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Animal Models in Psychiatry, I

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Preface to the Series

When the President of Humana Press first suggested that a series on methods in the neurosciences might be useful, one of us (AAB) was quite skeptical; only after discussions with GBB and some searching both of memory and library shelves did it seem that perhaps the publisher was right. Although some excellent methods books have recently appeared, notably in neuroanatomy, it is a fact that there is a dearth in this particular field, a fact attested to by the alacrity and enthusiasm with which most of the contributors to this series accepted our invitations and suggested additional topics and areas. After a somewhat hesitant start, essentially in the neurochemistry section, the series has grown and will encompass neurochemistry, neuropsychiatry, neurology, neuropathology, neurogenetics, neuroethology, molecular neurobiology, animal models of nervous disease, and no doubt many more "neuros." Although we have tried to include adequate methodological detail and in many cases detailed protocols, we have also tried to include wherever possible a short introductory review of the methods and/or related substances, comparisons with other methods, and the relationship of the substances being analyzed to neurological and psychiatric disorders. Recognizing our own limitations, we have invited a guest editor to join with us on most volumes in order to ensure complete coverage of the field. These editors will add their specialized knowledge and competencies. We anticipate that this series will fill a gap; we can only hope that it will be filled appropriately and with the right amount of expertise with respect to each method, substance or group of substances, and area treated.

Alan A. Boulton
Glen B. Baker
Preface to the Animal Models in Neuropsychiatry Volumes

This and several subsequent volumes in the Neuromethods series will describe a number of animal models of neuropsychiatric disorders. Because of increasing public concern over the ethical treatment of animals in research, we felt it incumbent upon us to include this general preface to these volumes in order to indicate why we think further research using animals is necessary and why animal models of psychiatric disorders, in particular, are so important. We recognize that animals should only be used when suitable alternatives are not available. We think it self-evident, however, that humans can only be experimented upon in severely proscribed circumstances and alternative procedures using cell or tissue culture are inadequate in any models requiring assessments of behavioral change or of complex in vivo processes. However, when the distress, discomfort, or pain to the animals outweighs the anticipated gains for human welfare, then the research is not ethical and should not be carried out. It is imperative that each individual researcher examine his/her own research from a critical moral standpoint before engaging in it, taking into consideration the animals' welfare as well as the anticipated gains. Furthermore, once a decision to proceed with research is made, it is the researcher's responsibility to ensure that the animals' welfare is of prime concern in terms of appropriate housing, feeding, and maximum reduction of any uncomfortable or distressing effects of the experimental conditions, and that these conditions undergo frequent formalized monitoring. In the third of these volumes on animal models, we have included a chapter on the ethics of animal models by Dr. E. Olfert, a veterinarian who also directs a laboratory animal care facility. As indicated in Dr. Olfert's chapter, it is essential to conform to national and local animal welfare regulations, whether codified in law or by self-regulatory bodies. We urge readers who wish to adopt any of the procedures described to follow closely not only the letter of their own national and local regulations, but also the spirit of these guidelines.

The Editors
Preface

The two Animal Models in Psychiatry volumes are loosely organized by subject. The first volume contains a number of chapters concerned with schizophrenia, psychoses, neuroleptic-induced tardive dyskinesias, and other disorders that may involve dopamine, such as attention deficit disorder and mania. The second volume deals with affective and anxiety disorders, but also includes chapters on subjects not easily classified as either psychotic, or affective, or anxiety-related, such as aggression, mental retardation, and memory disorders. Four chapters on animal models of schizophrenia or psychoses are included in the present volume because of the importance of these disorders in psychiatry. Likewise, three chapters in the subsequent volume deal with depression.

The first of the two volumes begins with an introduction by Paul Willner reviewing the criteria for assessing the validity of animal models in psychiatry. He has written extensively on this subject, and his thorough description of the issues of various forms of validity provides a framework in which to evaluate the subsequent chapters. As will be seen, the remaining chapters in both volumes will refer frequently to these issues. The second chapter, by Melvin Lyon, describes a large number of different procedures that have been proposed as potential animal models of schizophrenia. This is a departure from the usual format, consisting of detailed descriptions of specific models. It was felt that the importance of schizophrenia in psychiatry required a more general overview of the models that are used for this mental illness. Nestor Schmajuk (Chapter 3) describes a hippocampal lesion model of schizophrenia that particularly addresses the cognitive and attentional dysfunctions of schizophrenia. One of the strongest supports for the dopamine hypothesis of schizophrenia is the observation that chronic administration of psychomotor stimulants can induce a psychosis similar in
many respects to that experienced by schizophrenics. Chapter 4 by Mathew Martin-Iverson describes a behavioral procedure involving chronic stimulant treatment that examines the effects on the organization of behavior over time and explores the roles of dopamine receptor subtypes in the disorganization produced by stimulants. Gaylord Ellison continues this theme of stimulant-induced psychosis with his description of the development of hallucination-like behavior with chronic continuous infusions of stimulants (Chapter 5). An exciting aspect of this model of stimulant-induced hallucinations is the disruption of normal social behaviors that are likely to be especially relevant to schizophrenia. The appendix to this chapter describing the slow-release amphetamine pellets provides an inexpensive alternative to the rather costly osmotic minipumps that can make a large hole in research grants. Melvin Lyon (Chapter 6) points out the importance of interactions between dopamine and glutamate in his review of models of mania. A major problem with the treatment of schizophrenia is the iatrogenic development of tardive dyskinesias. Two chapters describe animal models of this disorder. Helen Rosengarten's rapid jaw movement model (Chapter 7) indicates the importance of considering both D1 and D2 dopamine receptor subtypes in understanding the development of tardive dyskinesias. The appearance of clozapine as a drug that binds to D1 receptors and that may have a decreased propensity for inducing tardive dyskinesias, as well as the existence of selective D1 antagonists currently undergoing clinical trials to determine their efficacy in treating schizophrenia demonstrate the significance of this model. A computerized methodology developed by Gaylord Ellison and Ronald See (Chapter 10) for measuring oral dyskinesias induced by neuroleptics presents a reliable system that may resolve the controversy surrounding animal models of tardive dyskinesia that quite possibly arose from differences in relatively subjective assessments of mouth movements across different labs. Anorexia nervosa is a psychiatric disorder that has received considerable media
attention lately. David Pierce and Frank Epling's behavioral model of activity anorexia (Chapter 8) discloses the critical relationship between exercise and anorexia, providing an ethological framework within which to understand this disorder. I anticipate that application of neurobiological and pharmacological techniques within this model may well reveal the relevant neurochemical systems, such as the endogenous opiates described by the authors, that underlie anorexia and may well suggest future treatments. Joram Feldon and Ina Weiner's elegant work (Chapter 9) with the latent inhibition model of attention deficit disorders provides a well-characterized model of certain kinds of deficits that occur in both attention-deficit hyperactivity disorder and schizophrenia. This work indicates the utility of modeling symptoms, knowledge of which can lead to greater understanding of a number of different disorders that overlap in their symptoms. The observation that many (if not most) psychiatric patients suffer coexisting disorders indicates that this may be the most appropriate tack to take, at least at present.

*Mathew T. Martin-Iverson*
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Methods for Assessing the Validity of Animal Models of Human Psychopathology

Paul Willner

1. Background Considerations

Animal models are used very widely to investigate or illuminate aspects of human psychopathology. However, the extent to which it is possible to extrapolate from animals to people, and, therefore, the value of information derived from an animal model, will depend to a large extent on the validity of the model. This chapter outlines some methods that may be used to assess the validity of an animal model of psychopathology. It must be emphasized that these methods are primarily conceptual: They concern ways of evaluating experimental data and weighing different sources of evidence. The methods described may be used prescriptively, to indicate where a data base stands in need of expansion, or to indicate critical experiments. However, the validation exercise is more usually applied to form a view of the adequacy of a model on the basis of existing data.

Animal models are tools for our use: They are not developed as part of a beauty contest, with a prize for the most convincing. If a model cannot readily be used, it is of little value, however elegant. Thus, the successful construction of a valid model should not be seen as an end in itself, but as a useful step in the investigation of a scientific problem. As such, validity can be assessed only in relation to the broader objectives of the research program.

The two major uses of animal models of psychopathology are as screening tests for the development of new treatments, and as simulations within which to study aspects of the disorder (see Willner, 1991). As described below, these two objectives place very different requirements on an animal model. This can mean that different models are appropriate for different purposes; alternatively, the same model may be used for both purposes, but different considerations apply when assessing its suitability. The important point is that the assessment of validity takes place within a practical and scientific context. As an example, consider the use of animal models in antidepressant research. Practical considerations dictate that a screening test should be completed in the shortest possible time, and a response to acute drug treatment is a highly desirable feature (provided that the test accurately predicts clinical efficacy). However, if we are interested in using a model to study the physiological mechanisms of the clinical action of antidepressants, a valid model must involve chronic drug treatment; furthermore, this should be administered within a context of abnormal behavior, rather than prophylactically (see, e.g., Muscat et al., 1990; Sampson et al., 1990). These considerations of chronicity are largely irrelevant to the validation of a screening test; in the screening context, these features are highly undesirable on practical grounds.

In addition to a need for clarity as to the scientific objectives, it should also be recognized that conclusions arising from the use of a model are essentially hypotheses, which must eventually be tested against the clinical state. An assessment of the validity of a simulation gives no more than an indication of the degree of confidence that we can place in the hypotheses arising from its use. However, the fact that a simulation appears to be valid carries no guarantee that such predictions will be fulfilled; conversely, predictions derived from a manifestly invalid model may prove successful. The validity of a model is a matter of judgment, rather than measurement. The assessment of validity is therefore an interim and ongoing activity.

Against this background, there are a number of yardsticks on which a judgment may be based. Validating an animal model of psychopathology is, in principle, no different from validating
any other psychological device, such as a psychometric test (Vernon, 1963) or a psychiatric diagnosis (Carroll, 1989), and the same generic approaches to validation are applicable:

1. **Predictive validity** means that performance in the test predicts performance in the condition being modeled;
2. **Face validity** means that there are phenomenological similarities between the two; and
3. **Construct validity** means that the model has a sound theoretical rationale (Willner, 1984a, 1986, 1991).

These three perspectives address three broad and different aspects of a model, from which a picture of its overall validity may be built.

Earlier attempts to develop criteria for validating animal models of human behavior have tended to concentrate largely on the assessment of face validity (Abramson and Seligman, 1977; McKinney and Bunney, 1969). The identification of two further categories reflects two ways in which the literature has developed in recent years. First, there has been a considerable expansion in the literature dealing with the pharmacological exploitation of animal models, much of which contributes to the assessment of predictive validity. Second, there has been significant growth in our understanding of the psychological mechanisms underlying psychopathological states, and examination of construct validity provides a convenient way of bringing animal models into contact with this very relevant literature. The exercise of distinguishing different types of validity has practical value: It allows ready identification of areas in which information about a particular model is weak or missing, and ensures that comparisons between different models are made on the basis of comparable data.

2. **Assessment of Predictive Validity**

The concept of predictive validity implies that manipulations known to influence the pathological state should have similar effects in the model: Manipulations known to precipitate or exacerbate the disorder should precipitate or exacerbate