Behavioral Genetics of the Mouse

Genetic Mouse Models of Neurobehavioral Disorders

VOLUME 2

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Edited by Susanna Pietropaolo,
Frans Sluyter and Wim E. Crusio

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Behavioral Genetics of the Mouse Volume II

Genetic Mouse Models of Neurobehavioral Disorders

The second volume of *Behavioral Genetics of the Mouse* provides a comprehensive overview of the major genetically modified mouse lines used to model human neurobehavioral disorders: from disorders of perception, of autonomous, and motor functions to social and cognitive syndromes, drug abuse, and dependence as well as neurodegenerative pathologies.

Mouse models obtained with different types of genetic manipulations (i.e., transgenic, knock-out/in mice) are described with their pathological phenotypes, with a special emphasis on behavioral abnormalities. The major results obtained with many of the existing models are discussed in depth, highlighting their strengths and limitations.

A lasting reference, the thorough reviews offer an easy entrance into the extensive literature in this field, and will prove invaluable to students and specialists alike.

Susanna Pietropaolo is a researcher at the Centre National de la Recherche Scientifique (CNRS). She is an expert in the behavioral analysis of the laboratory mouse, with a special interest in social behaviors. Her recent research focuses on mouse models of social dysfunction, including autism and Fragile X syndrome.

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Wim E. Crusio

Behavioral genetics is the study of the role of genetics in animal (including human) behavior. The genetic dissection of behavior in simple animals can provide insight into the mechanisms that regulate human behavioral traits. Once behaviors are understood at the genetic level, it allows the development of animal models of human pathological behaviors, such as stress, anxiety, depression and addiction, which in turn furthers our understanding of these behaviors and opens windows of opportunity for the discovery of treatments. The Cambridge Handbooks in Behavioral Genetics series covers the behavioral genetics of different animal species, some because of their usefulness in medical research and others for the simplicity of their nervous systems. The series is of interest to researchers across several disciplines of the life sciences, primarily those with an interest in the behavioral sciences. The books are advanced texts, from graduate student upwards, and are useful resources for advanced genetics courses, such as genetics of model organisms, mammalian molecular genetics, developmental genetics and animal models of human disease.

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To Maya, my best genetic contribution, so far.
Susanna Pietropaolo

To my brother, Steven.
Frans Sluyter

To Hans van Abeelen (1936–1998), who was my teacher, mentor, and dear friend.
Wim E. Crusio

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Section 7: Neurodegenerative disorders

Chapter 1

Introduction

Genetic mouse models of neuropsychiatric disorders

Frans Sluyter, Susanna Pietropaolo, and Wim E. Crusio

Animal modeling is an interactive process in which one or more species (the "models") are studied to gain insight on a trait or disorder in humans including the testing of (new) hypotheses and (pharmaco)therapies. Roughly speaking, a model's usefulness depends on the strength of its validity, which has three components: face, predictive, and construct validity. These, in turn, depend on the information we have about the trait or disorder. Thus, the more we know about the cause(s), genetic and/or environmental, and the exact pathophysiology of a disorder, the better we are able to model certain aspects of that disorder. In recent decades, mice have replaced rats to become the animal model of choice for behavioral neuroscientists. The most important reason for this has been the rapid advances in genetic engineering over the last two decades, to the extent that there is now a wealth of distinct mouse techniques available to mimic (or test hypotheses on) the pathophysiology of a disorder. In addition, both the mouse brain and genome are similar to those of humans.

Psychiatric disorders are among the most fascinating human diseases as they touch directly on that which makes us human: our minds. Whereas, say, a heart patient may be sick and suffering, cardiac disease touches the mind only indirectly (by the stress it generates, for example) and the afflicted patient remains recognizably the same person. Not so with many psychiatric disorders, which not only can be life-long debilitating diseases, but directly affect and in some cases dramatically change a patient's mind. Modeling a disordered mind and its consequent behavior, however, can be very challenging, because it is difficult to develop animal tests that convincingly and consistently mimic human symptoms. In addition, for most psychiatric disorders we lack objective and reliable information about their etiology. Psychiatric diagnoses are, to a great extent, subjective and based on the presence of a minimal number of symptoms from a list of symptoms during a certain period of time (DSM-5, 2013). For instance, a diagnosis of depression, or major depressive disorder in DSM terms is based on the presence of five symptoms out of a list of nine (DSM-5, 2013), which means that theoretically two persons with the same diagnosis may share only one symptom. This heterogeneity is corroborated even further by the fact that the diagnostic criteria for depression are partly shared with anxiety disorders and that one single episode of mania changes the diagnosis to bipolar disorder, which is presumably a distinct pathophysiological entity (Krishnan and Nestler, 2008). It is therefore not surprising that the search for genes (or DNA markers) underlying (or reliably associated with) depression has been largely disappointing as opposed to, for example, the recently published list of genetic markers for hormonally mediated cancers, for which objective and reliable biomarkers exist. (See Sakoda et al., 2013 for a commentary on the dozen high-impact papers reporting over 70 new susceptibility loci for breast, ovarian, and prostate cancers.) In addition to the lack of objective biological markers and variation in symptoms, the impossibility of modeling typically human symptoms such as guilt and suicidal ideation raises another barrier in modeling depression. Consequently, most models of depression, including genetic mouse models, basically test hypotheses about the disorder (e.g., by changing the underlying genetics of a neurobiological pathway known to be involved in a subset of affected individuals, see also Chapter 22 for a critical assessment of mouse models for depression).

There are exceptions, though. The genetic causes of neurodevelopmental disorders such as Fragile X or Rett syndrome are known and these disorders can be reliably modeled using genetically engineered mice, i.e., *Fmr1* and *Mecp2* knockout (KO) mice, respectively. These models have high construct validity as they capture the essence of Fragile X and Rett syndrome and can be studied invasively – an (ethical) impossibility in humans – to learn about the pathophysiology underlying these disorders and to search for suitable treatments. For instance, brain Rho GTPases have been identified as an innovative therapeutic target in *Mecp2* knockouts and the administration of cytotoxic necrotizing factor 1 (CNF1, which activates Rho GTPases) has been shown to markedly improve Rett symptomatology in these mice (see Chapter 13). Similarly, *Fmr1*-KO mice have been employed to design pharmacological and non-pharmacological therapeutic approaches, some already leading to clinical trials (see Chapter 14).

Genetic mouse models are also helpful in modeling the effects of rare genetic variants. An excellent example hereof is

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the study of Bevilacqua et al. (2010), who discovered an association between impulsivity and the gene coding for the 5-HT2B receptor (*HTR2B)* in a Finnish subpopulation. Violent offenders whose crimes were characterized by a high degree of impulsivity were statistically more likely to lack functional 5-HT2B receptors as a result of a mutated *HTR2B* gene. Bevilacqua et al. (2010) subsequently generated *Htr2b* knockout mice and tested these animals for five separate measures of impulsivity and novelty seeking. They found that knockouts were more active in a novel environment, displayed an increased number of contacts with a novel object, and were less likely to wait for a larger but later reward, a behavioral profile similar to the genetically affected violent offenders.

In fact, some think that the effects of individual mutations on the pathogenesis of psychiatric disorders may be more important than hitherto thought. Thus, based on recent findings from whole-exome and whole-genome sequencing, Mitchell et al. (2011) postulate that psychiatric disorders are actually umbrella terms for large numbers of distinct genetic disorders that happen to result in similar spectra of symptoms. They further propose to capture these (*de novo*) mutations (which may also include duplications and translocations) in mouse models with direct construct validity, i.e., where the genetic manipulation results in a defect homologous to the actual cause of the condition in humans. These "direct" animal models of genetic etiology can then be further analyzed using the full arsenal of modern behavioral neuroscience. Insel (2007) calls these types of animal models "model animals," making a careful distinction between models that phenotypically resemble aspects of mental disorders (old-fashioned animal models) and models with the molecular and cellular abnormalities found in mental disorders (model organisms).

However, the prevailing opinion regarding the pathogenesis of neurobehavioral disorders is still the polygenic/threshold model in which what is inherited is not so much a disorder as a liability to a disorder contributed to by multiple genetic and environmental effects. Each of these, by themselves, would only have a small effect on risk, but when the collective burden of such alleles passes a putative threshold, the system would be pushed into a pathogenic state. The polygenic/threshold model is more about probability as opposed to the mutation model, which is more about causality. Moreover, and perhaps more importantly from an animal modeling point of view, the relatively small contribution of each effect makes it difficult to find genetic disease variants and construct appropriate models. The result is that for most neurobehavioral disorders, precise genetic information is either lacking or not very reliable. Consequently, in this framework genetic models are either speculative or only capture a small part of the underlying etiology. As for the speculative side of genetic modeling, Nestler and Hyman (2010) call this "reversing the direction of validation," in which observed pathology in genetic (mouse) models may be sought in human patients, either in postmortem tissue or non-invasive imaging.

Ideally, genetic mouse modeling is a two-way street where human (liabilities to) pathologies, either on a genetic or on a neuro-circuitry level, are mirrored in model animals, which, in turn, inform and steer human studies. As long as we are clear and honest about what we (attempt to) model and as long as we keep the limitations of modeling in mind, genetically engineered mice can be very effective in elucidating the pathophysiology of neurobehavioral disorders and ultimately in finding successful (pharmaco)therapies. Last but not least, although the vast majority of genetic mouse models presented in this volume are the result of active gene (or chromosome) engineering, we should not forget about the traditional genetic mouse models, i.e., artificial selection lines and inbred strains, which still have added value in understanding and modeling neurobehavioral disorders. An outstanding illustration hereof is the work of Phillips et al. (Chapter 27) who used a variety of short-term bidirectionally selected lines to gain insight into the neurobiology of amphetamine addiction.

Although this book presents quite a few success stories where genetic mouse models have been very effective in elucidating disease mechanisms, it would not be fair to skip the equally numerous failures. For example, sometimes a mutation with a dramatic effect in humans has much more moderate effects in mice. An example of this is the *Fmr1* KO mouse (Chapter 14). Although this animal has the same molecular defect as human patients with Fragile X syndrome (i.e., no fragile X mental retardation protein (FMRP) expression) and does display many of the same symptoms that human patients show, the severity of the disorder is much reduced in mice.

Another problem is the rather frequent failure to replicate findings obtained in different laboratories. Ever since the landmark study by Crabbe et al. (1999), this is often brushed away as being unavoidable variation due to interlaboratory differences. This is not the complete truth for several reasons. First of all, it is often overlooked that the Crabbe et al. study actually showed that many behavioral differences *can* be reliably reproduced in different laboratories and this often over decades (Wahlsten et al., 2006). Second, and in our opinion even more seriously, we feel that many failures to replicate are due to conceptual inadequacies in our arsenal of behavioral tests. Many tests have never been properly studied and validated. For many other tests, validation has been only cursory, testing just two groups of animals, one of them treated with some pharmacologically active substance of supposedly known effect and the other the controls. It is becoming increasingly clear that tests that purportedly measure the same behavioral quality often give divergent results even in the same lab and in the hands of the same experimenters. An example is the study of Mineur et al. (2006), who tested animals from different inbred strains in both the Porsolt forced swim test and the tail suspension test. Although both tests are supposed to measure the very same behavioral construct, namely depression-like behavior ("behavioral despair"), the results of both tests were dramatically

different. Thus, it would appear that the refinement and finesse of our current behavioral tools do not match those of our genetic tools. Improving our understanding of our behavioral methods will therefore be an important challenge in the near future for neuroscience, and neurogenetics in particular.

We would like to finish this introduction on a more optimistic note, however. The past two decades have shown the power of the "new genetics" (now also including more neurocircuitry-focused techniques such as optogenetics) to generate mice that are genetically tailored to suit the needs of behavioral neurogeneticists wishing to model a human neuropsychiatric disorder. And despite some unavoidable problems, this volume presents numerous examples of the power of this approach, leading to important insights into the mechanisms underlying these fascinating ailments, with potentially significant benefits for human well-being.

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Chapter 2

Developing mouse models of neurobehavioral disorders

When is a model a good model?

F. Josef van der Staay, Saskia S. Arndt, and Rebecca E. Nordquist

Animal models in neurobehavioral research

To make sense of a discussion of animal models, one first has to understand both the purpose of such models, and their benefits to research, as well as the limitations on their interpretation.

(McMillen, 1997: 409)

In line with the above statement, a model is a good model when it serves its purpose (Geyer and Markou, 1995) and advances scientific insight. This prompts a number of questions: What is a model? What is the purpose of a model? How is a model developed and validated? How can we evaluate a model, i.e., decide whether this is indeed a good model? We will try to address these questions, with emphasis on model evaluation.

We define animal models in the behavioral neurosciences, which include models of neurobehavioral disorders, as follows:

An animal model with biological and/or clinical relevance in the behavioral neurosciences is a living organism used to study brain–behavior relations under controlled conditions, with the final goal to gain insight into, and to enable predictions about, these relations in humans and/or a species other than the one studied, or in the same species under conditions different from those under which the study was performed.

(van der Staay, 2006: 133–134)

Purpose of animal models

Animal models are developed for a specific purpose (Festing, 2004; Holmes, 2003; Massoud et al., 1998). For example, animal models of neurobehavioral disorders are used to enhance our understanding of their underlying substrates and mechanisms. The relation between brain and behavior can be investigated experimentally by using pharmacological agents, lesions, or animals with naturally occurring or experimentally induced deficits to distinguish between processes, subprocesses, and modulating influences (Cernak, 2005; D'Mello and Steckler, 1996). Of particular interest is the identification of new targets, pathways, and mechanisms of drug action (Matthews and Kopczynski, 2001; Snaith and Törnell, 2002; West et al., 2000).

Animal models simplify complex phenomena, but at the same time the use of an animal model should allow the confirmation and/or rebuttal of specific hypotheses (Marcotte et al., 2001). If the animal model is too complex to provide clearer answers than other methods, then its availability and application does not advance scientific insight and it is not useful (Massoud et al., 1998). However, if ethical considerations prevent experimental manipulation of the target species, e.g., humans, then it may be "permissible" to use phylogenetically "lower" species in animal models to gain information.

Animal models can also be used to translate insights gained in preclinical animal studies to the clinical setting (and vice versa; Porges, 2006; Waldman and Terzic, 2010). For instance, animal models can be used to assess the effects of putative neuroprotective, antidegenerative, revalidation-supporting, mental health-promoting, and/or cognition-enhancing compounds or treatments (Allain et al., 1998; Frazer and Morilak, 2005; Hitzemann, 2000; Willner, 1998; Wong et al., 2002), and to evaluate the risks (safety, teratology, toxicology) associated with these treatments (Bolon, 2004; Cavero, 2010).

Validity of animal models

Nearly three decades ago, Willner (1986) argued that animal models should possess three types of validity: *face validity, predictive validity*, and *construct validity* (Figure 2.1), a categorization that has since been adopted by many researchers (e.g., Chesselet and Richter, 2011; Homberg, 2013). External validity, i.e., the degree of generalizability of experimental results obtained in the laboratory to the "outside world," has since been added to this list (Guala, 2003). Others have reduced or extended the types of validity that a model should possess (Belzung and Lemoine, 2011; Cryan and Sweeney, 2011; Tordjman et al., 2007; Young et al., 2010). It should be noted that the validity of a model is not a measure of the truth of findings obtained with the model (Massoud et al., 1998).

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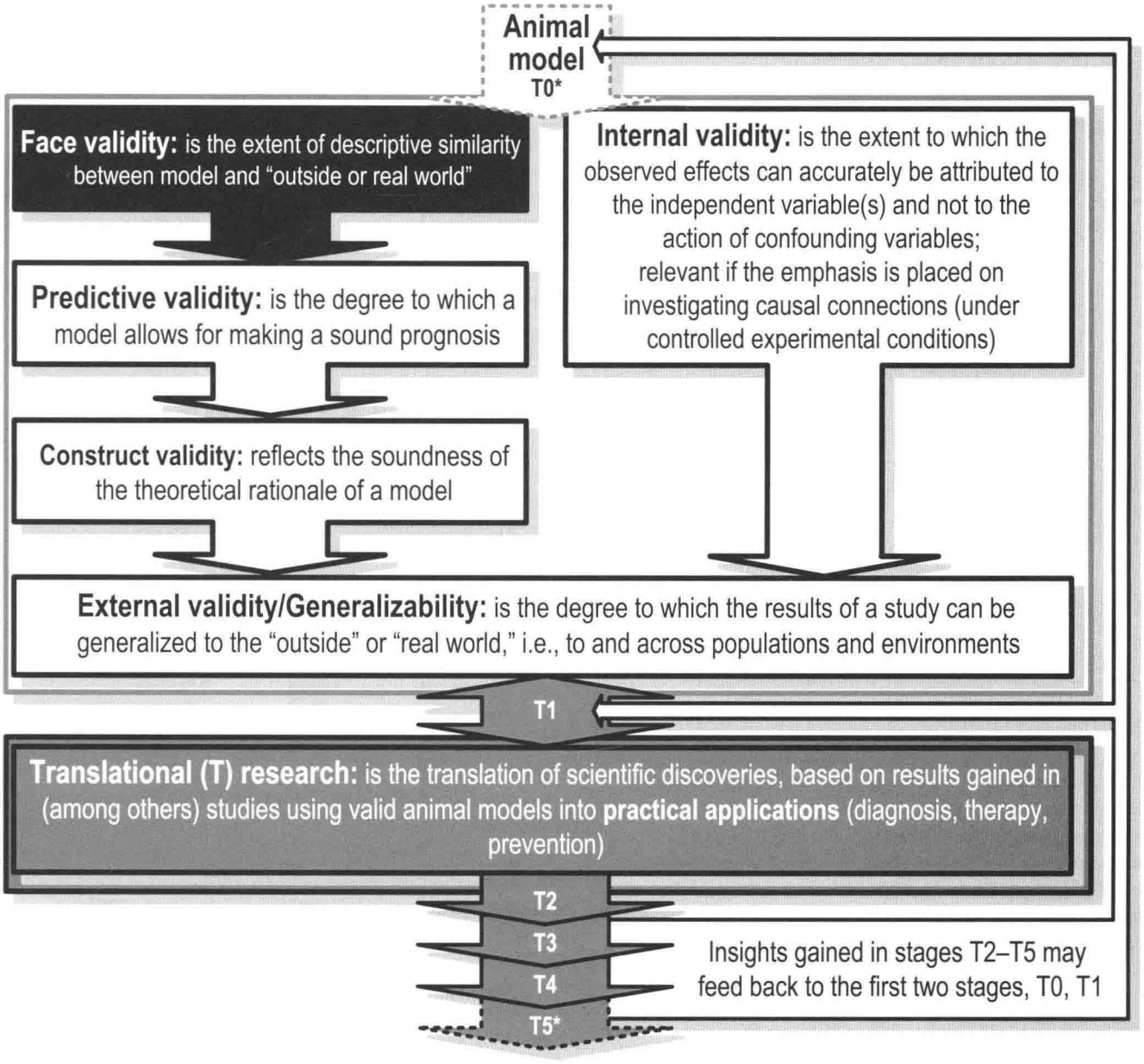

Figure 2.1 Hierarchy of validities in animal models, and stages in translational research.

The upper left column shows the hierarchy of validities that is taken as the basis for animal model development. Face validity is in a special position, as a lack of face validity does not *per se* invalidate an animal model. Validity is subdivided into two classes: internal and external validity. This differentiation is only applicable to experiments that investigate causal relationships (modified and extended from Fig. 10.1 in van Zutphen et al., 2009: 201).

Translational research distinguishes between different stages, most commonly T1–T4 (Drolet and Lorenzi, 2011; Waldman and Terzic, 2010), of which T1 is "the transfer of new understandings of disease mechanisms gained in the laboratory into the development of new methods for diagnosis, therapy, and prevention and their first testing in humans" (Woolf, 2007).

*: Waldman and Terzic (2010) suggested extensions of translational stages to include T0, preclinical research (*in vitro* and *in vivo* animal model-based research), and T5, improving the wellness of populations by reforming suboptimal social structures.

The bidirectional and recursive relationship between animal models, translation to applications, and reverse translation to animal models is indicated in Figure 2.1 by the two-headed arrow to the first stage of translational research (T1). However, insights gained in later translational stages may also feed back to earlier stages, including T0 and T1.

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Models are validated to increase confidence in the model. Validation provides information about the plausibility and consistency of the interpretation of data generated with the animal model. Validity is a major criterion for establishing the worth of animal models (Holmes, 2003), although it should be recognized that no animal model is valid in all situations and for all purposes. Validity is restricted to a specific use of the model, and thus must always be open for discussion and re-evaluation (Silva, 1993).