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Animal Models Relevant to Schizophrenia and Autism: Validity and Limitations

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Abstract Development of animal models is a crucial issue in biological psychiatry. Animal models provide the opportunity to decipher the relationships between the nervous system and behavior and they are an obligatory step for drug tests. Mouse models or rat models to a lesser extent could help to test for the implication of a gene using gene targeting or transfecting technologies. One of the main problem for the development of animal models is to define a marker of the psychiatric disorder. Several markers have been suggested for schizophrenia and autism, but for the moment no markers or etiopathogenic mechanisms have been identified for these disorders. We examined here animal models related to schizophrenia and autism and discussed their validity and limitations after first defining these two disorders and considering their similarities and differences. Animal models reviewed in this article test mainly behavioral dimensions or biological mechanisms related to autistic disorder or schizophrenia rather than providing specific categorical models of autism or schizophrenia. Furthermore, most of these studies focus on a behavioral dimension associated with an underlying biological mechanism, which does not correspond to the complexity of mental disorders. It could be useful to develop animal models relevant to schizophrenia or autism to test a behavioral profile associated with a biological profile. A multi-trait approach seems necessary to better understand multidimensional disorders such as schizophrenia and autism and their biological and clinical heterogeneity. Finally, animal models can help us to clarify complex mechanisms and to study relationships between biological and behavioral variables and their interactions with environmental factors. The main interest of animal models is to generate new pertinent hypotheses relevant to humans opening the path to innovative research.

Keywords Psychiatry · Autism · Schizophrenia · Animal models · Neurobiological similarity · Behavioral similarity · Genetics · Brain

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Introduction

Several animal models of autistic disorder or schizophrenia have been proposed and studied (for a review, see Andres 2002; Gray 1998; Kilts 2001; Lipska and Weinberger 2000; Marcotte et al. 2001; Moser et al. 2000; Murcia et al. 2005). They have been developed to better ascertain and understand the mechanisms underlying autism and schizophrenia. Animal models have been considered particularly useful given that, for the moment, no markers or etiopathogenic mechanisms have been identified for these disorders.

This article focuses on animal models of autistic disorder and schizophrenia because they represent developmental psychiatric disorders (Chua and Murray 1996; Weinberger 1987) occurring at different periods of the lifespan (autism spectrum disorder occurs in early childhood whereas schizophrenia occurs later, especially during adolescence) and share some common dimensions which will be described in the next section.

First, definitions of autistic disorder and schizophrenia will be provided based on DSM-IV-TR and ICD-10 (International Classification of Diseases) classifications (American Psychiatric Association 2000, and World Health Organization 1993, respectively). Similarities and differences between these two disorders will be examined. Second, animal models relevant to autistic disorder and schizophrenia will be reviewed with regard to their types of validity. Third, the limitations of these models will be discussed underlining the need to develop animal models to study a behavioral profile associated with a biological profile relevant to autistic disorder or schizophrenia through a multidimensional approach.

Definitions of autistic disorder and schizophrenia

Diagnostic criteria according to DSM-IV-TR and ICD-10 classifications

Autism is defined according to DSM-IV-TR and ICD-10 criteria as a pervasive developmental disorder with onset prior to 3 years old and impairments in three major domains: (a) reciprocal social interactions, (b) verbal and non-verbal communication, (c) restricted repetitive and stereotyped behaviors, interests or activities. A detailed description of DSM-IV-TR diagnostic criteria for autistic disorder is presented in Table 1.

Schizophrenia is defined according to DSM-IV-TR and ICD-10 criteria as a multidimensional disorder involving emotional and cognitive dysfunctions, which include flat or inappropriate affects, perception and thinking distortions, language and communication impairments and disorganized or catatonic behaviors. This disorder is characterized by positive and negative symptoms. No single symptom is pathognomonic of schizophrenia; the diagnosis involves the recognition of a constellation of signs and symptoms associated with impaired occupational and social functioning. A detailed description of DSM-IV-TR diagnostic criteria for schizophrenia is presented in Table 2.

The positive symptoms (Criteria A1-A4, see Table 2) include distortions or exaggerations of inferential thinking (delusions), perception (hallucinations), language and communication (disorganized speech), and behavioral monitoring (grossly disorganized or catatonic behavior). These positive symptoms may comprise two distinct dimensions, which may in turn be related to different underlying neural mechanisms and clinical correlations: the «psychotic dimension» includes delusions and hallucinations, whereas the «disorganization dimension» includes disorganized speech and behavior. Negative symptoms (Criterion A5, see Table 2) include restrictions in the range and intensity of emotional expression (affective flattening), in the fluency and productivity of thought and speech (alogia), and in the initiation of goal-directed behavior (avolition).

In both DSM-IV-TR and ICD-10 classifications, schizophrenia has to be distinguished from schizoaffective disorder, mood disorder and psychotic disorder due to a substance use or a general medical condition.

Similarities and differences between autistic disorder and schizophrenia

Historical diagnostic overlaps between autism and schizophrenia exist since the appearance of autism in the nomenclature of psychiatric disorders. Originally autistic disorder and schizophrenia were intimately linked. Indeed the term «autism» is derived from the Greek «autos», which means «self» and was introduced for the first time by the Swiss psychiatrist Eugen Bleuler in 1911 to describe social withdrawal in adults with schizophrenia. In 1943, the American psychiatrist Leo Kanner borrowed from Bleuler the term «Autism» to define a syndrome observed in 11 children which, at that time, was a part of the diagnostic category «Childhood Schizophrenia».

Since the early 1970s, autism and schizophrenia belong to two different diagnostic categories. However, they still share some common features: they are both considered as developmental psychiatric disorders

Table 1 DSM-IV-TR diagnostic criteria for autistic disorder

A. A total of six (or more) items from (1), (2), and (3), with at least two from (1), and one each from (2) and (3):
(1) qualitative impairment in social interaction, as manifested by at least two of the following:
(a) marked impairment in the use of multiple nonverbal behaviors such as eye-to-eye gaze, facial expression, body postures, and gestures to regulate social interaction
(b) failure to develop peer relationships appropriate to developmental level
(c) a lack of spontaneous seeking to share enjoyment, interests, or achievements with other people (e.g., by a lack of showing, bringing, or pointing out objects of interest)
(d) lack of social or emotional reciprocity
(2) qualitative impairments in communication as manifested by at least one of the following :
(a) delay in, or total lack of, the development of spoken language (not accompanied by an attempt to compensate through alternative modes of communication such as gesture or mime)
(b) in individuals with adequate speech, marked impairment in the ability to initiate or sustain a conversation with others
(c) stereotyped and repetitive use of language or idiosyncratic language
(d) lack of varied, spontaneous make-believe play or social initiative play appropriate to developmental level
(3) restricted repetitive and stereotyped patterns of behavior, interests, and activities, as manifested by at least one of the following:
(a) encompassing preoccupation with one or more stereotyped and restricted patterns of interest that is abnormal either in intensity or focus
(b) apparently inflexible adherence to specific, non-functional routine or rituals
(c) stereotyped and repetitive motor mannerisms (e.g., hand or finger flapping or twisting, or complex whole-body movements)
(d) persistent preoccupation with parts of objects
B. Delays or abnormal functioning in at least one of the following areas, with onset prior to age 3 years: (1) social interaction, (2) language as used in social communication, or (3) symbolic or imaginative play.
C. The disturbance is not better accounted for by Rett's Disorder or Childhood Disintegrative Disorder

involving psychotic symptoms (according to DSM-IV-TR, the term «psychotic» has been defined conceptually as a loss of ego boundaries or a gross impairment in reality testing) with impairments in the same main behavioral domains (communication, social interactions, and stereotyped behaviors, interests or activities). Communication impairments, and more generally, abnormalities in cognitive development are reported in autistic disorder as well as in early onset schizophrenia (Alaghband-Rad et al. 1995; Asarnow et al. 1994; Baum and Walker 1995; Cantor et al. 1982). These cognitive dysfunctions include attention,

Table 2 DSM-IV-TR diagnostic criteria for schizophrenia

A. *Characteristic symptoms*: Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
(1) delusions
(2) hallucinations
(3) disorganized speech (e.g., frequent derailment or incoherence)
(4) grossly disorganized or catatonic behavior
(5) negative symptoms, i.e., affective fattening, alogia, or avolition
Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behavior or thoughts, or two or more voices conversing with each other.
B. *Social/occupational dysfunction*: For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).
C. *Duration:* Continuous signs of the disturbance persist for at least 6 months. This 6-months period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).
D. *Schizoaffective and mood disorder exclusion*: Schizoaffective disorder and mood disorder with psychotic features have been ruled out because either (1) no major depressive, manic, or mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.
E. *Substance/general medical condition exclusion*: The disturbance is not due to the direct physiological effects of a substance (e.g., a drug of abuse, a medication) or a general medical condition.
F. *Relationship to a pervasive developmental disorder*: If there is a history of autistic disorder or another pervasive development disorder, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

learning and communication disorders. Thus, impairments in verbal communication (delay in the development of spoken language, poor or disorganized speech) and non-verbal communication (reduced facial expression or body language, poor eye contact, abnormal emotional expression such as flat, bizarre or inappropriate affects) are found in individuals with early onset schizophrenia or autistic disorder. In addition, social development is impaired in both schizophrenia and autistic disorder. The degradation of social skills is a hallmark of schizophrenia (Mueser et al. 1991) and the distinguishing feature of subgroups within schizophrenia (Carpenter et al. 1988). Deterioration of social skills is associated with the chronic phase of schizophrenia and its deficit form (Carpenter et al. 1988) or negative syndrome. Social isolation observed in schizophrenia and even in the childhood of individuals with early onset schizophrenia is similar to the autistic withdrawal described by Kanner (1943). One issue is whether this schizophrenic social isolation is spontaneous or results from a rejection by others because of inappropriate behaviors (Friedlander 1946).

Tantam (1988) argued that individuals with autistic disorder display symptoms that can also be considered as schizoid personality traits. More recently, Konstantareas and Hewitt (2001) reported that none of 14 men with paranoid schizophrenia met criteria for autism whereas 7 out of 14 males with autism met criteria for schizophrenia on the Structured Clinical Interview (SCID). More precisely, symptom overlap concerned negative symptoms of schizophrenia such as affective flattening, alogia, avolition—apathy, anhedonia—asociality, lack of interest in social interaction and poor communication. This symptom overlap can be observed in particular between high functioning autistic disorder or Asperger's disorder and early onset schizophrenia which tends to be characterized by negative symptoms with social interaction impairments (Bailer et al. 1996) and a chronic course (Krauss et al. 2000).

Furthermore, retrospective studies conducted on patients with schizophrenia or longitudinal studies of children with autistic disorder reported frequent associations between these two disorders (antecedents of autistic disorder in the childhood of the schizophrenic group and appearance of schizophrenia in the autistic group) (Alaghband-Rad et al. 1995; Bender and Faetra 1972; Jansen et al. 2000; Van Engeland and Van Der Gaag 1994). However, other retrospective and longitudinal studies found no significant association between these two disorders (Larsen and Mouridsen 1997; Volkmar and Cohen 1991).

From a biological point of view, abnormal stress responses (in particular responses of the hypothalomo-pituitary-adrenal axis to psychosocial stress) are reported in schizophrenia (Jansen 1998; Jansen et al. 2000) as well as in autistic disorder (for a review, see Tordjman et al. 1997). This common biological feature is associated in both disorders with major anguish, difficulties to adapt to novel situations, abnormal behavioral responses to environmental stimuli and stressful situations (Jacobson and Ackerman 1990; Tordjman et al. 1997; Van Den Bosch et al. 1992; Wiedl 1992). In addition, some studies reporting pain insensitivity in individuals with schizophrenia or autism led to the same theory, in both disorders, of abnormally high activity of central endorphins and the therapeutic use of the opioid antagonist, naloxone or naltrexone (Brambilla et al. 1984; Kline et al. 1977; Singh et al. 2006; Tordjman et al. 1999). However, the studies measuring endorphins in schizophrenia or autism offered conflicting results (Berger et al. 1981; Brambilla et al. 1984; Kline et al. 1977; Lindstrom et al. 1986; Tordjman et al. 1997; Watson et al. 1979). In fact, the reduced behavioral pain reactivity observed in individuals with autism or schizophrenia is more related to a different mode of pain expression due to cognitive impairments than to a real endogenous analgesia (Guieu et al. 1994; Tordjman et al. 1999). Finally, genetic factors possibly involved in both childhood onset schizophrenia and autistic disorder have been also discussed by Yan et al. (2000). Furthermore, the promoter polymorphism of the serotonin transporter gene influences the severity of autistic behaviors in the social and communication domains, (Tordjman et al. 2001a), and the severity of hallucinations and thought disorder in schizophrenia (Malhotra et al. 1998). These results open the path to future common research on the genetics of autism and schizophrenia, and underline the importance of using a methodology in which genetic transmission is studied in concert with a detailed examination of behavioral phenotype (Tordjman et al. 2001a).

However, some differences between schizophrenia and autism have to be underlined, such as age at onset, positive symptoms more characteristic of schizophrenia and stereotyped motor behaviors more characteristic of autism. Indeed, autism spectrum disorder occurs in early childhood with an age at onset prior to 3 years, whereas schizophrenia occurs later. According to DSM-IV-TR, the onset of schizophrenia typically occurs between the late teens and the mid-30s with onset prior to adolescence rare (although cases with age at onset of 5 or 6 years have been reported but never prior to 3 years). In addition, positive symptoms (criteria A1-A4, see Table 2) including delusions, hallucinations, positive formal thought disorder,

disorganized or catatonic behavior are significantly more frequent in individuals with schizophrenia than in individuals with autistic disorder (Konstantareas and Hewitt 2001). It is noteworthy that in case of a previous diagnosis of autistic disorder, the additional diagnosis of schizophrenia is warranted only if prominent delusions or hallucinations are present for at least a month (criterion F, see Table 2). Inversely, motor stereotypies (repetitive movements) are more frequently observed in autistic disorder than in schizophrenia, even if repetitive interests can be displayed by individuals with schizophrenia (Tordjman et al. 2001b).

Animal models of schizophrenia or autism and their validity

A certain number of criteria have been proposed in order to improve the validity of animal models with regard to the mental disorders that they were supposed to model. Thus, McKinney (1977) developed and proposed four main criteria:

- similarity of the inductive conditions (inductive conditions are obtained most of the time in animal models through manipulations such as environmental or pharmacological manipulations),
- behavioral similarity,
- similarity of underlying neurobiological mechanisms,
- similarity of the treatment response based on a shared pharmacological identity.

Later, Robbins and Sahakian (1979) kept only three criteria:

- behavioral similarity (face validity),
- shared etiology involving similarity of underlying neurobiological mechanisms (construct and etiological validity),
- pharmacological similarity (predictive validity).

As defined by Rand (2004), face validity (reproducing the disease symptoms) refers to the phenomenological similarity between the behavior exhibited by the animal model and the specific symptoms of the human condition. The correspondence between three main behavioral impairments observed in schizophrenia or autism and their relevant behavioral measures in mice are presented in Table 3.

Construct validity of a model is most commonly defined as the accuracy with which the model measures that which it is intended to measure in order to test etiopathogenic hypotheses based on the study of risk factors and mechanisms possibly involved in the pathogenesis of a disorder. The concept of etiological validity is closely related to the concept of construct validity. A model has etiological validity if the etiologies of the phenomenon in the animal model and the human condition are identical. In reference to animal models of human psychopathology, the term predictive validity is often used in a narrow sense to refer to the model's ability to identify correctly drugs with potential therapeutic value in humans (i.e., reproducing and predicting a treatment effect based on a pharmacological similarity).

In fact, it is common to distinguish three main groups of animal models (Rand 2004): homologous, isomorphic and predictive models. An animal model may be considered homologous if the symptoms shown by the animal and the course of the condition are identical to those of humans. Models fulfilling these requirements are few and most homologous models are «partial», but an example is well-defined lesion syndromes in neuroscience (Rand 2004). An animal model is considered isomorphic if the animal symptoms are similar but the cause of the symptoms differs between human and model. The spontaneous models are often isomorphic, displaying phenotype similarity between the disorder in the animal and the corresponding disorder in the human (Rand 2004). Finally, an animal model is considered predictive based on its ability to characterize a therapeutic activity of a drug for a disorder. Isomorphic models display face validity (but not exclusively), whereas homologous models are useful for their construct and etiological validity (but not exclusively), and predictive models have predictive validity (but not exclusively).

Predictive and homologous models relevant to schizophrenia or autism will now be reviewed and their different types of validity (predictive, face, construct and etiological validity) will be discussed. Isomorphic aspects will be also considered but mainly in terms of behavioral similarity (face validity) and not as a category of animal models in itself.

Animal models of schizophrenia

The potential benefits for understanding the neurobiology and improving treatment from the study of valid models of a disorder as prevalent and overwhelming as schizophrenia have resulted in the proposal of a variety of related animal models. Animal models have been developed in order to screen and test the effects of antipsychotic drugs (predictive validity). In addition, several animal models of schizophrenia, which can be classified as homologous, have been generated based on hypotheses that describe underlying deficits in

Table 3 Clinical aspects of schizophrenic and autistic disorder and relevant behaviors in animal models (based on Murcia et al. 2005 and Lipska and Weinberger 2000)

Behavioral Impairments	Behavioral measures in mice	
	Schizophrenia	Autistic disorder
Social interaction	Reduced contacts with unfamiliar partners	Decreased in huddle, groom, barber, play behavior (chase, spar, wrestle, pin), social exploration (approach, nose groom), sexual activity (follow, sniff, mount, genital groom), aggression (threat, attack, bite, etc.)
Cognitive and communication impairments	Sensorimotor gating (PPI, P50) deficits, deficits in latent inhibition, deficits in delayed alternation and spatial memory tests	Pup distress call, mating call, submissive call
Stereotyped behaviors and other behaviors	Dopamimetic-induced stereotypies, reduced haloperidol-induced catalepsy, hyperlocomotion induced by dopamimetics, NMDA antagonists or stress	Repeated motor activities (spontaneous activity, exploration, circling, digging, jumping, etc.) Self-injurious behaviors and other self- involved behaviors (self-grooming, scratching, wasching, etc.)

schizophrenia in both physiological and psychological terms (Weiss and Kilts 1994).

Predictive models

The psychostimulant model

Animal models using psychostimulants, such as amphetamine (amphetamine increases the quantity of dopamine in the synaptic cleft by several mechanisms; Fone and Nutt 2005), have a good predictive validity with respect to their ability to predict dopaminergic treatment effects (more specifically, dopamine antagonist treatments) for schizophrenia based on pharmacological similarities. The prevailing hypothesis that schizophrenia reflects a hyperactivity of brain dopaminergic systems (potential construct and etiological validity) has stimulated the development of this group of models. Initially, these models arose because of the apparent similarity (face validity) between the effects of high doses of amphetamine in normal humans and the symptoms of schizophrenia. Typically, rodent studies have focused on increased locomotor activity or stereotypies, whereas primate studies have examined motor effects and alterations in social interactions induced by amphetamine-like drugs (Geyer and Markou 2002). Similarly, the exposure of rats to high ambient pressure (high pressure of a helium–oxygen mixture) results in neuroleptic-reversible increases in spontaneous locomotor activity associated with increases in the dopamine content of the nucleus accumbens and caudate putamen (Abraini et al. 1993). Abraini et al. (1993) conclude that the pressure-induced disorders in neurotransmission and spontaneous behavior in rats could constitute a valid animal model of schizophreniform psychosis and a useful tool for both the investigation of the biological mechanisms underlying schizophrenia (construct and etiological validity) and the development of new antipsychotic drugs (predictive validity). However, the face validity of these animal models, in terms of similarity between symptoms of schizophrenia and stereotyped behaviors or locomotor hyperactivity induced by psychostimulants in animals, is questionable with regard to the fact that motor stereotypies or hyperactivity are not a key feature of schizophrenia (see the section on the definition of schizophrenia). Despite these comments, the face validity concerning social interaction impairments induced by amphetamines remains of interest and will be discussed later.

The hallucinogen model

This model was initially developed because of the apparent face validity of the effects of LSD (lysergic acid diethylamide discovered over 50 years ago) on perception (hallucinations and exaggerated responses to sensory and cognitive stimuli), similar to some symptoms of schizophrenia. It is noteworthy that Nielsen et al. also described apparent amphetamine-induced hallucinatory behaviors in monkeys, reversed rapidly by neuroleptic drug administration (Nielsen et al. 1983). Although many similarities were noted between the effects of LSD-like drugs in humans and the symptoms of schizophrenia, two major differences prompted the widely accepted, but not necessarily justified, conclusion that this class of drugs does not provide a useful model of schizophrenia. First, tolerance was found to develop rapidly to the subjective effects of LSD-like drugs, whereas the symptoms of

schizophrenia persist for a lifetime. Second, the hallucinations produced by LSD and related drugs occur typically in the visual modality, whereas hallucinations characteristic of schizophrenia occur in the auditory modality (Geyer and Markou 2002). However, the hallucinogen model might provide an interesting animal model related to schizophrenia with potentially good predictive validity. Indeed, pharmacological similarities have been recently found between hallucinogens, which produce their characteristic subjective effects by acting as 5-HT2A agonists, and atypical antipsychotic drugs used in schizophrenia and acting as 5-HT2A antagonists. In addition, the hallucinogen animal model is of special interest for schizophrenia considering that hallucinations can be viewed as one of the key characteristics of schizophrenia and specific of psychosis. Thus, the hallucinogen model has a face and predictive validity with regard to both characteristic abnormalities exhibited by patients with schizophrenia (such as hallucinations) and the effects of antipsychotic drugs. Such a model would suggest that 5-HT2A antagonism by itself might be effective in the treatment of certain forms of schizophrenia. Indeed, a selective 5-HT2A antagonist, M100907, is currently being tested as a putative antipsychotic drug in phase 3 clinical trials, and may be important for the predictive validity of the hallucinogen model (Geyer and Markou 2002).

Homologous models

These models aspire to provide direct relevance between the behavior shown in the animal model and the behavioral responses seen in schizophrenia (see Table 3) as well as the underlying processes that are thought to characterize schizophrenia**.**

Homologous animal models of schizophrenia can be subdivided into two types. The first one reflects the point that signs and symptoms of schizophrenia express disturbances in cognitive operations. Modeling neurobehavioral processes that are believed to be disturbed in schizophrenia has focused largely on deficits in information processing and stimulus filtering (Braff and Geyer 1990; Freedman et al. 1991). A second type of homologous model reviewed in this article reproduces a salient symptom or behavioral dimension seen in schizophrenia, such as social interaction impairments, and studies its possible underlying mechanisms.

Cognitive impairments

The latent inhibition (LI) of a conditioned response by pre-exposure to the to-be-conditioned stimulus is a well-studied model. Operationally, it is proposed that the neutral presentation of a stimulus retards the subsequent learning of a conditioned association to the stimulus (Lubow 1973). Conceptually, LI paradigms are models of the ability to accurately categorize a stimulus based on its changing salience. Disrupted LI have been reported in patients with schizophreniform disorder or schizophrenia in the acute stages of the disorder (Weiner 2003). The phenomenon of LI attempts to reproduce attention deficits in schizophrenia that are expressed as the use of inefficient and inflexible processing strategies to filter stimuli. LI also shares parallels with non-attentional constructs of schizophrenia such as deficits in the control of behavior and the influence of prior experience on the perception of current events.

Furthermore, LI paradigms have shown that they could be affected by amphetamines (disrupted LI is described in normal amphetamine-treated humans; Solomon et al. 1981; Weiner et al. 1984), and more recent studies have shown its sensibility to antipsychotic drugs (potentiated LI is described in normal humans treated with antipsychotic drugs; Christison et al. 1988; Dunn et al. 1993; Feldon and Weiner 1991). Consequently, animal manipulations that induce disrupted LI are considered to provide an animal model of positive symptoms of schizophrenia with face, construct and predictive validity (Weiner 2003).

Blocking strategies, like LI tasks, represent models of selective attention and the influence of context and prior experience on current perception and learning. Blocking tasks also involve a stimulus pre-exposure, conditioning, and behavioral testing component. Stimulus pre-exposure involves the conditioned association of the stimulus (CS-A) with a non-conditioned stimulus (UCS). In conditioning, a compound stimulus (CS-A plus CS-B) is presented followed by the same UCS. In testing, the conditioned response to CS-B is measured; pre-exposure weakens (or ''blocks'') the response to CS-B. As a model of differential processing of stimuli based on their relevance, LI and blocking tasks differ on the simultaneous presentation of different stimuli (blocking) versus sequential processing of the same stimulus (LI).

Prepulse inhibition of the startle reflex to an auditory or tactile stimulus when the startling stimulus is preceded by a weak pre-stimulus (prepulse inhibition, PPI) is an additional animal model of information processing-stimulus filtering deficits in schizophrenia (Braff et al. 1978). The PPI effect is often proposed to represent an animal behavioral model of sensorimotor gating functions. The model is postulated to reproduce gating deficits found in schizophrenia, i.e., deficits in the mechanisms that enable to filter most of the

sensory and cognitive stimuli. Based on this hypothesis, the model has been used to study the neural and pharmacological substrates of schizophrenia (Braff and Geyer 1990; Swerdlow et al. 1986, 1990, 1991). Like LI and blocking paradigms, PPI is dramatically reduced or absent in patients with schizophrenia, which confers a rather good face validity to animal models that mimic this cognitive impairment. The construct validity of these animal models is limited to the cognitive dimension of schizophrenia.

Rats with *neonatal toxic damage of the ventral hippocampus* display in adulthood a variety of abnormalities reminiscent of schizophrenia and are used as an animal model of this disorder (Lipska et al. 2002). Bilateral lesioning of the region (and amygdalia) affects specific behaviors (attention, arousal, habituation), cognitive operations (learning, memory), and physiological reactions (skin conductance) that parallel a constellation of deficits associated with schizophrenia (Lipska and Weinberger 2002; Schmajuk 1987). Behavioral deficits following hippocampus lesions can be reversed by administration of antipsychotics (Schmajuk 1987).

Social interaction impairments

Environmental manipulations—induced social impairment in rodents Abnormal behavioral and biological responses to stressful situations observed in individuals with schizophrenia (Van Den Bosch et al. 1992; Wiedl 1992) have prompted the development of animal models based on stressful environmental manipulations in rodents. Social impairment induction conditions have included prenatal stress (Shalev and Weiner 2001), postnatal stress (Shalev et al. 1998), early handling (Peters et al. 1991), maternal separation (Ellenbroek et al. 1995), and early social isolation (Roubertoux et al. 2005; Wilkinson et al. 1994). These treatments are chosen because they are stressful and they engage dopamine agonistic processes (Salamone et al. 1997; Tordjman et al. 2003). An obvious limitation of the use of these social interaction models in rodents is the conceptual distance between interactive behavior in rodent pairs and deficits in social skills and social withdrawal exhibited by schizophrenic patients in complex human social contexts. This limitation raises issues with regard to the face, construct and etiological validity of social interaction models in rodents.

Amphetamine—induced social isolation in monkeys Based on an ethological analysis of monkeys in the context of their complex well-organized social structure, social interaction models in monkeys may provide an interesting animal model, which is more adapted than rodent models. Monkey social behavior in models of schizophrenia has largely been studied in conjunction with amphetamine-induced social isolation (Ellenbroek et al. 1989), which is thought to be analogous to social withdrawal symptoms seen in the negative forms of schizophrenia. Amphetamine administration to monkeys reduces markedly the duration and number of both active and passive social behaviors, with a resulting increase in spatial distance between monkeys that live together socially (Ellenbroek et al. 1991). Amphetamine-induced social isolation is observed following both chronic or acute drug administration, as well as various social interaction impairments. Even if social isolation is not specific of schizophrenia, it is one of the main characteristic dimensional features of this disorder, as seen in the section on the definition of schizophrenia. This amphetamine-induced social isolation animal model shows a good behavioral similarity to schizophrenia (face validity) and offers interesting perspectives in terms of construct and etiological validity. The predictive validity of the amphetamine animal models has been already previously discussed.

Animal models of autistic disorder

Predictive models

Predictive animal models relevant to autistic disorder have been used mostly to study the potential treatment effect of opioid antagonists, such as naloxone, based on the opioid theory of autism. A number of researchers have suggested that excessive brain opioid activity could explain the purported decreased pain sensitivity observed in autism, and contribute to or even determine the pathogenesis of autism (Frescka and Davis 1991; Panksepp 1979; Panksepp and Sahley 1987; Sher 1997). There are apparent symptom similarities (face validity) between autism and opiate addiction or behavioral states following administration of opiate and opioid agents in animals (Chamberlain and Herman 1990; Herman and Panksepp 1978; Kalat 1978; Panksepp et al. 1978, 1980a, b, 1985; Sahley and Panksepp 1987; Sandman 1992; Sandman et al. 1979, 1991). Autistic children and opiate-addicted animals appear less sensitive to pain, less emotional and social. Additionally, stereotyped behaviors and social interaction impairments (which represent two main behavioral domains of autistic impairments) following administration of opioid agents in animals are reversed

by naloxone (Herman and Panksepp 1978; Panksepp et al. 1978; Van Wimersma et al. 1988). However, the predictive validity of these animal models remain to be ascertained considering the inconsistent results of studies measuring opioid levels (Tordjman et al. 1997) and the absence of clear benefits of opiate antagonist therapies (naloxone or naltrexone) in individuals with autism (Campbell et al. 1990; Sandman 1992; Sandman et al. 1991; Willemsen-Swinkels et al. 1995). One study (Willemsen-Swinkels et al. 1995) found even that naltrexone actually increased stereotypies in autism. Furthermore, as developed previously in the autism definition section, recent studies do not support the hypothesis of pain insensitivity in individuals with autistic disorder which led to the theory of opioid in autism (this hypothesis is similar to ideas proposed several years ago for babies; Poznanski 1976). Future studies are required to better assess and understand the decreased behavioral pain reactivity in autism.

Homologous models

The animal models that will now be described are based on behaviors observed in individuals with autistic disorder (see Table 3) and neuroanatomical abnormalities related to candidate regions in the brain for this disorder. Such models are useful to test the ability of brain defects in a specific region, which are provoked by different types of manipulations (electrode, chemical or infectious agents, etc.), to produce abnormal animal behaviors relevant to autistic-like behaviors.

Single trait model: social interaction

Early acid lesion of the amygdala in rat embryos on day 7 led to more severe social interaction impairments than when the rats were lesioned on day 21. In addition, exposure of neonatal rats to borna virus provoked a loss of cerebellar neurons associated with social interaction impairments, and more precisely reduced play behaviors in the infected animals (Hornig et al. 1999; Pletnikov et al. 1999; both articles reviewed in Pletnikov et al. 2003). Infection-based animal models of autistic disorder are of interest with regard to immunological abnormalities that have been ascribed in this disorder. Indeed, several immunological defects have been reported in children with autistic disorder, including decreased complement proteins and T lymphocytes, abnormal proliferative responses to mitogens and increased serum concentrations of autoantibodies to cerebellar neurofilaments, myelin basic protein, neuro-axon filament protein, serotonin receptors and $\alpha 2$ adrenergic receptors (for a review, see Krause et al. 2002; Torres 2003; Van Gent et al. 1997). Finally, mice with a deficient *Dvl1* gene (a gene widely expressed in embryonic development and in the adult central nervous system) exhibited reduced social interaction (Lijam et al. 1997). Interestingly, mutations have been identified for two families with autistic disorder in the coding sequence of the gene *Wnt2* localised on chromosome 7q31 and involved in the same pathway as the *Dvl1* gene (Wassink et al. 2001).

Multiple trait model: social interaction and stereotypies

The GS guinea-pig model focused on the study of both social interaction and stereotypies (Caston et al. 1998). The GS guinea pig was derived from three albino Peruvian long hair littermates and showed naturally occurring cerebrocortical and cerebellar defects (hypofoliation of cerebellar vermian lobules VI and VII) within the first 3 weeks of development (Lev-Ram et al. 1993). The GS animals interacted significantly less frequently with each other compared to controls. In addition, GS animals learned more rapidly than their controls (Hartley guinea-pigs) to walk on a rotated wooden cylinder (rotarod), which interestingly is related to a repeated motor activity involving a stereotyped behavior. GS animals exhibited also significantly less exploratory behavior in a novel environment and were significantly less responsive to 50–95 dBA pure tones than Hartley guinea-pigs.

Taken together, these autistic-like behaviors associated with cerebellar abnormalities suggest that GS guinea-pigs might be an interesting animal model for studying autism. Indeed, early imaging studies reported cerebellar abnormalities (Bauman and Kemper 1985; Bauman et al. 1985; Gaffney et al. 1987), especially hypoplasia of cerebellar vermian lobules VI and VII in some individuals with autistic disorder (Courchesne et al. 1987, 1994). This was an interesting observation with regard to the contribution of the cerebellum to learning, language, sociability and affectivity (Ito 1998; Thach 1998). However, other studies could not replicate Courchesne's finding (Filipek et al. 1992; Garber et al. 1989; Holtum et al. 1992; Kleiman et al. 1992; Piven et al. 1992; Tanguay 2000). Methodological issues concerning the control group and not controlling for confounding variables such as IQ and age were discussed as potential sources of bias in Courchesne's studies (Piven et al. 1992). More specifically, Piven et al. (1992) demonstrated that hypoplasia of vermian lobules VI and VII found in some individuals with

autism was only significant when compared with a control group of individuals with superior IQs. In addition, a reduced volume of the cerebellum has been reported in other disorders associated with mental retardation such as Down's syndrome (Baxter et al. 2000) and vermian hypoplasia was also identified in various neurodevelopmental disorders (Schaefer et al. 1996). Taken together, these findings suggest that cerebellar vermian abnormalities are more related to the level of cognitive functioning rather than being specific of autism. Consequently, the GS guinea-pig model is interesting in terms of reproducing two main autistic behavioral dimensions (face validity), but its construct and etiological validity is questionable with regard to the controversal cerebellar vermian abnormalities described in autism. More promising are the histoanatomic observations of a reduced number of purkinje cells reported in some individuals with autism (Bailey et al. 1998; Raymond et al. 1996; Ritvo et al. 1986). However, further studies are warranted to confirm this neuropathological finding in autism before developing relevant animal models.

Similarly, Rodier's research team developed an animal model, which was supposed to reproduce the cerebellar vermian anomalies associated with autism (Ingram et al. 2000a). Based on the high incidence of autism (5 out of 15 cases) following thalidomide intoxication occurring between the 20th and 24th day of pregnancy (Strömland et al. 1994), which corresponds to the period when the neural tube begins to form, Rodier's group exposed rat embryos to a teratogene, valproic acid, at the period of neural tube closure. This chemical teratogenic model led to a reduction of the vermal posterior lobe. The main interest of this model is to demonstrate that early chemical exposure can provoke late developmental cerebellar anomalies. However, the face and construct or etiological validity of this model of autism are questionable considering that animal behaviors have not been studied and cerebellar vermian anomalies reported in individuals with autism are, as seen previously, controversial. Finally, Rodier developed also another animal model supposed to reproduce certain neuroanatomical brain abnormalities observed in autism. Indeed, Rodier et al. (1997) conducted a brain neuroanatomical study of a dead female with autistic disorder and reported a significant loss of motor neurons such as the facial nucleus and the superior olive, associated with a reduced size of the middle pontine region (Rodier et al. 1997). These anomalies were similar to the ones provoked by the *HOXA 1* gene knockout in mice (Chisaka et al. 1992). This animal model is interesting in terms of potential construct and etiological validity but has again a problem of face validity with regard to the absence of mice behavioral observations. Following these results, Rodier's research group conducted genetic research suggesting that allelic variants of *HOXA 1* on chromosome 7 and *HOXB 1* on chromosome 17 might be susceptibility loci for autism spectrum disorders (Ingram 2000b). These results were not confirmed by other studies (Collins et al. 2003; Devlin et al. 2002; Gallagher et al. 2004; Li et al. 2002; Romano et al. 2003; Talebizadeh et al. 2002). However, a linkage has been found recently between a specific *HOXA 1* variant and a cranial morphology in autistic disorder (Conciatori et al. 2004).

Multiple trait model: social interaction, communication and stereotypies

Oxytocin and vasopressin, as peptides involved in social interaction, communication and repetitive or stereotyped patterns of behavior, have been implicated in studies of autism (Insel et al. 1999). Decreased plasma oxytocin levels have been reported in children with autistic disorder (Green et al. 2001; Modahl et al. 1998). Animal models have been developed based on oxytocin and vasopressin peptide studies in rodents.

Central administration of oxytocin and vasopressin reduces the isolation calls of infant rats, and both peptides induce stereotyped behaviors in mice. Inversely, oxytocin or vasopressin deficits in rodents lead also to behavioral abnormalities. Indeed, oxytocin gene knockout provokes in mice pups reduced exploration behaviors and separation distress calls (Insel et al. 1999; Young et al. 1997), as well as failure to develop social recognition due to an amygdala oxytocin deficit (Ferguson et al. 2000, 2001). A vasopressin deficit found in Brattleboro rats, a strain displaying a spontaneous mutation in the arginine vasopressin ($Vp\alpha$) gene, is associated with reduced social memory and other cognitive impairments compared to controls (Engelmann and Landgraf 1994). Similarly, it is noteworthy that either a serotonin deficit or increase can lead to behavioral abnormalities (Kahne et al. 2002).

Knowing that oxytocin and vasopressin genes are co-localized on human chromosome 20p13, oxytocin and vasopressin studies in rodents offer promising avenues for genetic research and potential therapeutic efficacy in autistic disorder. Taken together, oxytocin and vasopressin studies in animals represent interesting animal models relevant to autistic disorder with good face validity (behavioral similarity in the three main domains of autistic impairments), and potential construct, etiological as well as predictive validity.

Similarly, the amygdala lesion in Bachevalier monkeys (1996) might be a very useful animal model because it allows researchers to study in concert, as the oxytocin–vasopressin rodent models, the three main domains of behavioral impairments in autistic disorder. Indeed, bilateral temporal lesions in new-born rhesus monkeys led in adulthood to social interaction and communication impairments as well as stereotyped behaviors. Consequently, this animal model has a good face validity and potential construct and etiological validity.

Animal models of schizophrenia and autism: limitations

The main problem with animal models is their validity or rather the conditions for validating them. The pertinence of using animal models in clinical and biological psychiatry is based on the postulate that humans and animals share basic neurobiological mechanisms associated with complex behaviors. These bio-behavioral homologies are the consequence of common origins, as indicated by evolutionary mechanisms. This leads us to discuss the limitations of animal models of mental disorders such as schizophrenia and autism, based on the similarity of underlying biological mechanisms tested in animals by certain manipulations and the similarity of observable behaviors.

Similarity of underlying biological mechanisms

Biological substrates and metabolic pathways can differ in animals and humans. For example, new classes of opioid receptors have been discovered in humans (Tordjman et al. 2003) but not in animal models. This could explain that the beneficial effect of naltrexone and naloxone (non-selective opioid antagonists) on stereotypies in animal models is not similar to the effect observed in individuals with autistic disorder displaying stereotyped behaviors. In addition, a gene that has a strong structural similarity at the DNA as well as at the RNA level of organization or a strong functional similarity, in two species can however result in different phenotypes in these species. Genetic homology of a gene in two species can be seen at three different levels: (1) the percentage of identical bases, for this gene in the two species; (2) the percentage of identical amino acid in the two species; and (3) the identity of the function of the gene in the two species. A gene that is homologous across several species is called ''orthologous''. The *minibrain* gene gives a good illustration of the ''orthology'' concept. It was first reported in drosophila but it was found also in the mouse and in humans where it is mapped in the region on MMU16 and around 21q22.2, with D21S17 and ETS2 as boundaries, respectively. The DNA or RNA structures of the *minibrain* gene are similar in flies, mice and humans (Guimera et al. 1996) and they have similar neuronal functions (reduced mushroom bodies in flies, reduced brain size in mice and humans). Phenotypic differences can appear, however, between animals and humans and be the consequence of the specificity of the metabolic or cellular pathways in two species. This is well illustrated by the Lesch-Nihan syndrome (LNS).

Lesch-Nihan syndrome is a X-linked recessive disorder due to a mutation in the hypoxanthine phosphoribosyltransferase (*HPRT*) gene. Several mutations may alter or modulate HPRT production. The *HPRT* mutation producing LNS has a relatively low incidence (1/100,000 male) and it results in a recessive phenotype. The mutation results in a lack of HPRT inducing an abnormal metabolism of the purines (over-production and over-excretion of purines). Patients with the LNS mutation have in fact no or residual levels of HPRT. This aberrant metabolism is associated with cognitive disorders and self mutilation typical of the LNS. Very little is known about the metabolic and cellular pathways leading to the LNS phenotype. Plasma dopamine-β-hydroxylase is low and concentration of dopamine in the basal ganglia is critically reduced in LNS. The abnormal catecholamine metabolism that is found in schizophrenia plus the self-injurious behavior sometimes associated with autism have stimulated psychiatrists' interest in LNS. Invalidation of the *Hprt* gene that is present in mice should provide an excellent animal model of LNS (Hooper et al. 1987; Kuehn et al. 1987). Unfortunately, none of the mice lacking HPRT displayed self injurious behavior. This intriguing result could be explained by a metabolic difference in mice and humans. Non-mutant mice did not salvage circulation hypoxanthine. The result could suggest that mice are preserved against HPRT loss and that purine metabolism is less HPRT dependent in the mouse than in humans. Wu and Melton (1993), examined adenine phosphoribosyltransferase (APRT) the second enzyme involved in the purine salvage pathway. They show first that HPRT/APRT was lower in mice than in humans at different ages. They administered then an inhibitor of APRT (9-ethyladenine) to mice lacking HPRT. These mice indicated a high frequency of self-injurious behaviors.

Some manipulations and their effects in animal models are not relevant to humans. Thus the effects of

prenatal stress on offspring studied by constraining rat females at different times of gestation are difficult to apply to pregnant women. In the same vein, it appears difficult to conclude about biological mechanisms underlying aggressive behaviors in humans from a mouse model of aggression in which the tested male is placed in a neutral cage followed by a standard opponent a few minutes later (Tordjman et al. 2003). Indeed, this behavioral testing in mice does not reproduce a situation commonly seen in humans, and thus the effects of this environmental manipulation cannot be really generalized to humans. However, it can be argued that this situation may be relevant to aggressive behaviors in humans following an invasion of one's territory by an intruder, which can be seen for example in gang phenomena. Conversely, some human environmental factors are not really reproducible in animal models. Animals do not live in the same environment as humans. What is the degree of similarity between constraint gastric ulcers that are induced in rats deprived from movement and those related to socio-professional conflicts in human?

In any case, it is noteworthy that by definition a model is reductive, and as underlined by Zarifian (1989), a model is always an abstract, approximate and reductive construction, which must be confronted with the complexity of reality.

In addition, certain manipulations supposed to induce an abnormal behavior, such as brain lesions, may destroy entire brain regions and provoke many other biological and behavioral abnormalities. Chemical or infectious agents can provoke global effects not focused on one specific brain region. It appears difficult in these animal models to control or assess the extension and time course of the lesions. A biological anomaly initially provoked in an animal model risks in fact to lead to a cascade of biological and behavioral events involving interactions between different biochemical and neuro-anatomical systems. Thus, these animal models do not necessarily test specifically one underlying biological mechanism.

Similarity of observable behaviors

The relevance of animal behaviors to human behaviors is questionable. The circumstances in which motor stereotypies appear in captive and domestic animals (motor stereotypies defined as repetitive movements without any goal; Houpt and Mc Donell 1993), shed light on our understanding of stereotyped behaviors in individuals with autistic disorder or schizophrenia. However, the extent to which motor stereotypies observed in animals, such as rocking, share similarities with more characteristic autistic stereotypies, such as toe-walk, remains an important issue. In addition, is it possible to compare self-injurious behavior in autistic disorder to excessive self-grooming in a mouse model, as proposed by Murcia and collaborators (2005)? Can we really speak, like these authors, of ''behavioral measures of an autistic mouse''? Similarly, when hyperactivity in schizophrenia is studied through developing an animal model measuring hyperlocomotion in mice, this correspondence seems also questionable.

Furthermore, it seems difficult to reduce a mental disorder to one behavioral trait measured in an animal model. Thus, hyperlocomotion in mice does not represent a specific behavioral feature of schizophrenia and cannot summarize by itself this disorder. One of the main limitations of animal models is the lack of specificity of the behaviors studied with regard to a particular mental disorder. It is probably more interesting to develop animal models displaying a syndrome or a behavioral profile related to autistic disorder or schizophrenia, rather focusing on only one trait or behavior. Thus, a pertinent model of autistic disorder should display social interaction and communication impairments as well as stereotyped behaviors, which represent the three main autistic behavioral domains according to DSM-IV-TR or ICD-10 criteria. This is one of the main goals of Crawley's research team which is in the process of designing a set of tasks with face validity for the defining features of autism: deficits in appropriate reciprocal social interactions, deficits in social communication, and high levels of ritualistic repetitive behaviors (Crawley 2004). As underlined by Fisch (2005), some studies using factor or cluster analyses suggest also that three dimensions (cognitive abilities, social function and restrictive interest or activities) are necessary in the assessment and conceptualization of autism (Dihoff et al. 1993; Szatmari et al. 2002).

It seems important to develop multi-trait models to better understand multidimensional disorders such as autism or schizophrenia. Animal models based on diagnostic categories might be problematic considering that definitions of diagnostic categories of mental disorders, such as autism or schizophrenia, evolve over time due to conceptual shifts and technological progress. In addition, diagnostic categories used to establish benchmark criteria may have limited utility or insufficient empirical support (Fisch 2005). The problems created by benchmark criteria could be avoided by adopting a multidimensional approach (Robins and Helzer 1986). One of the main interests of animal models is not to validate a specific categorical model of

autism or schizophrenia, but rather to study behavioral and neurobiological mechanisms possibly involved in autistic disorder or schizophrenia through a multidimensional approach.

It might be also interesting to develop animal models focusing on one precise behavioral dimension shared by different mental disorders to better understand some common underlying mechanisms. New models could be proposed in which a dimensional conception of mental disorders would replace a categorical nosographical one. Innovative perspectives could be envisioned concerning the identification, follow-up and treatment of mental disorders (or subtypes of mental disorders), which are currently considered to belong to different nosographical categories, but which could overlap through shared common dimensions.

Finally, the association tested in an animal model between a behavioral trait and an underlying biological mechanism, is also questionable regarding the fact that a same abnormal behavior, such as stereotypies in rodents, can be produced by different biological mechanisms, such as for example, activation of numerous opioid receptor types. Sterotypies have been also described in several inbred strains of mice and in mice carrying an extra-copy of MMU16 (Turner et al. 2001). Animal models of mental disorders should provide a model allowing researchers to test the association between a behavioral profile and a biological profile (see Roubertoux and Kerdelhué 2006). As underlined by Murcia et al. (2005), any animal model of autism must accurately replicate a combination of the behavioral, neuropathological, biochemical and genetic basis for autistic disorder. The greater the number of features that are represented, the closer the model's approximation to autism spectrum disorder will be.

Conclusions

Animal models reviewed in this article test more behavioral dimensions or biological mechanisms related to autistic disorder or schizophrenia rather than providing specific categorical nosographical models of autism or schizophrenia. Thus, it appears more appropriate to speak about animal models of behavioral and biological mechanisms relevant to autistic disorder or schizophrenia, instead of speaking about animal models of autism or schizophrenia.

In addition, the study in an animal model of one behavioral feature associated with one underlying biological mechanism does not correspond to the complexity of mental disorders. It could be useful to develop animal models to test a behavioral profile associated with a biological profile through a multidimensional approach. Furthermore, it would be of interest to study the behavioral and biological effects of environmental factors applied to animal models, such as social isolation, in order to investigate the role of these environmental factors in autistic disorder or schizophrenia.

Finally, animal models can help us to clarify complex mechanisms (even if they are simplified) and to better understand relationships between biological and behavioral variables and their interactions with environmental factors. The ability to study neurophysiological processes under experimental control using brain measures and pharmacological, cerebral, environmental and genetic manipulations that are not possible in humans, makes animal models valuable to test an etiopathogenic mechanism potentially involved in a mental disorder and to develop an effective treatment. Animal models offer an opportunity to open a discussion between clinicians and biologists and shed new light through creative ideas that allow us to go beyond our usual way of thinking. The use of animal models should allow, according to Soubrié and Simon (1989), the development of human psychopharmacology, with its own specific models, based on data from animal studies. From this perspective, the main interest of animal models would be perhaps to generate new pertinent hypotheses relevant to humans. Studies of animal models can thus help us to construct models that are specific to the psychopathology and neurobiology of human behavior, opening the path to innovative hypotheses and research. The use of animal models in psychopharmacological research has been often criticized. Harlow and McKinney (1971) summarized the situation in the following way: «One must be crazy to use animal models to study human psychopathology, but it would be crazy not to do it because of the possible benefits of work conducted on animals».

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