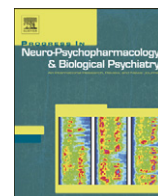




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## Editorial

# Novel experimental models and paradigms for neuropsychiatric disorders: Editorial

Neuropsychiatric disorders are increasingly becoming the major health burden in modern society, primarily due to our limited understanding of these diseases, and the lack of sufficient treatments. However, even with the latest technological advances, clinical research still has its limitations (e.g., in terms of controllability of the environment or accessibility of tissue samples). Therefore, preclinical (experimental) animal models or paradigms are an important tool to elucidate the neurobiological underpinnings of specific aspects of neuropsychiatric diseases.

When modelling complex diseases, there is always the challenge to bridge the gap between the preclinical animal model and the actual disease. No model system can comprehensively capture the extent of a complex psychiatric disorder, and experimental results in animals are not necessarily translatable to the human situation. Despite this, animal models have proven to be invaluable for the understanding of neuropsychiatric diseases. Thus, it is critical to constantly improve the available models in terms of their validity and to challenge the existing models rather than to oversimplify the results obtained from them.

Recent developments from clinical psychiatry also require a new generation of disorder analogues, specifically those that will elucidate the mechanisms of pathogenesis by comparing integrative and disorder-specific models (Laporte et al., 2008). For example, an interesting approach is introducing a “triple” open-field/plus-maze/light-dark-box paradigm (Ramos, 2008; Fraser et al., 2010). Representing a combination of three traditional paradigms, this model of anxiety reduces intra-individual variability (thereby enhancing data reliability), minimizes the number of animals needed, and increases the rapidity and throughput of behavioral testing within the same “exploratory” domain.

Another direction is in *conceptual* innovation that focuses on integration of animal modelling across several different, clinically relevant, domains (Table 1). It is becoming clear that throughput and utility of animal models of brain disorders can be markedly increased by analyzing several domains and their interplay (Kalueff et al., 2008c; LaPorte et al., 2010). This includes applying new concepts to the use of old apparatuses (e.g., combining Morris water maze with the Porsolt forced swim test), or developing entirely novel multi-domain paradigms (see Table 1 for examples). Such innovative approaches benefit the field by enabling more comprehensive behavioral characterization, increased throughput, and improved ethical consideration through reduced animal use. Enhancing experimental validity (by reducing the affects of previous test history), this strategy also provides a much-needed opportunity to examine complex phenomena such as the “continuous” nature of brain pathogenesis, complementing the traditional single-domain models that continue to dominate neurophenotyping research (Kalueff et al., 2007; LaPorte et al., 2010).

The following strategic directions of progress in this field are particularly important: 1) Refinement and revalidation of existing

paradigms; 2) Development of conceptually new animal models; 3) Innovative modelling using novel model species; and 4) Paralleling behavioral models with novel sensitive biomarkers (Guo, 2004; Kalueff et al., 2007). In the current Special Issue, we have invited a number of distinguished active scientists to share their views on these topics in the form of review or experimental papers.

The first group of papers in this issue highlight the importance of translational approaches for modelling neuropsychiatric disorders. One of the first questions here is the choice of the model system. This is not a trivial decision, and in many cases driven by practical or financial restraints. However, it should be clear that the translational results from a specific model can only be as good as the model system. Thus, while some research questions can be answered in one species, others will be better addressed in another species. The review by Neumann and colleagues illustrates this issue by comparing four different rodent models of neuropsychiatric diseases. A second key problem is discussed in papers by Burrows et al. and de Mooij-van Malsen et al., highlighting the need to focus on both environmental *and* genetic risk factors. It is well known that most, if not all, neuropsychiatric diseases are associated with genetic and environmental risk factors to varying degrees. Therefore, a valid model of neuropsychiatric disorders should also attempt to comprise both risk elements. Another critical aspect, highlighted by Viaud-Delmon et al., is the utility of a systems biology approach when interpreting the data of animal models. A specific phenotype, such as anxiety, can result from many different biological phenomena, including vestibular deficits discussed here (also see Kalueff et al., 2008a for a recent review).

Finally, model systems should also strive to achieve validity on many different levels, including their predictive validity. This implies that a pharmacological treatment that is effective in humans should also show similar effects in the animal model, supporting its utility for the development of novel drugs, as well as the thorough characterization of existing drugs. The latter issue is discussed by Olivier et al., demonstrating that the effects of antidepressants in adults are not necessarily the same for children and adolescents—thus, adding an important ontogenetic perspective to brain pathogenesis.

The zebrafish is rapidly becoming a popular model species in biological psychiatry research, and several papers have provided novel valuable insights. Larval zebrafish have long been used as a model for brain pathologies, and their main advantage is the ability to study multiple animals simultaneously within a high-throughput battery. However, such models have some limitations, as they do not exhibit the rich behavioral repertoire of the adult animals, and lack fully developed mediatory and endocrine systems. Thus, the advantages of using adult zebrafish in neurobehavioral research are becoming widely recognized in the field. Likewise, zebrafish have long been viewed as mainly a tool to analyze genetic mechanisms of

**Table 1**  
Examples of different strategies in animal modelling of affective disorders.

Model	Primary domain targeted	Additional domains targeted	References
"Triple" open-field/light-dark/ elevated maze model	Exploration (anxiety)	–	(Ramos, 2008; Fraser et al., 2010)
Elevated T-maze	Exploration (anxiety)	Memory	(Carvalho-Netto and Nunes-de-Souza, 2004)
Suok test	Exploration (anxiety)	Vestibular functions, stress-evoked motorisensory disintegration	(Kalueff et al., 2008b)
Morris-Porsolt test	Despair (depression)	Memory	(Schulz et al., 2007)
Chick vocalization	Fear (anxiety)	Depression (despair)	(Kalueff et al., 2008b)

brain functions. However, the field is now recognizing broader applications for this model organism to neurobehavioral phenotyping and modeling of psychiatric disorders, with the number of laboratories involved in this line of research growing steadily each year. Buske and Gerlai made an interesting observation that zebrafish social (shoaling) behavior develops with age, indicating that social behavior in this model has a strong developmental trajectory. Echavarría and colleagues describe zebrafish tasks in which attention is involved, and summarize several specific subdomains which are relevant to neurology of attention. A paper by Stewart et al. demonstrate the novel tank test as a sensitive assay to study zebrafish affective (anxiety-like) behavior and its bi-directional modulation by various drugs. In line with this, Steenbergen et al. focused on stress research and disease mechanisms, also discussing how zebrafish stress models can contribute to the field of drug discovery. Complementing data obtained with other model species, zebrafish evidence in these papers strongly supports this species as a useful model in the field of biological psychiatry.

Rodents are the most commonly used species to model psychiatric diseases. However, the many available models for psychiatric diseases differ tremendously in their individual face, construct and predictive validity. In the current Special Issue, the authors describe a number of alternative approaches or novel views on existing models. A core feature of many models seems to be the social environment, either as a stressor or as a positive stimulus. Branchi and colleagues developed a very interesting mouse model of postnatal social enrichment, where mouse pups are reared by several mothers in a communal nest setting. This model is a good example of how social experiences of neonates can critically shape the adult individual. An opposite approach is taken in the adult chronic social defeat model, where aggression and hierarchy are used to create a social stress situation. Damodo et al. gives a nice example of how variable the outcome of those paradigms can be dependent of the genetic background of the stressed mice. Another interesting approach is taken by Kudryavtseva et al., focusing not only on the defeated mouse, but also on the dominant individuals (showing constant and abnormally high aggression). Finally, Laviola and colleagues demonstrate how a smart study design can combine several risk factors, including individual predisposition, sex and environmental factors.

In addition to aquatic and rodent models, this Special Issue also covers novel primate behavioral paradigms. For example, Senoo et al. reported an interesting model of developmental behavioral disorders evoked in marmosets by disturbances in circadian rhythms earlier in ontogenesis. Similarly, Koshiba and colleagues applied multivariate correlation analyses to place the marmoset behavioral 'semantics' in a context of social interaction, which may be used to evaluate animal social emotionality and to model social behavior in human psychiatric disorders.

Taken together, the current Special Issue covers a wide spectrum of model species, and presents a wide variety of novel creative ways in

which behavioral disorders can be modelled and explored using animal tests. But this is a never-ending and creative process, and the day when a new paradigm is developed and validated would be the moment when the researchers start thinking of a better model.

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Allan V. Kalueff  
Guest Editor

Dept. of Pharmacology, Tulane University Medical Center,  
New Orleans, USA

Corresponding author. Department of Pharmacology,  
Tulane University Medical School, 1430 Tulane Avenue, New Orleans,  
LA 70112, USA. Tel.: +1 504 988 3354.  
E-mail address: avkalueff@gmail.com.

Mathias V. Schmidt  
Guest Editor

Molecular Physiology of Stress,  
Max Plank Institute of Psychiatry, Munich, Germany

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