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EDITORIAL

Rodent models of psychiatric disorders—practical considerations

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Introduction

Animal models for psychiatric disorders are traditionally more controversial than models for somatic diseases (Nestler and Hyman 2010; Fernando and Robbins 2011; Mitchell et al. 2011). The main arguments for this attitude are as follows. (1) Psychiatric disorders compromise mood, affects, perception, cognition, executive functions, etc. To what extent, if at all, the animal (in particular, rodent) correlates of these behavioral domains model those in humans remains controversial. This aspect of a model, i.e., its similarity with the human condition, is regarded as face validity. Face validity is extremely important for psychiatric animal models, since human disorders are currently only defined by clusters of psychopathological signs and symptoms, because, for all major psychiatric diseases, the underlying pathophysiological mechanisms are unknown. (2) Therefore, animal models cannot be based on imitating such mechanisms (such as destroying pancreatic β-cells by streptozotocin for studying the mechanisms of the sequelae of diabetes). Moreover, psychiatric disorders do not obey simple genetics that can be mimicked by a single mutation. Thus, current models of psychiatric disorders also lack so-called construct validity. (3) No established biomarkers for psychiatric disorders exist that can be used as surrogate markers in animal models. Hence, validation depends largely on predictive validity, i.e., the response to drugs with known efficacy in patients (e.g., so-called anxiolytics, antidepressants, antipsychotics). However, usually, these drugs affect a neurotransmitter system the disturbance of which has not been established as the underlying cause of the treated disorder.

Despite this negative starting point, animal models have, without doubt, also significantly advanced our understanding of psychiatric diseases. In this regard, animal models seem to have their strengths in modeling single symptoms or clusters of a few symptoms only (so-called endophenotypes) rather than the disorder in its complexity. Examples are anhedonia in depression, decreased sociability in autism and hyperlocomotion in attention deficit hyperactivity disorder (ADHD). However, each of these three might also be a feature of a schizophrenia model. This also corresponds to the human situation, in which a single sign or symptom is not disease-specific. Nevertheless, the identification of mechanisms underlying endophenotypes and their definition with respect to genetics, neurotransmitters, brain systems, electrophysiological properties, etc. is easier than doing the same for a complex syndrome.

If one searches PubMed with the key words “animal models psychiatry”, the number of hits has tripled over the last 10 years, indicating a growing interest in and the need for improved animal models in psychiatry. This motivated us to edit a collection of review articles on the topic for a special issue of Cell and Tissue Research. We decided to focus on rodents in order to keep concepts and principles comparable from one review to the next. In doing so, we did not want to neglect the fact that immense knowledge has also come from studies with non-human primates and from species such as *Drosophila* and zebra fish. Because of space limitations, we further restricted ourselves and the contributions mainly to animal models of depression, anxiety and schizophrenia, which still represent the core disorders of general psychiatry, without ignoring many more that seem equally important (e.g., addiction, eating and obsessive/compulsive disorders).

Practical considerations have been a special concern, since the reproducibility of results and the concepts derived are not only a problem in clinical trials and genetic and neuroimaging

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studies in humans but also in rodents. For example, the spectacular monocausal concept (based on mouse experiments) that antidepressants exert their effects by increasing hippocampal neurogenesis (Santarelli et al. 2003), has had to be revised and redefined (Holick et al. 2008), a hot topic that has also been discussed based on the latest state of art in the present edition (Tanti and Belzung 2013). Despite the abovementioned disadvantage of validity, rodent models offer the possibility of studying, in specific endophenotypes, the functions of the brain more mechanistically with high-technic invasive or post-mortem methods, allowing better scientific insight and additional value compared with human studies. Therefore, we decided to start this issue with a number of reviews that cover key methods and tools that have been used in rodents to analyze mechanisms of neural plasticity.

Animal models in psychiatry: methods beyond behavioral analyses to investigate the central nervous system

Targeted mutagenesis has been a groundbreaking method and key technology for studying gene-function relationships in vivo, in particular the role of specific genes in behavior. Recent refinements of methods, such as (brain) region-specific or temporally conditional knock-out techniques, have added even more importance to this molecular genetic approach, which is reviewed in this issue by Jan Deussing (2013). Targeted mutagenesis could serve to study the function of candidate genes or polymorphisms identified in human psychiatric disorders, e.g., disc-1 in schizophrenia, brain-derived neurotrophic factor (BDNF) polymorphisms in affective disorders, or amyloid precursor protein (APP) gene mutations in Alzheimer's disease. Lately, the possibility of generating humanized mice allows the study of polymorphisms that do not exist in mice, e.g., the BDNF val66met polymorphism (Chen et al. 2006). For decades, the conceptual framework of psychiatric disorders was that of neurotransmitter dysbalances and almost all psychopharmacological drugs obeyed this principle. Therefore, Anderzhanova and Wotjak (2013) introduce microdialysis, a method to monitor and quantify dynamic changes in neurotransmitters, their metabolites and bioactive compounds including drugs in the extracellular fluid of specific brain regions, as another key method in modeling psychiatric animal models. The authors not only provide a practical guideline for measuring relative changes in neurotransmitter release but also discuss means for measuring absolute neurotransmitter concentrations in the extracellular milieu, such as zero-net-flux microdialysis. Neuropathological changes and associated alterations in neural plasticity have been studied for decades in brains of deceased psychiatric patients but without much success, possibly at least in part because of technical/biological problems (e.g., post-mortem tissue decomposition). This can be overcome in experimental animals. Oliver von Bohlen und Halbach (2013) summarizes histochemical methods for studying morphological changes in animal models, giving special attention to anatomical correlates of connectivity such as alterations in fiber densities, dendritic arborisation and spines. Moreover, he also describes the way to investigate neuronal activity in fixed brain tissues, in particular with respect to cellular transcriptional activity (Herdegen et al. 1997). Changes in gene expression are taken as a topic by Molteni et al. (2013), who introduce gene expression profiling of brain tissue as a functional read-out of rodent models for psychiatric disorders. They focus here on the expression of inducible transcription factors and the modulation of the neurotrophin BDNF (Chourbaji et al. 2008a, 2011), both of which have been especially associated with affective disorders (Riva and Gass 2007) but their principles can be applied to psychiatric disease models in general. Moreover, they discuss genome-wide expression studies aimed at identifying, in a hypothesis-free manner, all genes that might be differentially regulated under a given experimental setting. Neuroimaging has been regarded as a silver bullet in translational research, because it can be performed by equal measures in healthy humans, psychiatric patients, normal animals and animals subjected to disease models. In essence, however, this applies so far mainly to more static measures such as morphometry and spectroscopy and less to functional magnetic resonance imaging (MRI). Moreover, these investigations have to be performed under anaesthesia or restraining conditions. Wentz et al. (2013) report on recent developments in optogenetics enabling the functional investigation of neuronal circuits in vivo by the excitation or inhibition of specific neuronal subpopulations within milliseconds. This method can be applied when the animal is performing a behavioral task or when it is in an MRI scanner, allowing the correlation of cognitive functions with specific network activation patterns.

Developmental and sensory characteristics when analyzing rodent behavior

Unlike humans, rodents rely heavily on their excellent sense of smell and most of their interactions have a strong olfactory component. This can be experimentally exploited but might also result in pitfalls. Huckins et al. (2013) report here the way in which to test olfactory function in rodents and review behaviors in which olfaction plays a prominent role, e.g., maternal care, foreaging, aggression and the establishment of social hierarchies. Another factor that is commonly disregarded by experimenters when using rats and mice is that rodents emit and perceive calls in the ultrasonic range above the human hearing threshold. This plays a prominent role not only in mother-offspring interactions but also in appetitive and aversive situations in adulthood and might confound experiments in which several animals cohabit/are tested in the same

room. Wöhr and Schwarting (2013) summarize, for this issue, the (patho)physiology of ultrasonic vocalizations and propose them as a translational tool for studying the neurobiology underlying socio-affective communication. This seems to be particularly relevant for neurodevelopmental disorders characterized by social and communication deficits, such as schizophrenia and autism. One critical developmental phase for neuropsychiatric disorders is puberty, a period in which dramatic changes of neural plasticity occur in the brain. For this issue, Schneider (2013) delineates the time course of adolescence and puberty in laboratory rodents and reconsiders related neurodevelopmental processes as potential primers of heightened susceptibility for mental health disorders.

Rodent models of anxiety and fear

With respect to rodent models of emotional behavior, anxiety has raised the least concerns about inappropriate anthropomorphic projections. There is no doubt that animals can become anxious, e.g., in predator–prey relationships or other real or subjective (life-)threatening situations. Rodents show an inborn avoidance of light, height and water, an aspect that has been exploited extensively when generating models. Moreover, the fear of specific objects, subjects, or situations can be conditioned and the underlying mechanisms of the emotional response and its learning or extinction can be studied. In this issue, we highlight three such models. Toth and Neumann (2013) discuss not only paradigms that induce social avoidance and fear in rodents, such as social isolation, social instability, social defeat/chronic subordinate housing and maternal separation but also physical stressors such as electric foot shocks or restraint. Behavioral read-outs for the assessment of social avoidance and fear are different forms of social approach/preference/interaction tests, usually by using an experimentally manipulated individual and one or several non-manipulated conspecifics. These models should help to elucidate mechanisms of human social anxiety disorder, which is highly prevalent and poorly understood and which has to date unsatisfactory therapeutic options. Moreira et al. (2013) report the way in which to model panic disorder in rodents. This common disorder is characterized in humans by sudden surges of intense fear, a desire to flee and feelings of imminent death, going crazy, or losing control, plus neurovegetative changes such as palpitation, hypertension, tachycardia, difficulty in breathing and sweating. Obviously, this cluster of signs and symptoms cannot be translated one-to-one into rodent behavior. Therefore, the strategy for modeling panic disorder has lately been to stimulate brain areas and neural circuits postulated to be involved in the pathophysiology of the human disease, such as the dorsal periaqueductal gray and the medial hypothalamus. The behavioral read-outs are variable forms of escape/flight responses. These models will be instrumental for discovering or at least validating more effective drugs for this disorder. Matar et al. (2013) introduce various animal models of posttraumatic stress disorder (PTSD), with an emphasis on behavioral alterations triggered by exposure to predator scent. Of particular interest is the classification according to cut-off criteria, which allows the differentiation between PTSD-susceptible and PTSD-resilient rats, thus resembling the situation in humans in whom 5-15 % confronted with a trauma develop PTSD as its aftermath. This differentiation might facilitate the establishment of novel pharmacological interventions that have the potential to find their way into clinical practice.

Rodent models of depression

Major depressive disorder is a complex disease involving many brain circuitries. The clinical symptomatology is inconsistent and heterogeneous and the pathogenesis is a complicated interplay of genetic and environmental factors. The episodic and recurrent nature of the disease and the fact that several symptoms are only verbally expressed makes it a challenge to establish valid and legitimate animal models of this disease (Wiborg 2013). Disease and vulnerability genes are rare and respective transgenic models have been reviewed previously elsewhere (Cryan & Momberau 2004; Urani et al. 2005)

Current models have so far not resulted in the development of novel non-monoaminergic-based antidepressants with clinical efficacy. Thus, the refinement of the present models of depression is clearly required. O'Leary and Cryan (2013) give a detailed overview regarding the way that depression-like states can be elicited in rodents. To achieve this, the main behavioral measures are various forms of acute or chronic stress. Other models are based on genetics (e.g., selective breeding, targeted mutagenesis), lesioning of neural circuits, or treatment with/withdrawal from psychopharmacological agents. The authors explain the difference between a model and a test, the latter representing a mere behavioral read-out (e.g., the forced swim test) and the former requiring an inducing manipulation as an independent variable (such as foot shocks in learned helplessness). Instead of trying to produce a depression model in its entirety, the modeling of specific features coupled with attempts at understanding their underlying mechanism (according to the endophenotype concept) has been one strategy to improve and refine depression models. Anhedonia is one of the core symptoms of major depression; this is the inability to experience pleasure, operationally defined as diminished interest or pleasure in response to stimuli that were previously perceived as rewarding during the premorbid state. Ove Wiborg (2013) makes an important distinction between the motivational and hedonic aspects of anhedonia. Both might be disturbed in depression, the former involving a wide range of brain regions and networks and the latter being associtaed mainly with the limbic parts of the

brain. The chronic mild stress (CMS) model affects mainly reward sensitivity while having less effect on motivation. Sucrose consumption tests are classic read-outs for anhedonia. The pathophysiological concept proposed to underlie CMS-induced anhedonia is a hippocampal synaptopathy leading to glutamate excitotoxicity and a compromised activation of ventral tegmental area (VTA)-mediated dopamine release in the n. accumbens and ventromedial prefrontal cortex. Interestingly, the medial prefrontal cortex also detects the controllability of stressors. As Vollmayr and Gass (2013) emphasize, loss of controllability is a key feature of learned helplessness, which defines a depression-like coping deficit in aversive but avoidable situations. Thus, as a unique feature, learned helplessness mirrors important cognitive changes associated with depressive disorders. The model of learned helplessness has recently been used to identify glutamate and its receptors as targets for antidepressant pharmacotherapy, possibly with specific efficacy for the cognitive features of depression (Chourbaji et al. 2008b).

The great interest in social stress models reflects both the recognition that social stressors play a major role in human psychopathologies and the acknowledgement that natural and hence ethologically-based stress models bear important translational values. Chaouloff (2013) reviews the strengths and limitations of the commonly applied social defeat paradigm as a depression model. He cautions against attributing the full syndrome in rodents to either "human depression" or "PTSD" but favors the identification of the translational value of each of the single consequences of social defeat, in agreement with the endophenotype concept. He also argues (and this applies not only to social stress) that stress exposure with its potentially damaging consequences can also be considered as an event favoring adaptation and hence resilience. About a quarter of patients with depression suffer from bipolar disorder, i.e., have had one or more (hypo)manic episodes in the course of their disorder. Kara and Einat (2013) summarize the traditional difficulties in modeling simple mania or even bipolar disorder with its oscillatory nature. The most frequently used model for mania has been psychostimulant-induced hyperactivity. Recent developments combining targeted mutagenesis (bipolar disorder has a higher genetic load than unipolar depression) with the identification of new tests going beyond analyses of locomotion, might yield better insight into the pathomechanisms of this disorder and pave the way for more specific treatments beyond mood stabilizers and second generation antipsychotics.

As pointed out above, hippocampal neurogenesis was one of the most hoped for but also mostly hyped, cellular biomarkers for depression and was even postulated to be required for the response to antidepressants. Tanti and Belzung (2013) dissect, in a very careful and differentiated way, the current knowledge of the potential functions of hippocampal precursor cell proliferation and newly generated neurons in affective disorders. Among several other domains of a depressive syndrome, hippocampal neurogenesis seems to play an important role with regard to the cognitive functions necessary to achieve remission and in the regulation of the hypothalamic-pituitary-adrenal axis.

Modeling cognition and executive functions: schizophrenia and ADHD

In no other field of psychiatry does the gap between animal models and clinical syndromes seem wider than in schizophrenia. How should one model a disorder in which imperative or commentary auditory hallucinations, bizarre delusions and self-disorders represent the so-called first-rank symptoms? Interestingly, the focus of both clinical and preclinical research has recently been shifted from these "positive symptoms", which are often readily amenable to contemporary pharmacotherapy, to the more permanent cognitive deficits that determine the long-term course of the debilitating disease in about one third of all cases. Because of the urgent medical need for effective treatment of these symptoms, the NIMH has founded the "Measurement and Treatment Research to Improve Cognition in Schizophrenia" (MATRICS) initiative, including a consensus cognitive battery for clinical trials, in order to promote the drug discovery process. Attention, memory and executive functions, however, are behavioral domains that can also be readily tested in laboratory animals.

Yee and Singer (2013) present a conceptual framework and a practical guide for modeling and testing positive symptoms, negative symptoms and cognitive deterioration of schizophrenia in rodents. They give valuable hints on the choice of species, strain, sex, age and housing conditions and on the compatibility and organization of multiple tests. They suggest, as a top-down approach, the evaluation of individual differences revealed in schizophrenia-like behavior, i.e., a comparison of extremes of schizophrenia-like and anti-schizophrenia behavioral traits and attempts to identify their neural basis (e.g., genetic, neurochemical, or neuroanatomical). O'Tuathaigh et al. (2013) report genetic models of schizophrenia, usually achieved by targeted mutagenesis of candidate risk genes or copy number variations. They focus on various lines of mice bearing mutations of neuregulin-1, one of the strong candidate genes identified via genetic studies in human cohorts. Neuregulin-1 modulates glutamatergic neurotransmission, a key neurotransmitter in schizophrenia, affecting mainly N-methyl-D-aspartate (NMDA9 receptor activity (see also Inta et al. 2010). Constitutive and conditional mutagenesis of neuregulin-1 and its receptor Erbb4 consistently support the role of neuregulin-1/Erbb4 signaling in social behaviors linked with schizophrenia, whereas evidence is more equivocal for proxy measures of positive symptoms and is minimal for a role in cognition.

Leo and Gainetdinov (2013) report transgenic ADHD mouse models that are characterized by hyperactivity and impaired cognitive functions, thus showing superficial similarity to models of schizophrenia. Interestingly, in both disorders, dopamine and its receptors seem to play an important role. However, whereas mouse models of ADHD (similar to ADHD patients) exhibit a "calming" effect upon treatment with psychostimulants, mouse models of schizophrenia show hypersensitivity. So far, the best validated models seem to be mice with a compromised function of the dopamine transporter (DAT). DAT knock-out mice show face and predictive validity because of behavioral similarities, alterations in the catecholaminergic system and the effectiveness of psychostimulants. Promising but less well-characterized lines are tachykinin-1 receptor knock-out mice and mice with a humanized thyroid hormone β-receptor gene.

The analysis of spatial learning and memory is a gold standard method for investigating cognition in rodents. Although deficits in working memory attributed to the prefrontal cortex are hallmark symptoms in schizophrenia and ADHD, deficient hippocampus-dependent episodic memory characterizes dementia and most probably pseudodementia in depression. Morellini (2013) summarizes the four principle paradigms commonly used to measure spatial memory: the Y or T mazes, which are exclusively used for measuring working memory, the radial arm maze, which is the spatial version of spontaneous object recognition and the water maze test, which measures both forms of spatial memory depending on the conditions and protocol used. The possibility of recording and measuring specific neuronal firing patterns in distinct neuronal subtypes, e.g., "place cells", provides ideal experimental models for studying cellular substrates and neurophysiological mechanisms of mental processes.

Translational aspects: measuring human behavior in rodents and leading compounds for treatment

The acoustic startle response (ASR) is a simple ubiquitous reflex that can be easily measured in laboratory rodents, in healthy humans and in patients. Moreover, the different modulations of the ASR, namely prepulse inhibition (PPI) and potentiation by fear, can also be observed both in animals and humans. Thus, the translational value of the startle reflex seems much higher than that of other, more complex behaviors discussed in this issue. Interestingly, patients with schizophrenia show reduced PPI. However, as Fendt and Koch (2013) elegantly sum up in their review, ASR modulations such as PPI or the fear-potentiated startle are not and will never be animal models of complex psychiatric syndromes such as schizophrenia or anxiety disorders. PPI is not well suited as a biomarker predicting the clinical course of schizophrenia or the transition from prodromal to first-episode states in high-risk patients. However, PPI seems a reliable robust quantitative phenotype that is useful for probing the neurobiology and genetics of gating deficits in schizophrenia. Thus, ASR modulations can model specific aspects, symptoms, or "endophenotypes" of schizophrenia. Sometimes, such simple endophenotypes can predict more complex behaviors and therefore, the understanding of simple endophenotypes can help to improve our comprehension of the complex pathological phenotype.

Talpos and Steckler (2013) critically point out that, despite the rapid establishment of a theoretical framework for "translational psychiatry", only a few examples exist for a hypothesis-driven translation, starting with a pre-clinical finding and ending with a positive clinical result. They argue that part of the disconnection between pre-clinical and clinical results is based on the paradigms used at both the pre-clinical level (the measurement of behaviors that might not be relevant for a patient population) and the clinical level (the use of test batteries that cannot be modeled in a pre-clinical environment). The authors propose that automated cognition batteries that require responses to stimuli displayed upon a video monitor might decrease the distance between pre-clinical and clinical behavioral studies. The vast majority of human cognitive tests and certainly the entire CANTAB battery, require the processing of visual stimuli. The use of touch-screen-equipped operant boxes forces rodents to solve problems by means of a "human-like" approach reliant on vision. Thus, cognitive functions can be measured in a similar manner in the rodent as in a clinical setting. Talpos and Steckler (2013) emphasize four criteria for successful translational research: it should be (1) goal directed, (2) systematic and iterative, (3) predictive and capable of enhancing confidence and (4) be of sufficient value to shape the decision-making process.

Despite more than half a decade of psychopharmacological research and the advent of molecular medicine since the late 1990s, no antidepressant beyond those affecting monoaminergic mechanisms and no antipsychotic beyond those affecting dopaminergic and serotonergic mechanisms have entered the market. This highlights the problem that many substances work in animal models but not in clinical studies. Several examples exist of promising substances not being developed as far as marketing authorization following successful preclinical and early clinical trials, e.g., the substance P antagonist MK-869 in depression and the mGlu2/3 receptor agonist LY404039 in schizophrenia (Kramer et al. 1998; Patil et al. 2007). Micale et al. (2013) give an updated overview on compounds that have been successfully tested in animal models and are currently in the pipeline for early clinical studies. Substances that directly influence glutamatergic signaling have become the focus in depression and in schizophrenia. Interestingly, substances coined for one disorder seem to be problematic for the other. Thus, ketamine has an antidepressant effect but is psychotomimetic. mGluR5 antagonists

are antidepressant, whereas mGluR5 agonists or positive allosteric modulators have been developed as antipsychotics.

Finally, the identification of new drug targets for core psychiatric disorders will be essential for the whole field, otherwise the pharmaceutical industry and other global players might withdraw and invest energy, intelligence and money into other fields of medicine. Moreover, for millions of psychiatric patients worldwide, we need to improve the therapies of their disabling disorders, whose principles are in essence the same as they were 50 years ago. The quality of psychiatric animal models will be an essential factor in achieving this aim.

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