Chapter

Animal Models in Psychiatric Disorder Studies

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Abstract

Among the diseases affecting the brain, special attention has been paid to psychiatric disorders (PDs) due to high prevalence and significant debilitating clinical features. Many difficulties need to be overcome to find good animal models for PDs, due to their multifactorial origins, high heterogeneity and symptoms, as for instance the hallucinations and delusions, which usually cannot be easily assessed employing ordinary experimental animal models. The use of animal models reproducing at least some specific traits that can be studied individually, known as endophenotypes, is often reported. However, since altered biological pathways are common to many of these disorders, each of these behaviors may also reflect different PDs. In this context, it is possible to perform several approaches, to elicit changes in the endophenotypes of interest, not only in vertebrate models like rodents, but also in invertebrate models which have important advantages due to high conservation of essential pathways, lower complexity, and shorter life cycle compared to mammals. Therefore, animal models are also helpful for elucidating the etiology underlying PDs, by allowing easier access to biological samples that are usually not accessible in clinical studies, as for instance, fresh brain samples, from embryos to adults.

Keywords: animal model, psychiatric disorders, neurodevelopment, biomarkers, CNS, endophenotypes

1. Introduction

According to the World Health Organization (WHO), psychiatric disorders (PDs) comprise a broad range of dysfunctions, with several and some common symptoms. PDs are generally characterized by the combination of symptoms as abnormal thoughts, emotions, behavior, and social interaction. The most common PDs include schizophrenia (SCZ), bipolar disorder (BD), major depression disorder (MDD), attention deficit hyperactivity disorder (ADHD), intellectual disabilities, drug abuse disorders, among others [1].

1.1 The need and the value of animal models for PD studies

There are several reasons to use animal models in the studies of disorders affecting the brain. The poor understanding of the etiopathogenesis and pathophysiology of PDs is clearly reflected by the unmet clinical need for better pharmacological

treatments. Therefore, good models are clearly needed to clarify the neurobiology involved in PDs, as well as for the identification of biomarkers useful to assist diagnosis and/or for the development of novel therapies. It is also implausible to move forward in clinical trials with a novel drug tested only in a cell model, without any evidence about its efficacy in animal experiments. The value of animal models to drug development has been demonstrated empirically. For example, the first and the most efficacious drugs available for complex PDs such as SCZ (e.g., chlorpromazine and clozapine) was discovered observing the alterations in behaviors of experimental animals in response to each drug administration. In fact, in the last decades, most of the CNS drugs approved were discovered employing a phenotypic screening approach in animal models [2, 3].

1.2 Challenges to model PDs in animals

A reliable animal model must share several similarities with the studied target to allow a successful translation from the basic to the clinical research. However, several limitations need to be overcome. First, the heterogeneous behavioral symptom characteristics of PDs are in some grade uniquely expressed in humans, and they are certainly impossible to be reproduced authentically in animals as rodents, fishes or worms [4]. Second, there is a lack of an objective measure to unequivocally diagnose mental illness [5], which adds complexity to the modeling any mental disorder in experimental animals. Third, in order to develop meaningful animal models for PDs with potential translational power, the disease phenotypes must be represented in the experimental animals. The selection and update of these phenotypes, in agreement with the recent findings in clinical psychiatry and neuroscience, represents a challenge, as evidenced by the recognized gap between the clinical and basic scientific research [6]. In addition, a rising question is what are the specific traits or phenotypes that an animal model should express to be translatable to specific disorder? (**Figure 1**).

1.3 How to develop an animal model for PD studies

The traditional approach to establish an animal model in PDs is based on three classic constructs proposed by Willner in 1984: face validity, which determines how much a phenotype presented by a patient is represented by the animal model (corresponds to similarity between the model and the PDs assessed, that includes symptoms, signs, and pharmacological features); construct validity, which demonstrates whether it is possible to reproduce the pathological condition based on processes that are already known to be altered (correspondence between the physiological dysfunctions in the human population and in the animal model); predictive validity, which tries to evaluate if a pharmacological or non-pharmacological intervention is capable to reverse the pathological condition (in other words, if the treatment that is effective in reversing PDs in humans would reverse the changes seen in animals) [7–10]. However, in practice, no animal models fully meet these three criteria of validity.

Many authors have proposed that instead of these three proposed criteria defining an external validation, in addition, the validity of an animal model should not be simply organisms that resemble human dysfunction, but they would also reproduce the processes by which animals and humans enter this state, and therefore, this could be better exploited by adding a new validation criteria [9]. For instance, the validity by homology, which proposes, for instance, an invertebrate model, such as *Drosophila*, may not be the ideal animal model for studying complex changes in a brain circuitry, but in turn, it may represent a great choice to study the genetic control of early embryonic development [11]. In fact, the nematode *Caenorhabditis elegans* is a reliable model with conserved neurobiological systems

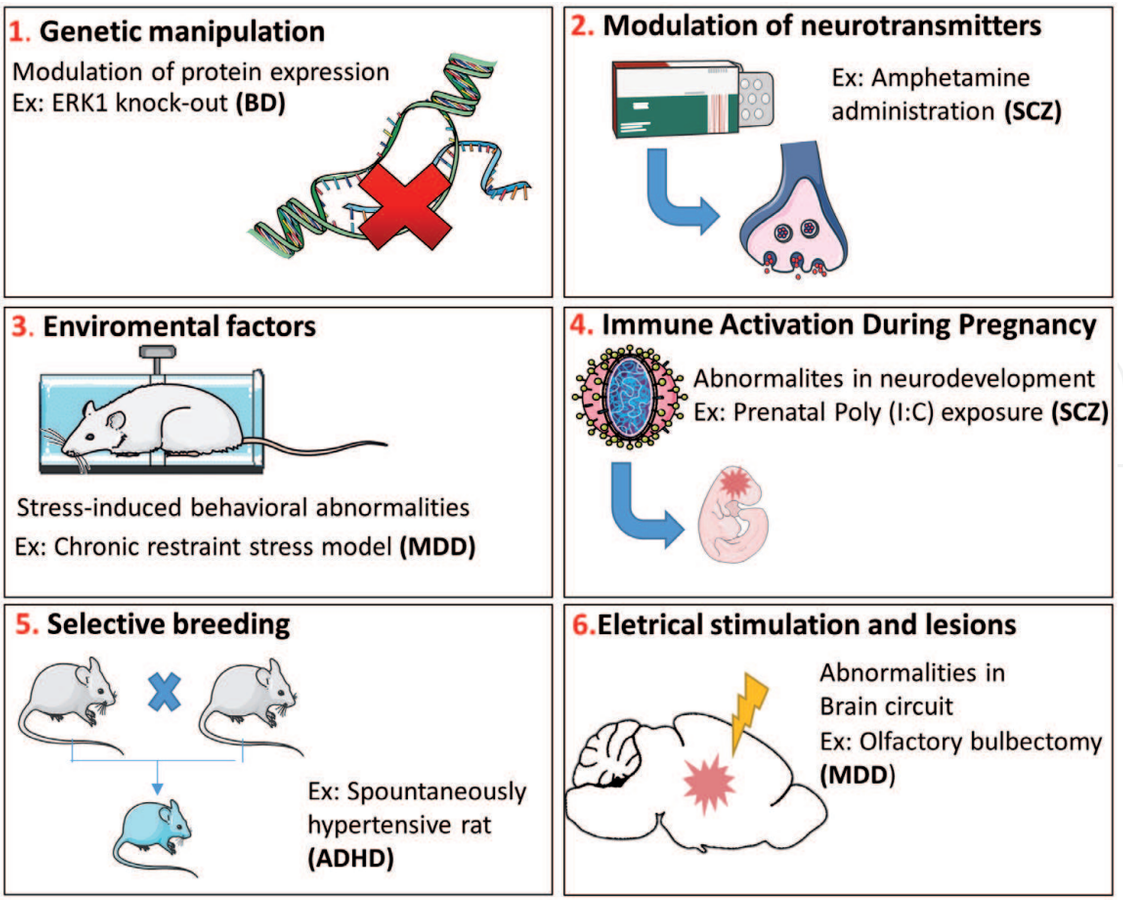

Figure 1.
Different approaches to construct animal models for neuropsychiatric disorders studies.

that has been helpful in the discovery of molecular mechanisms that underlie learning and memory, and, in addition, this animal model has a fully sequenced genome and other several molecular and genetic tools available for researchers [12, 13].

1.4 Symptoms versus endophenotypes in experimental model animals

There is a consensus about the low reliability of the diagnostic construct provided for the employment of Diagnostic and Statistical Manual of Mental Disorders or DMS (which is a manual that determines the criteria for the clinical diagnosis of PDs). The heterogeneity implicit in this classification system and the imprecise quantification of the symptoms make it impossible to deconstruct PDs within model organisms. In fact, an etiology-based nosology system has been advocate for psychiatry, and it has been proposed to identify the endophenotypes that occur in both healthy individuals and subjects with different psychopathologies [14]. Endophenotypes are basically quantitative trait-like deficits that are possible to assess by laboratory-based methods rather than by clinical observation. An endophenotype should be state-independent, heritable, occurring at a high rate in affected families, and in addition, it should be associated to genetic variants of the disorder, as it should be involved the same brain circuits associated with the symptoms of the illness in patients (**Table 1**).

The Research Domains Criteria (RDoC) framework was introduced as an alternative categorization system for psychopathological states [15–17]. This system provides a platform to improve the translatability of studies from animals to humans, since it supports the endophenotype-based comparison of animals and humans on an objective neurobiological basis across all behavioral domains. In fact, the endophenotypes have been reverse-translated into animal models successfully and allows the evaluation

Endophenotype	Description	What can be evaluated
Locomotor activity	Distance travelled, time spent, and frequency of the movements measured during or after a habituation period or after some stimuli (i.e. drug administration)	Behavioral sensitization (BD; ADHD; SCZ); Depressive-like behaviors (MDD); etc...
Latent inhibition	Latent inhibition is the ability of a pre-exposed nonreinforced stimulus to inhibit later stimulus-response learning	Cognitive impairments (SCZ); etc...
Pre-pulse inhibition (PPI)	Decrease of the startle reflex after exposure to a pre-pulse before the pulse	Cognitive impairments (SCZ); etc...
Working memory and learning	Describes short-term memory, in a olfactory domain and spatial domain	Cognitive impairments (PDs in general); etc...
Social interaction	Evaluation of time spent on exploring a social stimulus.	Anxiety-like behaviors; Depressive-like behaviors; etc...
Rearing	Measure of activity, investigation and exploratory behavior induced by a drug or/and novelty	Anxiety-like behaviors; etc...
Grooming	A maintenance behavior evaluated by the cleaning of the fur; is displayed as reaction to unexpected stimuli and in conflict situations	Anxiety-like behaviors; Depressive-like behaviors; etc...
Aggressiveness	Evaluation of attack and defensive behavior as reaction to a stimuli or other animal	Anxiety-like behaviors; Depressive-like behaviors; etc...
Food intake	Amount of food ingested by the animal	Anxiety-like behaviors; Depressive-like behaviors; etc...
Sucrose preference test	Assesses the sensitivity to reward based on the rodent's natural preference for sweets. This test measures the amount of a sweet-tasting solution that the animal ingests	Depressive-like behaviors; etc...
Fear conditioning	Classical conditioning paradigm, in which an aversive stimulus is paired with some neutral stimuli. Used to assess associative fear learning and memory in rodents.	Cognitive impairments (PDs in general); etc...
Forced swim test	Measures the scoring of swimming and climbing (active behavior), and immobility (passive behavior) when animals are placed in an inescapable cylinder filled with water	Depressive-like behaviors; etc...

Table 1.
Most common endophenotypes used to evaluate behaviors associated with psychiatric disorders (PDs).

of the neural neurobiological substrates and their circuit dysfunctions [18]. Thus, it has been demonstrated that the modeling of neurobiological and behavioral endophenotypes to reproduce PDs in experimental animals is possible.

The ideal animal model should be derived from risk factors or the causative agent of the human disease. One of the strategies used during the construction of a model is focused on a specific factor that can reproduce the condition as a whole or an aspect of the disease [19]. The choice for the methodology used in establishing a model is fundamentally important to guide which aspect of the disease should be explored, and it is an essential component in the validation of a model known as construct validity.

2. PDs and animal models

In the following sections, selected examples of animal models used in the context of investigating PDs will be demonstrated, indicating which changes are observed in behavioral and molecular levels.

2.1 Animal models in schizophrenia (SCZ)

Schizophrenia (SCZ) is a severe brain disorder, characterized by a set of positive and negative symptoms and cognitive disorders, which are the basis for the clinical diagnosis of individuals who needs to present at least two or more of those symptoms, according to the DSM. SCZ is one of the most debilitating mental disorders, affecting about 21 million people worldwide. The antipsychotics used to treat SCZ patients can soften the development of the disorder, and this pharmacological treatment was the basis for the most accepted theory to explain the neurobiology of SCZ, as noticed by the alterations in the dopamine transmission. In addition, several other theories have been suggested soon after, as for instance, the serotoninergic, glutamatergic, GABAergic, and the neurodevelopmental susceptibility hypothesis, among others [20]. However, none of these theories had allowed the characterization of the etiology or the identification of strong biomarker for the diagnosis of SCZ. Many efforts are being made to characterize a model for SCZ, but there is a great difficulty in reproduce endophenotypes that frame all the groups of symptoms related to this disease, or which allow associating all risk factors that are already known. Below, we exemplify some of these models, and for a more detailed review of SCZ models can be found elsewhere [21].

Most of the models are based on the theory of neurotransmitter imbalance, and they are induced by the disruption of these pathways, other models explore changes in the levels of expression of candidate genes involved in the processes of SCZ susceptibility. It should be considered that SCZ is a multifactorial disorder, and thus, the genetic component should be evaluated in addition to changes in the environment, as in contrast to the models based on genetic alterations, there are those taking into account the environmental changes, such as the prenatal insults, which impose changes in the neurodevelopment processes. Some of these models are exemplified in **Table 2**.

All of these models show behavioral and molecular changes that can be associated with SCZ.

2.2 Animal models in major depressive disorder (MDD)

Major depressive disorder (MDD) is a common, complex, and heterogeneous mental disorder, characterized by persistent sadness and loss of interest in general activities, affecting about 10% of the population worldwide, and which is caused by multifactorial mechanisms not fully understood yet, characterizing MDD as a disorder with many variations in clinical features among the patients, imposing a consequent high variability in the diagnosis, time course of response and remission [45], which is one of the main reasons justifying the intensive search for animal models and biomarkers, aiming for advances in MDD diagnosis [46]. In addition, these advances could be helpful for a better classification for depressive spectrum, and thereby for improving the treatment [47]. The animal models of depression have been developed based on acute or chronic stress exposure, exogenous administration of glucocorticoids, injuries in brain regions and/or genetic manipulations [48–50]. There is a great variation in the number of protocols that

Model	Endophenotype	Molecular alterations	References
Drug-induced models			
Amphetamine model of SCZ	**Acute:** ↓ Latent inhibition; ↑ locomotion **Chronic:** Same as acute but with ↓ PPI	↑ Mesolimbic dopamine response; ↑ Acetilcholine in PFc	[22–26]
Glutamatergic manipulation (Phencyclidine; MK-801; Ketamine)	↑ Locomotion; ↓ working memory; ↓ Reversal learning performance; ↓ Social interaction; ↓ PPI	↓ PV-immunoreactive neurons in PFc and hippocampus	[27–29]
Genetic manipulation			
DISC-1 mutations			
Missense mutations models	↓ PPI; ↓ latent inhibition; ↑ Depressive-like phenotype	↓ Brain volume; ↓ PDE4B activity and binding to DISC1; ↓ PV-immunoreactive; ↓ Dendritic density	[30–32]
Dominant-negative isoforms of DISC1	↑ Amphetamine sensibility; ↓ working memory	↓ Dopamine, DOPAC; ↓ PV-immunoreactive	[33, 34]
Knockdown	↑ Amphetamine sensibility; ↓ PPI; ↓ working memory	↓ Dopamine; ↓ PV-immunoreactive	[35]
Overexpression	↑ Amphetamine sensibility; ↑ rearing behavior; ↑ locomotion; ↓ learning in rotarod task	↑ Increase in high-affinity D2R; ↑ Translocation of dopamine transporter; ↑ Dopamine inflow	[36]
Neuregulin1, ErbB4, and dysbindin			
Knock-out	↑ Amphetamine sensibility; ↑ locomotion; ↓ PPI; ↓ Working memory; ↓ social interaction	**Neuregulin1; ErbB4:** ↓ Hippocampal spine density; ↑ Lateral ventricles; **Dysbindin:** ↑ HVA/DA ratio; ↑ Excitability of PFc pyramidal neurones	[37–39]
Developmental models			
Neonatal excitotoxic hippocampal lesion	↓ PPI; ↓ Working memory; ↓ Social interaction; ↑ Amphetamine sensibility; ↑ MK-801/PCP sensibility; ↑ locomotion	↑ Mesolimbic dopamine response; ↑ Acetilcholine in PFc	[40, 41]
Methylazomethanol (MAM) and polyinosinic-polycytidylic acid (poly I:C)	↑ Locomotion; ↑ Amphetamine sensibility; ↑ MK-801/PCP sensibility; ↓ Social interaction; ↓ PPI; ↓ Working memory	↓ PV-immunoreactive neurons in PFc and hippocampus	[42–44]

All of these models show behavioral and molecular changes that can be associated with SCZ.
PPI = prepulse inhibition; PFc = prefrontal cortex; PV = parvalbumin; PDE4B = cAMP-specific 3",5"-cyclic phosphodiesterase 4B; DISC1 = disrupted-in-schizophrenia 1; DOPAC = dihydroxyphenylacetic acid; HVA = homovanillic acid; DA = dopamine; poly I:C = Polyinosinic:polycytidylic acid.

Table 2.
Some examples of SCZ models induced by drugs, genetic manipulation, and prenatal insults.

can be used to induce these changes, in which the stressor, time of exposure to the stimulus, and other parameters may vary. For more detailed review of MDD models, see also [51] (**Table 3**).

Model	Endophenotype	Molecular alterations	References
Stress-induced models			
Learned Helplessness	↓ Locomotion; ↑ aggressiveness ↓ Grooming; ↓ response to rewards ↑ Sleep disturbance	↓ Norepinephrine ; ↑ BDNF; aberrant miRNA brain- region specific expression	[52–57]
Unpredictable chronic mild stress	↓ Food intake; ↓ growth rate; ↓ Locomotion; ↑ aggressiveness; ↓ Response to rewards	↑ Corticosterone; ↓ glucocorticoid receptor expression; ↓ endogenous ATP	[58–61]
Chronic restraint stress model	↑ Aggressiveness; ↑ fear conditioning; ↓ locomotion; ↓ food intake	↑ CA3 dendritic atrophy and damage; ↓ neurogenesis in dentate gyrus; ↑ apoptotic cell death; ↑ corticosteroid	[62–64]
Social defeat	↓ Locomotion; ↓ exploratory activity; ↓ Aggression; ↓ sexual behavior; ↑ Anhedonia; ↑ sleep disturbance ; ↓ Growth rate	↓ Volume and cell proliferation in hippocampus and PFc; ↑ corticosteroid; ↓ serotonin; ↓ BDNF	[65–67]
Early life stress model	↑ Anxiety-like behavior; ↑ Depression-like behavior; ↑ Novelty responsivity	↑ BDNF expression PFC and hippocampus	[68, 69]
Brain lesion model			
Olfactory bulbectomy	↑ Locomotion; ↓ working memory; ↓ response to rewards; ↓ food intake; ↑ sleep disturbance; ↑ responsivity to stressors	Dysfucntion in HPA and neuro-immune axis; ↓ neurotransmitters; ↑ neuronal degeneration; ↑ BDNF; ↓ neuropeptides	[70, 71]
Selective inbreeding			
Wistar-Kyoto	↓ Locomotion; ↑ immobility in forced swim test; ↑ social avoidance; ↑ freezing to context	↑ Adrenal glands; ↑ corticosterone	[72, 73]
Flinders Sensitive Line rat	↓ Activity in enclosed arena; ↑ immobility in forced swim test; ↓ sucrose intake under stress	↓ Serotonin synthesis; dysfunction in dopaminergic and noradrenergic systems	[74–77]

BDNF = brain-derived neurotrophic factor; miRNA = microRNA; ATP = adenosine triphosphate; PFc = prefrontal cortex; HPA = hypothalamic–pituitary–adrenal axis.

Table 3.
Examples of models for MDD induced by stressors, injuries in brain regions, and by selective inbreeding.

2.3 Animal models in bipolar disorder (BD)

Bipolar disorder (BD) is a chronic mood disorder, characterized by fluctuations between mania and depressive episodes, which affects approximately 1% of the global population irrespective of nationality, ethnic origin, or socioeconomic status [78]. Due to the complex mood alterations, misdiagnosis in BD is very common, as other mental illnesses as depression and SCZ share several common symptoms, in addition to the specific and common endophenotypes and brain structural changes [79, 80]. The search for advances in diagnosis is important for these disorders, since early diagnosis would be essential to foster earlier suited pharmacological treatment in BD, which was proved to be beneficial to prevent the cognitive deficits and disabilities in these BD patients [81], as also demonstrated for SCZ patients [82]. The major limitation in evaluating a model for BD is the difficulty in reproducing the phases of mania and depression observed in the clinic. Many of these models present only one of these parameters, and they are often developed by genetic alterations in genes known to be involved in this disorder or stressors, mainly involved in the circadian cycle as also demonstrated for other PDs. Another interesting approach used for the development of animal models for BD is the one induced by psychostimulant sensitization (which causes mania-like behavior), as withdrawal from psychostimulants is accompanied by depressive-like behavior, which together leads to changes and compulsory behaviors. Some of these models are exemplified in **Table 4**. A more detailed review of BD models can be found elsewhere [93].

BDNF = brain-derived neurotrophic factor; ERK1 = Extracellular signal-regulated kinase 1; DAT = dopamine transporter.

Model	Endophenotype	Molecular alterations	References
Genetic manipulation			
BDNF haploinsufficient	↑ Locomotion; ↑ agressive behavior; ↑ food intake	↓ Brain volume; ↓ BDNF; ↓ dopamine	[83, 84]
ERK1 Knock-out	↑ Amphetamine sensibility; ↓ learing in fear conditioning; ↑ locomotion; ↓ immobility in forced swim	↓ Phospho-RSK1/3 in PFC and striatum; shift of activity rhythm	[85–86]
DAT Knock-down	↑ Locomotion; ↓ anxiety; ↑ rearing	↑ Dopamine	[87–89]
Environmental stress			
Sleep deprivation	↑ Locomotion; ↑ agressive behavior; ↑ exploratory behavior	—	[90, 91]
Photoperiod lenghts	↑ Anxiety; ↑ helplessness	Switch in dopamine neurotransmission to somatostatin	[92]
Sensitization model			
Chronic amphetamine administration followed by withdrawal	↑ Locomotion; ↑ anxiety; ↑ anhedonia; ↓ motivation; ↓ working memory	↓ Dopamine responsiveness ↑ serotonin sensitivty	[94–96]

BDNF = brain-derived neurotrophic factor; ERK1 = Extracellular signal-regulated kinase 1; DAT = dopamine transporter.

Table 4.
Examples of models for BD induced by genetic manipulation, environmental stressors, and induced by sensitization, which lead to some aspects of molecular and behavioral changes related to BD.

2.4 Animal models in attention-deficit/hyperactivity disorder (ADHD)

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder, affecting approximately 2.2–2.8% of worldwide, with multifactorial inducement, as reflected by the heterogeneity found in this disorder, and as indicated by the diversity in its psychiatric comorbidities [97]. This disorder is defined by inappropriate levels of attention deficits and/or hyperactivity behavior, which directly interfere with the normal life and functioning of an individual [98]. While there is no cure for ADHD, currently available treatments can help reducing the symptoms and improving the general functioning, although with a peculiar wide variability due to the clinically and scientifically difficulties to exactly determine the specificity and the origin of the symptoms [99]. As for other PDs, due to the high heritability, animal models for ADHD are mostly derived from genetic alterations or breeding selection or from neonatal insults that can lead to neurodevelopmental changes. Models related to dopaminergic neurotransmission are also important to evaluate ADHD, as also listed in **Table 2**, and which includes the administration of psychostimulants as amphetamine. A more detailed review on ADHD animal models can be found elsewhere [100] (**Table 5**).

Model	Endophenotype	Molecular alterations	References
Genetic manipulation			
Spontaneously hypertensive rats	↓ Attention; ↑ motor impulsiveness ↑ Locomotion; ↑ exploratory behavior	↑ Dopamine ↓ Dopamine transporter 1 expression ↓ Brain volume	[101–104]
Coloboma mouse mutant	↑ Locomotion; ↑ exploratory behavior; ↑ amphetamine sensibility	↑ Noraedrenergic function ↓ Dopamine ↓ DOPAC and HVA	[105–108]
Neonatal insults			
6-hydroxydopamine	↓ Working memory; ↑ locomotion; ↑ Exploratory behavior	↓ Dopamine ↑ Dopamine receptor 4 ↓ Serotonin transporter binding in striatum	[109–111]
Neonatal anoxia	↑ Locomotion; ↑ exploratory behavior; ↓ spatial memory	Transient changes in neurotransmitters ↑ Dopamine turnover ↓ Noraepinephrine and 5-HIAA ↓ CA1 cell density	[112–114]

DOPAC = 3,4-Dihydroxyphenylacetic acid; HVA = Homovanillic acid; 5-HIIA = 5-Hydroxyindoleacetic acid.

Table 5.
Examples of models for ADHD induced by genetic manipulation in susceptibility genes and selective inbreeding and by prenatal insults.

3. Conclusion

There is a consensus about the critical role of animal models for the advance and understanding the functioning of brain and brain disorders, as well as for the development of new treatments. However, it is important to use them judiciously and avoid the over interpretations derived for the findings, as it is noticeable that the results obtained on experimental animals are not necessarily confirmed in clinical studies.

As it has been shown, there are several approaches to obtain an animal model for studies in psychiatry, but there is still a limitation in reproducing all the conditions involved in the pathophysiology of the disorder, and it is extremely crucial to recognize this limitation. An alternative that has proved to be efficient is to direct the study to a specific symptom domain that can answer at least in part, the significance of these findings to concretely improve the knowledge in PDs, and thereby bring advances in treatment. The crisis of the classification system is evidenced in the diagnostic inflation in psychiatry, which adds complexity to the preclinical research and complicates the modeling of PDs within the available experimental laboratory animals. The recent and alternative approaches as the RDoC to study the brain and behavior are in a relative infancy, but promises bringing new perspectives in how models that can be improved to become indeed helpful to benefit the quality of life of patients with PDs.

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