	$\downarrow$	ND	BD	ND	$\uparrow$	Eells et al. (2006), Rojas et al. (2007)
$COMT^{+/-}$	ND	=	$\uparrow$/=	ND	=	ND	Babovic et al. (2008), Gogos et al. (1998), Papaleo et al. (2008)
$COMT^{-/-}$	ND	=	$\uparrow$	ND	ND	$\downarrow$	Babovic et al. (2008, 2007), Gogos et al. (1998), Huotari et al. (2002), Papaleo et al. (2008)
COMT–Val Tg	ND	=	$\downarrow$	ND	ND	$\uparrow$	Papaleo et al. (2008)
$Grin1^{D481N/K483Q}$	$\uparrow^{b}$	=	$\downarrow^{b}$	ND	$\downarrow$	$\downarrow$	Ballard et al. (2002), Labrie et al. (2008)
DAT KO	ND	$\downarrow^{b}$	$\downarrow$	ND	ND	$\downarrow^{a,b}$	Barr et al. (2004), Gainetdinov et al. (1999), Giros et al. (1996), Powell et al. (2008), Spielewoy et al. (2001)
$SynGAP^{+/-}$		$\downarrow$	$\downarrow$		=	$\downarrow^{b}$	Guo et al. (2009)
Alpha5 $GABA_A$ in hippocampus	$\downarrow$	$\downarrow$	$\downarrow$	ND	ND	ND	Gerdjikov et al. (2008), Hauser et al. (2005), Yee et al. (2004)
GLAST KO	ND	=	ND	ND	=	$\uparrow^{a}$	Karlsson et al. (2008, 2009)
DISC1 deletion	ND	ND	$\downarrow$	ND	ND	ND	Koike et al. (2006), Kvajo et al. (2008)
DISC1 Q31 L	$\downarrow^{b,NR}$	$\downarrow^{a,b,NR}$	$\downarrow$	ND	$\downarrow$	ND	Clapcote et al. (2007)
DISC1 L100P	$\downarrow^{b}$	$\downarrow^{a,b}$	$\downarrow$	$\downarrow$	=	ND	Clapcote et al. (2007)
DISC1-C Tg	ND	ND	$\downarrow$	ND	$\downarrow$	ND	Li et al. (2007)
DISC1-DN	ND	$\downarrow$	ND	ND	ND	ND	Hikida et al. (2007)

(continued)

Table 3 (continued)

Experimental manipulation	Behavioral, cognitive, and pharmacological functions						References
	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	
DISC1-hu Tg	ND	=	↓	ND	↓	ND	Pletnikov et al. (2008)
D2R tg	ND	=	↓	ND	ND	ND	Kellendonk et al. (2009, 2006)
Reeler$^{+/-}$	ND	↓	=	=	ND	↑	Krueger et al. (2006), Tueting et al. (2006)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control genetic background

ND not determined, *NR* no effects of APD treatment

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

showing structural as well as functional alteration in selective brain regions, including the prefrontal cortex, temporal regions, and ventral striatum as critical components in schizophrenia (Deakin and Simpson 1997; Harrison 1999, 2004; Laruelle and Abi-Dargham 1999; Lewis et al. 1999; Weinberger et al. 2001; Weinberger and Lipska 1995). The use of selective brain lesions in adult animals has been instrumental in providing a first approximation to the functional importance of such identified structures in relation to schizophrenia. For example, selective lesions of the entorhinal cortex can disrupt selective attention, enhance reaction to low doses of systemic amphetamine, and impair reversal learning (Table 4). It appears, however, that similar lesions fail to affect spatial as well as nonspatial working memory performance [(Marighetto et al. 1998; Pouzet et al. 1999; Yee and Rawlins 1998); Table 4].

Admittedly, whilst selective experimental lesions are indispensable in animal neuropsychological research, their utility as a model of schizophrenia seems limited in comparison to models of neurological disorders with more discrete or localized neuropathology such as the MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) model of Parkinson's disease (Dauer and Przedborski 2003; Langston and Ballard 1984). Moreover, selective lesions introduced into adult animals also bear little resemblance to the subtle and developmental neuropathology observed in schizophrenia (Benes 2000; Harrison 1999). One promising approach, however, has been to incorporate the selective lesion approach within the context of neurodevelopment. Lipska et al. (1993) pioneered the neonatal ventral hippocampal (nVHP) lesion model in rats based on the neurodevelopmental hypothesis of schizophrenia (Weinberger 1987). This model has been shown to mimic the postpubertal onset of behavioral abnormalities, congenital hippocampal area damage, or dysfunction of the limbic dopaminergic system [reviewed in (Lillrank et al. 1995; Lipska and Weinberger 2000); Table 4]. More recent attempts have also focused on neonatal lesions of the entorhinal cortex (Schmadel et al. 2004), medial prefrontal cortex (Bennay et al. 2004; Schwabe et al. 2004), as well as the amygdala (Daenen et al. 2001, 2003; Hanlon and Sutherland 2000), which have thus far yielded mixed results, however (Table 4).

3.4 Neurodevelopmental Models

Over the last two decades, the neurodevelopmental hypothesis of schizophrenia (Weinberger 1987) has been highly influential in shaping our current thinking about modeling the disease in animals (Ellenbroek and Cools 2000b; Lillrank et al. 1995; Lipska and Weinberger 2000; Meyer and Feldon 2010; Weiss and Feldon 2001; Piontkewitz et al. 2012). One aim common to the neurodevelopmental approaches is to identify the etiological processes whereby the brain, following specific triggering events, develops into a "schizophrenia brain" over time.

One important feature of neurodevelopmental animal models is that the early cerebral insult does not necessarily induce static effects on brain and behavioral functions. Rather, the structural and functional effects of early brain lesions are

Table 4 Summary of schizophrenia-relevant abnormalities as identified in various neuropathological models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent Inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
Entorhinal cortex lesions	↓[a]	ND	–	ND	ND	↑	Oswald et al. (2002), Pouzet et al. (1999), Yee et al. 1995)
Neonatal entorhinal cortex	ND	–	↓	ND	ND	↑	Schmadel et al. (2004)
Amygdala lesions	↑[a,NR,b]	↓[b]	ND	ND	ND	ND	Schiller et al. (2006), Shoemaker et al. (2003), Weiner (2003), Weiner and Feldon 1997)
Prefrontal cortex lesions	↑[a,NR,b]/=	↑/↓/–	↓/–	ND	ND	↑	Joel et al. (1997), Lacroix et al. (1998, 2000), Schiller et al. (2006), Schwabe et al. (2004), Yee (2000)
Neonatal prefrontal cortex lesions	ND	↑/↓	↓	ND	↓	↑	Brake et al. (2000), Lipska et al. (1998), Schneider and Koch (2005), Schwabe et al. (2004, 2006)
Neonatal ventral hippocampal lesions	↓	↓[a,NR,b]	↓	↓	↓[b,NR]	↑[a,b]	Al-Amin et al. (2001), Becker et al. (1999), Brady et al. (2010), Grecksch et al. (1999), Le Pen et al. (2003), Le Pen and Moreau (2002), Lipska (2004), Lipska et al. (2002, 1993, 1995), Lipska and Weinberger (1994, 2002), Sams-Dodd et al. 1997)
Nucleus accumbens shell lesions	↓[a]	↓	↓	ND	ND	↑	Gal et al. (1997), Kodsi and Swerdlow (1994), Weiner (2003), Weiner and Feldon (1997), Weiner et al. (1996)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control manipulation (sham lesions)

ND not determined, *NR* no effects of APD treatment

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

progressive in nature and are therefore often dependent on postnatal maturational processes (Meyer and Feldon 2010). This developmental component is particularly relevant to schizophrenia because the disorder's pathophysiological and neuropathological mechanisms are assumed to be progressive in nature (Borgwardt et al. 2009; Rapoport et al. 2005; Wood et al. 2008). Hence, neurodevelopmental animal models of schizophrenia allow a multifaceted, longitudinal monitoring of the disease process as it unfolds during the course of neurodevelopment from juvenile to adult stages of life and the concomitant evaluation of the influence of external environmental factors.

One class of developmental models in rodents makes use of environmental manipulations during postnatal brain development and maturation (Cirulli et al. 2003; Lehmann et al. 2000; Pryce and Feldon 2003; Pryce et al. 2002; Weiss and Feldon 2001). This class of models comprises early handling, maternal separation, and isolation rearing (Table 5). It is hypothesized that deviations from the "normal" maturation processes of the nervous system can be triggered by such manipulations, giving rise to an aberrant brain prone to the emergence of psychotic-like behavior. One difficulty of this approach is however the lack of a clear definition of a normal early-life environment in laboratory animals, and therefore the precise nature of the environmental manipulations remains somewhat ill-defined.

An alternative approach thus makes use of specific chemical agents to interfere with early (prenatal and perinatal) development of the CNS, such as methylazoxymethanol acetate (MAM), nitric oxide synthase (NOS) inhibitors, or cytosine arabinoside (Ara-C) to disrupt maturation of neurons and/or synaptogenesis during distinct periods of fetal brain development (reviewed in Lodge and Grace (2009); Table 5). Attempts in this direction have, however, yielded inconsistent results [e.g., see Jongen-Rêlo et al. (2004)]. Moreover, while these models may be instrumental in shedding light on the critical developmental processes involved, these toxic agents themselves have not been implicated in causing schizophrenia.

Another class of animal models is based on epidemiological evidence, including prenatal malnutrition (Brown and Susser 2008), obstetric complications (Cannon et al. 2002), prenatal stress (Selten et al. 1999; van Os and Selten 1998), and prenatal or perinatal exposure to bacterial or viral infections (Brown 2006, 2008; Brown and Derkits 2010). In contrast to experimental models in which the critical manipulations are conducted in adulthood, epidemiology-driven models of schizophrenia are based on interference with early brain development resulting from exposure to prenatal and/or perinatal environmental insults. One immediate consequence of such early brain disruption is that it leads to wide-ranging neurodevelopmental sequelae, eventually leading to multiple neuroanatomical and neurochemical abnormalities in adult life [reviewed in Meyer and Feldon (2010)]. Indeed, the emergence of wide-ranging neurodevelopmental sequelae and induction of a wide spectrum of schizophrenia-relevant behavioral, cognitive, and pharmacological abnormalities is a common feature of most epidemiology-driven models of schizophrenia and related disorders [Meyer and Feldon (2010); Table 5]. This offers an excellent opportunity to study the relationship between multiple structural and functional brain abnormalities with relevance to schizophrenia and to identify possible causal links between distinct brain and behavioral dysfunctions.

Table 5 Summary of schizophrenia-relevant abnormalities as identified in various neurodevelopmental models (rats/mice)

	Behavioral, cognitive, and pharmacological functions						
Experimental manipulation	Latent inhibition	Prepulse inhibition	Working memory/short-term memory	Sustained attention and vigilance	Social interaction	Sensitivity to psychoto-mimetics	References
Prenatal exposure to repeated restraint stress	↑/–	–	↓	ND	↓	↑	Bethus et al. (2005), Burton et al. (2006), Deminiere et al. (1992), Gue et al. (2004), Henry et al. (1995), Lee et al. (2007), Lehmann et al. (2000), Meunier et al. (2004), Shalev and Weiner (2001)
Prenatal exposure to variable stress	ND	↓	↓	ND	↓	↑	Koenig et al. (2005), Markham et al. (2010)
Prenatal corticosterone or dexamethasone treatment	↓/–	↓/–	ND	ND	↓	↑	Diaz et al. (1997, 1995), Hauser et al. (2006, 2009), Shalev and Weiner (2001)
Prenatal influenza exposure	ND	↓[a]	ND	ND	↓	↑	Moreno et al. (2011), Shi et al. (2003)
Prenatal poly(I:C) exposure	↓[a,b]	↓[a,b]	↓[b]	ND	↓	↑[a,b]	Bitanihirwe et al. (2010), Cardon et al. (2010), Li et al. (2009), Makinodan et al. (2008), Meyer et al. (2008a, 2005, 2006a, b, 2008b, c, 2006c), Ozawa et al. (2006), Piontkewitz et al. (2011, 2009), Shi et al. (2003), Smith et al. (2007), Vuillermot et al. (2011, 2010), Wolff and Bilkey (2008), Zuckerman et al. (2003a, b), Zuckerman and Weiner (2005)
Prenatal LPS exposure	ND	↓[a,b]	↓	ND	↓	↑	Basta-Kaim et al. (2011), Borrell et al. (2002), Coyle et al. (2009), Fortier et al. (2004, 2007), Golan et al. (2005), Romero et al. (2007, 2010)

Prenatal IL-6 exposure	↓	↓	ND	ND	↓	↑	Smith et al. (2007)
Prenatal turpentine exposure	ND	↓	↓	ND	ND	↑	Aguilar-Valles et al. (2010), Aguilar-Valles and Luheshi (2011), Fortier et al. (2007)
Prenatal MAM treatment	↓	↓	↓	↓	↓	↑	Featherstone et al. (2007b), Flagstad et al. (2005, 2004), Hazane et al. (2009), Le Pen et al. (2006), Leng et al. (2005), Lodge and Grace (2009), Moore et al. (2006), Penschuck et al. (2006), Phillips et al. (2012)
Developmental vitamin D deficiency	↓	–	ND	ND	ND	↑[a]	Becker et al. (2005), Burne et al. (2004, 2006), Eyles et al. (2006), Kesby et al. (2006), O'Loan et al. (2007)
Prenatal protein deprivation	↓	↓	ND	↓	ND	↑	Brioni et al. (1986), Palmer et al. (2008, 2004), Ranade et al. (2008), Tonkiss et al. (1998)
Cesarean section	ND	–	–	ND	↓	↑	Boksa et al. (1995), El-Khodor and Boksa (1998), Vaillancourt and Boksa (1998), Venerosi et al. (2004)

Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control treatment

ND not determined, *IL*, interleukin, *LPS* lipopolysaccharide, *poly(I:C)* polyriboinosinic-polyribocytidilic acid

[a]Normalization by typical (first-generation) APDs

[b]Normalization by atypical (second-generation APDs)

4 Selecting the Right Model for Assessing Antipsychotic Drug Actions

Even though a plethora of schizophrenia-relevant animal behavioral/cognitive paradigms exist (Table 1), it is a challenging task to pick the right one(s) in attempts to assess APD actions. Indeed, there is no gold standard test or test battery for this purpose. The obvious reason for this is that performance in distinct behavioral/cognitive tests is, at in least part, determined by functions governed by specific neural networks and neurotransmitter systems. For example, experimentally induced hyperlocomotor activity typically seen following systemic amphetamine treatment is mainly driven by increased dopaminergic signaling in striatal structures (Creese and Iversen 1975). It is therefore not surprising that major dopamine receptor blockers such as the typical APD haloperidol are highly efficient in mitigating amphetamine-induced hyperactivity, whereas pharmacological compounds with minimal dopamine receptor blockade potential are much less so (Castagne et al. 2009; Ellenbroek and Cools 2000a; van den Buuse 2010). For this reason, it may be more fruitful to evaluate the effects of APDs against psychotomimetic agents that are known to modulate multiple neurotransmitter systems concomitantly. One class of psychotomimetic compounds that has received increasing appreciation in this context are NMDA receptor antagonist such PCP or MK-801, which have appreciable and simultaneous effects on the glutamatergic, dopaminergic, and serotonergic systems (Abi-Dargham et al. 1997; Carlsson et al. 2001; Coyle et al. 2003; Javitt 2007) and which are capable of inducing behavioral/cognitive abnormalities pertinent to positive, negative, and cognitive symptoms of schizophrenia (Table 2). Compared to primary dopaminergic psychotomimetic drugs such as amphetamine, the use of NMDA receptor antagonists can thus be expected to provide a broader spectrum of disturbances, against which potential APD activity can be assessed more thoroughly.

It is also important to realize that the eventual effects of APDs can be critically influenced by pre-existing neuronal and/or neurochemical state parameters. For example, whilst many atypical APDs such as clozapine are capable of normalizing cognitive impairments induced by specific pharmacological (Table 2), genetic (Table 3), neuropathological (Table 4), or neurodevelopmental (Table 5) manipulations, the same compounds can impair cognitive performance in non-manipulated control animals (Arguello and Gogos 2006; Barak and Weiner 2011; Castner et al. 2004; Meyer and Feldon 2010; Meyer et al. 2005, 2010; Moser et al. 2000; Swerdlow and Geyer 1998; Weiner 2003). Hence, the direction of effects (i.e., beneficial vs. detrimental) associated with APD activity can be critically influenced by the "pathophysiological background" of the animals. One implication is that non-manipulated "control" animals may not be ideally suited for screening APD activity in behavioral and cognitive tests because they are unlikely to reveal the drugs' anticipated beneficial effects on behavioral and cognition.

Assessing APD activity in non-manipulated animals may further obscure the expected outcomes because of ceiling or floor effects. For instance, PPI of the acoustic startle reflex has become one of the most widely used behavioral

paradigms to study schizophrenia-relevant functions, and as such, it has proven to be successful in detecting beneficial effects of APDs against experimentally induced sensorimotor-gating deficiency (Swerdlow and Geyer 1998; Swerdlow et al. 2008). The PPI paradigm can also be used to detect APD activity per se, that is, to identify PPI-potentiating effects of APDs in otherwise non-manipulated animals (Swerdlow and Geyer 1998; Swerdlow et al. 2008). In these attempts, however, one needs to carefully consider the fact that some mouse and rat species show relatively high levels of PPI under basal (non-manipulated) conditions, and this can readily preclude the anticipated PPI potentiation by APDs (Depoortere et al. 1997; Ouagazzal et al. 2001). One possible way to circumvent this problem is to adjust the parametric conditions of the PPI procedure such as that the level of PPI is minimal under basal (non-manipulated) conditions, so that potential PPI-potentiating effects of APDs are not masked by ceiling effects. A similar rationale would also apply to the behavioral/cognitive paradigms, including the LI procedure. Indeed, the latter has been shown to reliably detect APD actions even in otherwise non-manipulated animals, especially when the amount of LI in non-manipulated control animals is kept at minimum using specific parametric conditions such as low number of CS pre-exposure and/or conditioning trials (Arguello and Gogos 2006; Barak and Weiner 2011; Castner et al. 2004; Meyer and Feldon 2010; Meyer et al. 2005; Moser et al. 2000; Swerdlow and Geyer 1998; Weiner 2003).

Basic researchers aiming to explore APD activity in animals are also facing the challenge of selecting the appropriate experimental manipulation. As mentioned before, there are models of schizophrenia employing specific experimental manipulations developed according to specific pathophysiological or etiological hypotheses. The use of selective lesions in adult animals and the acute administration of psychotomimetic agents are indispensable tools in the elucidation of the contribution of specific brain regions or neurotransmitters to the genesis of a specific symptom or collection of symptoms, and enjoy some degrees of predictive validity. However, they may be inaccurate, if not inadequate, in capturing the etiological mechanisms or ontology of the disease needed for a complete understanding of the disease and may be limited in the discovery of novel compounds for the treatment of negative and cognitive symptoms of schizophrenia (see Sect. 5).

Under the prevailing consensus of schizophrenia as a disease of neurodevelopmental origin, we have seen the establishment of neurodevelopmental animal models which aim to identify the etiological processes whereby the brain, following specific triggering events, develops into a "schizophrenia-like brain" over time. This approach is not only wider in its scope than conventional lesion and pharmacological models, but it also readily lends itself to address data and hypotheses concerning the subtle histopathological findings revealed in postmortem and imaging studies (Harrison 2004; Laruelle and Abi-Dargham 1999; Shenton et al. 2001), as well as the genetic (Harrison and Weinberger 2005; Kim et al. 2011; Sullivan 2005) and environmental (Brown 2011; McDonald and Murray 2000) risk factors.

The heuristic value of the neurodevelopmental models for preclinical schizophrenia research is that they can successfully account for several aspects of the disorder's epidemiology, pathophysiology, symptomatology, and treatment:

1. Many neurodevelopmental models such as the vHPC lesion, MAM, and prenatal immune activation models can mimic a broad spectrum of behavioral, cognitive, and pharmacological abnormalities directly implicated in schizophrenic disease. These models allow pharmacological screens against multiple and coexisting schizophrenia-related dysfunctions, which together may critically help to reduce potential confounds of "false-positive" outcomes in preclinical behavioral tests of compounds against negative and cognitive symptoms of schizophrenia.
2. In many neurodevelopmental models (e.g., vHPC lesion, MAM, and prenatal immune activation models), the full spectrum of behavioral, cognitive, and pharmacological abnormalities is dependent on postpubertal maturational processes and thus only emerges in adult but not prepubertal subjects (Meyer and Feldon 2010). This maturational dependency offers the opportunity to evaluate the efficacy of early preventive interventions based on "prodromal-like signs" of schizophrenia and to identify progressive brain changes of the course of time.
3. By adjusting dosage and/or timing of the experimental manipulation, many neurodevelopmental models can be modified in such a way that the experimental manipulation only leads to a restricted pathological phenotype in the offspring. This feature strongly facilitates the identifications of possible synergistic interactions between the experimental manipulation of interest and other genetic or other environmental risk factors implicated in schizophrenia etiology.
4. Because they are often based on epidemiological findings, many neurodevelopmental models (e.g., prenatal immune activation and obstetric complication models) have intrinsic etiological significance to schizophrenia.

5 Can Behavioral Models Predict Therapeutic Efficacy of Novel Compounds?

In most cases, an animal model of a particular disease is initially established based on what is known about a disease so that the critical anchor between the animal model and the human disease is what is already known about the latter (Feifel and Shilling 2010). Driven by the rapidly growing literature implicating specific genetic, epigenetic, and environmental abnormalities in the etiopathogenesis and pathophysiology of schizophrenia (Brown 2011; Kim et al. 2011; Meyer and Feldon 2010), a great deal of current interest in preclinical schizophrenia research has focused on the characterization of their effects on distinct neurobiological phenotypes pertinent to schizophrenic disease. Indeed, such "neuroscience- or genetics-driven experimental approaches" seem to increase our capability to identify novel neural mechanisms that may be involved in the pathogenesis of schizophrenia psychopathology and neuropathology (Kvajo et al. 2012; Meyer and

Feldon 2010; O'Connell et al. 2011). Unfortunately, these laudable research efforts are often undermined by incomplete ascertainment of the predictive validity, so that many experimental models lack clear information about whether or not the modeled behavioral/cognitive traits respond selectively to APDs (Tables 2, 3, 4, and 5). Therefore, it may not be surprising that basic schizophrenia research has provided only incremental advances with respect to predicting the therapeutic efficacy of novel compounds against schizophrenia-relevant symptoms (Barak and Weiner 2011; Feifel and Shilling 2010; Moore 2010).

In view of the limited efficacy of APDs to normalize negative and cognitive symptoms, there is increasing recognition of the importance to develop novel pharmacotherapeutic approaches against these symptoms (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010). With respect to the negative symptoms, animal models are readily capable of mimicking some associated core features such as deficits in social interaction, avolition, and anhedonia (Table 1), and several experimental models established in the context of schizophrenia have shown deficits in these domains following specific pharmacological, genetic, or environmental manipulations (Tables 2, 3, 4, and 5). However, anhedonia and other abnormalities related to the negative symptoms of schizophrenia are also prominent features of major depression and thus are by no means specific to schizophrenia (Treadway and Zald 2011). It therefore seems difficult, if not inappropriate, to assign strong validity for schizophrenia to an animal model that only displayed negative features in the absence of other co-expressed features that might link it more specifically to schizophrenia. As a consequence, the relative power of such approaches to predict therapeutic efficacy of novel compounds in the treatment of negative symptoms may be severely compromised and may lead to "false-positive" outcomes, i.e., to drugs that have shown promise in animal models but not in clinical trials (Moore 2010). The rate of such "false-positive" outcomes seems especially high for traditional back-translational psychopharmacological approaches such as acute or chronic treatment with PCP or other psychotomimetics: In such approaches, a number of drugs have been shown to mitigate or reverse negative psychopathological features, but only the minority of the tested compounds seem viable treatment options in the treatment of schizophrenia (Moore 2010). In spite of this criticism, it needs to be pointed out that there is thus far no in-depth analysis of the rate of such "false-positive" outcomes provided by traditional back-translational psychopharmacological approaches in animals. It also needs to be acknowledged that a number of factors can readily affect the outcome of clinical studies, including placebo effect rates or target biology differences between rodents and humans. Therefore, it would appear premature at this point of time to fully discard the validity of conventional psychopharmacological models in the preclinical schizophrenia research.

As recently discussed in detail elsewhere (Barak and Weiner 2011), there is also still a gap between the initial recommendations provided by MATRICS, CNTRICS, and other initiatives and the implementation of animal behavioral/cognitive strategies that might truly lead to the discovery of novel compounds with therapeutic efficacy against the cognitive symptoms of schizophrenia. Again, traditional back-translational psychopharmacological approaches have tested a number of

putative "cognitive enhancers" for potential application in the treatment of cognitive symptoms in schizophrenia, but it still appears that such compounds are not superior to atypical APDs in the normalization of experimentally induced cognitive abnormalities in animal models of schizophrenia (Barak and Weiner 2011). In other words: Most of the available models lack the capacity to differentiate between the potentially beneficial effects of "cognitive enhancers" and APDs in basic schizophrenia research. This lack of distinction is particularly unsatisfactory in view of the fact that currently available APDs show a limited therapeutic efficacy in improving cognitive symptoms of schizophrenia (Buchanan et al. 2007; Nelson and Winslow 2009; Tandon et al. 2010) so that there is a clear discrepancy between the experimental data derived from animal models and the human clinical condition. It thus seems highly warranted to develop and implement novel models in which the experimental manipulations lead to schizophrenia-relevant cognitive dysfunctions that are resistant to APDs but selectively sensitive to "cognitive enhancers" (Barak and Weiner 2011).

6 Concluding Remarks

There has been a great deal of efforts to establish behavioral and cognitive tests that allow translation of schizophrenia-relevant human symptomatology to experimental conditions in animal models (Arguello and Gogos 2006; Lipska and Weinberger 2000; Meyer and Feldon 2010; Tarantino and Bucan 2000). Parallel to these efforts, a wide variety of experimental manipulations exist and are currently being used to induce schizophrenia-relevant brain and behavioral pathology. Whilst traditional pharmacological models may be useful as quick screening tool for detecting at least some predictable APD activities, they seem inappropriate in the development and evaluation of novel compounds with potential antipsychotic and/or pro-cognitive properties. Neurodevelopmental animals may be more adequate for the latter goal because they can mimic multiple schizophrenia-relevant brain and behavioral pathologies and incorporate the developmental component of the disorder. Yet, the multiplicity of existing models is testimonial to the multi-factorial nature of schizophrenia, and there are ample opportunities for their integration. Indeed, one ultimate goal must be to incorporate the successes of distinct models into one unitary account of the complex disorder of schizophrenia and to use such unitary approaches in the further development and evaluation of novel antipsychotic treatment strategies.

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