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# Developing Translational Animal Models for Symptoms of Schizophrenia or Bipolar Mania

**MARK A. GEYER, Ph.D.***
*Department of Psychiatry, University of California San Diego, La Jolla, CA 92093-0804, USA. mgeyer@ucsd.edu*

## Abstract

Animal models have long been used to explore hypotheses regarding the neurobiological substrates of and treatments for psychiatric disorders. Early attempts to develop models that mimic the entirety of the diagnostic syndromes in psychiatry have evolved into more appropriate efforts to model specific symptoms. Such an approach reflects the facts that even in patients, clinical symptoms transcend diagnostic categories, and the specific etiologies of psychiatric disorders are unknown. An animal model can only be identified adequately by specifying both the manipulation (drug, lesion, strain) used to induce abnormalities and the measure(s) used to characterize them. A wide range of pharmacological, lesion, and developmental manipulations have been combined with various measures of information processing to develop useful animal models that parallel human tests. Prepulse inhibition of startle, event-related potential (ERP) measures of auditory gating, and Cambridge neuropsychological test automated battery (CANTAB) measures of cognition are examples of measures that can be used in both rodents and humans and that are robustly altered in both psychiatric disorders and animals manipulated with appropriate drugs or lesions.

The further development of cross-species models is critically important, given the new opportunities for the development and registration of specific treatments for the cognitive disorders of schizophrenia that are not ameliorated by available drugs. In moving beyond the focus on psychotic symptoms to the cognitive symptoms of schizophrenia, animal models that do not involve manipulations of dopamine $D_2$ receptors but that do utilize information processing measures that are correlated with cognitive disturbances are receiving increased attention.

Here, selected examples of how cross-species measures of psychiatric disorders are developed and validated are discussed. Specific animal paradigms that parallel the specific domains of cognition that are altered in schizophrenia provide one focus of the review. Another focus includes efforts to develop new human models of psychiatric symptoms that are designed to parallel existing tests used in rodents.

### Keywords

Translational biomarkers; Schizophrenia; Bipolar mania; Prepulse inhibition

## INTRODUCTION

As summarized by Hagan and Jones (2005), the drug discovery process involves multiple steps that feed forward and backward upon one another. The beginning of the process necessarily involves the construct, the conceptual identification of a molecular pharmacological target that

*Corresponding author: Tel.: 1 619-543-3582; FAX: 1 619-543-2493; E-mail: mgeyer@ucsd.edu.

might beneficially modify a clinically defined deficit. This initial idea must first be evolved into some small drug-able molecules that can constitute the first actual step in the process. These small molecules or proteins are used to confirm actions at the relevant biological mechanism using *in vitro* and eventually *in vivo* model systems. The resulting tool compounds are then used in appropriate animal models, for example in models of the cognitive deficits in schizophrenia or manic depressive psychoses. Due to the high costs of studies in human volunteers, higher throughput animal models are typically required for this phase of the process. Studies in healthy humans then proceed and, if they are successful, progress to initial studies in small numbers of affected patients. Only after these steps are completed are larger clinical trials undertaken to assess the appropriate dose levels, treatment regimens, and eventually clinical efficacy of a candidate compound. Throughout this drug discovery process, the information from each successive stage is fed back into the preceding stages, prompting appropriate refinements in an iterative process. Thus, early studies in healthy humans might identify unwanted side effects that prompt a return to earlier stages to identify alternative compounds having similar on-target effects but with different side effect profiles. Similarly, observations of preferential effects in some domains of cognition over others might prompt a revised selection of test paradigms in the animal model proof of concept studies, which in turn might influence subsequent more specific studies of specific cognitive tests in healthy volunteers and/or small studies of relevant patients. As noted by Hagan and Jones (2005, page 832), “Rational preclinical strategies for hypothesis testing and compound characterisation are therefore essential in order to enable informed choices between mechanisms and molecules. These strategies should not be restricted to behavioural models and a range of functional techniques may eventually prove useful. Establishing robust links between each stage of testing and building predictive algorithms is essential if pre-clinical models are to be relied upon to predict clinical efficacy.” It is the thesis of this review that this essential bidirectional cross-talk between the preclinical models and the clinical assessments of efficacy is best accomplished by developing and using physiological and behavioral measures and test paradigms that maximize the similarity of the observed phenomena across species. It is readily apparent that such efforts will be most cost-effective if the focus of decision making is on early proof of principle studies in late Phase I or early Phase II studies, given the enormous costs and risks of large-scale Phase III clinical trials. Thus, extremely valuable information could be derived from experimental paradigms based on comparable measures in both preclinical animal models and in early small-scale clinical tests. In addition, this focus on early clinical assessments enables the use of behavioral, imaging, or physiological assessments that more closely link to the preclinical tests without requiring the simplicity and low-cost needed for large-scale clinical trials.

## COGNITIVE DEFICITS IN PSYCHOTIC DISORDERS

As reviewed elsewhere (Geyer, 2006), Fenton and colleagues (Fenton *et al.*, 2003) identified a critical bottleneck limiting the development of treatments specifically directed at the cognitive deficits in schizophrenia. The domain of cognitive deficits has been long recognized as being a core aspect of the group of schizophrenia disorders that is not treated adequately by current antipsychotic treatments. Similar problems are evident in the treatment of bipolar mania. Although many antipsychotic treatments have been identified and marketed, the cognitive deficits remain as clinical problems in schizophrenia and most patients are burdened by significant psychosocial deficits (Green, 1996). In response, NIMH developed an initiative called “Measurement and Treatment Research to Improve Cognition in Schizophrenia” or MATRICS, which developed a broad consensus regarding how the cognitive impairments in schizophrenia might be assessed and treated (Marder and Fenton, 2004). MATRICS helped establish a way for FDA to consider registering compounds intended to treat cognitive deficits in schizophrenia, independent of treating psychosis *per se*.

Given the absence of any treatments known to ameliorate the cognitive deficits in schizophrenia, preclinical drug discovery programs have difficulty assessing the predictive validity of the many cognitive tests available (Floresco *et al.*, 2005). As a result, current efforts are based primarily on our understanding of the theoretical constructs and neurobiology related to cognition. The cognitive constructs or domains identified by the MATRICS program as being the primary cognitive deficits in schizophrenia include: working memory; attention/vigilance; verbal learning and memory; visual learning and memory; speed of processing; reasoning and problem-solving; and social cognition (Nuechterlein *et al.*, 2004). MATRICS also developed a Neurocognitive Battery of appropriate cognitive tests to be used in clinical assessments of potential cognitive enhancers, which is now publicly available. A subsequent program - "Cognitive Neuroscience measures of Treatment Response of Impaired Cognition in Schizophrenia" (CNTRICS) - is designed to bring the modern tools and concepts of cognitive neuroscience to bear upon the assessment of cognitive deficits in schizophrenia and the efficacy of pharmacotherapeutics in ameliorating these deficits (see http://cntrics.ucdavis.edu). The need to identify and develop cross-species tools with which to predict and evaluate novel treatments of cognitive deficits is being addressed by another NIMH-funded program: "Treatment Units for Research on Neurocognition in Schizophrenia" (TURNS). This multi-site clinical trials network is implementing the clinical trial design developed by the MATRICS program (see http://www.turns.ucla.edu). TURNS includes a Biomarkers Subcommittee designed to facilitate the inclusion of specific biomarkers in conjunction with clinical tests (see http://www.turns.ucla.edu). The supplementation of clinical neurocognitive assessments with biochemical, genetic, psychophysiological, or brain imaging measures having the potential to serve as biomarkers should facilitate the processes of drug discovery and development. There is a clear need for the identification of predictive pathways from the preclinical rodent models that are essential for the rapid screening of compounds of interest to the first proof-of-concept studies in humans that are essential for go versus no-go decisions in drug development (Floresco *et al.*, 2005; Hagan and Jones, 2005). Many groups are now exploring translational paradigms that have construct validity for the assessment of cognition and may be applicable across species. Accordingly, a Preclinical Subcommittee of TURNS has surveyed experts from academia and industry and assembled a listing of preclinical tests that may have utility as predictive measures of the clinical treatment of cognitive deficits in schizophrenia (Young *et al.*, 2006). These preclinical models, as ranked in this survey, are now being used especially by pharmaceutical companies to guide their preclinical drug discovery and validation programs.

## TRANSLATIONAL MEASURES OF GATING DEFICITS

Two instructive exemplars relevant to developing cross-species tests having utility in psychiatric drug discovery were developed as measures of the abnormalities in gating mechanisms that are hypothesized to contribute to deficits in attention, vigilance, and cognition in psychotic disorders. Specifically, measures of sensory or sensorimotor gating are among the most widely studied physiological markers used in laboratory studies of schizophrenia and bipolar disorder. The first of these exemplars is the auditory "sensory gating" paradigm pioneered by Freedman's group. This procedure involves a condition-test paired-stimulus paradigm in which the P50 event-related potential (ERP) elicited by the second of two audible clicks is normally reduced relative to the ERP elicited by the first click (Martin *et al.*, 2004). In schizophrenia or manic patients, however, this suppression of the P50 is diminished, apparently due to a reduction in short-term habituation. An analogous paradigm has been developed for use in rodents (Freedman *et al.*, 1999). This cross-species ERP paradigm has been critical in the identification of the $\alpha_7$ nicotinic receptor as a potential target for pro-cognitive co-treatments in schizophrenia (Freedman *et al.*, 1999).

Another cross-species gating paradigm, prepulse inhibition of startle (PPI), also assesses the gating construct and yet differs qualitatively from the P50 ERP paradigm. Since it involves both sensory stimuli and motor responses, PPI is considered a measure of "sensorimotor gating" rather than sensory gating (Braff and Geyer, 1990). In PPI, the startle response elicited by a strong sudden stimulus, usually acoustic or tactile, is measured in the presence or absence of a weak prepulse stimulus, which may be in the same or a different modality. The weak prepulse robustly inhibits the response to the subsequent startling stimulus. In contrast to P50 suppression, PPI is clearly not a form of habituation. In humans, startle is usually assessed via the eyeblink component of startle, using electromyography. In animals, the whole-body flinch aspect of the startle response is quantified using an accelerometer that is sensitive to dynamic movements. Like P50 gating, PPI is reduced in schizophrenia and manic bipolar patients (Braff *et al.*, 2001; Perry *et al.*, 2001). The early demonstrations of PPI deficits in schizophrenia were based on groups of patients who were, for the most part, treated with first generation or so-called typical antipsychotic drugs. More recent studies have demonstrated similar deficits even in first-break patients who had never been treated with any antipsychotics (Ludewig *et al.*, 2003). Thus, deficient PPI in schizophrenia is not attributable to medications or the course of illness, but it is also not reversed by first-generation antipsychotic treatments.

As reviewed elsewhere (Geyer *et al.*, 2001; Swerdlow *et al.*, 2001), the cross-species nature of startle and PPI facilitates the use of animal models of gating deficits that are extremely similar to the abnormalities seen in schizophrenia. Since the early finding that dopamine agonists disrupt PPI in rats, rodent PPI tests have evolved into at least four distinct models. These models have PPI measures in common but are distinguished by the manipulations used to disrupt PPI: 1) psychostimulant dopamine agonists; 2) hallucinogenic serotonin agonists; 3) psychotomimetic *N*-methyl-D-aspartate (NMDA) receptor antagonists; and 4) developmental manipulations such as isolation rearing or neonatal lesions of the ventral hippocampus. The first three models are based on changes induced by acutely administered drugs and have helped to identify relevant neural substrates. Nevertheless, they do not assess environmental or developmental contributions to PPI deficits as does the PPI model based on the deficits seen in adult rats reared in social isolation post-weaning (Powell and Geyer, 2002; Cilia *et al.*, 2005). Considerable evidence indicates that the dopamine PPI model is reliably predictive of existing antipsychotics, and that the NMDA PPI model is insensitive to typical antipsychotics but responsive to clozapine and some other multi-receptor antagonists. Given the MATRICS program, the utility of PPI models in the discovery process for pro-cognitive co-treatments becomes an important question. Although PPI cannot be considered to be a cognitive process *per se*, abnormalities in pre-attentive gating may be predictive of or contribute to complex cognitive deficits. Since the anticipated application is for co-treatments to be used in patients already treated with antipsychotic drugs, animal models that are responsive to first-generation antipsychotics are likely to be uninformative. It appears that neither PPI nor cognitive deficits in schizophrenia are reversed by most existing antipsychotics but may be partially ameliorated by drugs such as clozapine (Kumari *et al.*, 1999; Meltzer and McGurk, 1999). Since the same can be said of the PPI disruptions produced by NMDA antagonists (Geyer and Ellenbroek, 2003), the glutamate PPI model may have utility in the identification of pro-cognitive adjunctive treatments.

The PPI paradigm has also proven to be informative in studies of normal and genetically engineered mice (Geyer *et al.*, 2002). One striking aspect of PPI in mice that was not so apparent in earlier studies of rats is that antipsychotics improve baseline PPI. Hence, it has been suggested that strains of mice that exhibit low baseline levels of PPI may provide simple approaches to the identification of novel antipsychotic drugs (Olivier *et al.*, 2001; Ouagazzal *et al.*, 2001). It had been noted some time ago that clozapine, and not haloperidol, slightly improved baseline PPI in rats (Swerdlow and Geyer, 1993). More recent work has shown that antipsychotics, especially atypical compounds such as clozapine, produce relatively robust

increases in baseline PPI in rat strains characterized by low PPI (Palmer *et al.*, 2000; Feifel *et al.*, 2007). Capitalizing on the cross-species nature of PPI testing, researchers have now begun to test the ability of antipsychotic drugs to improve PPI in healthy humans who are selected on the basis of having low baseline PPI. Indeed, when healthy volunteers are stratified in terms of low versus high PPI, atypical antipsychotics such as clozapine or quetiapine increase PPI in low responders while having no effect in high responders (Swerdlow *et al.*, 2006; Vollenweider *et al.*, 2006). As with the PPI deficits in schizophrenia, this effect of clozapine-like drugs is not evident with haloperidol (Csomor *et al.*, 2008). Further research is warranted to determine whether this simple test might provide a proof of concept biomarker for the identification of either atypical antipsychotics or potentially procognitive adjunctive treatments.

## BI-DIRECTIONAL DEVELOPMENT OF TRANSLATIONAL MEASURES

The preceding example of cross-species development of psychiatric test paradigms illustrated transitions from human to animal and back to human tests. After the original demonstration of gating deficits in patients with schizophrenia, research naturally progressed to models in which pharmacological, developmental, and genetic manipulations were used to mimic the deficits in animals in order to develop predictive tools for drug discovery. Recently, this animal work revealed simple models of low versus high levels of PPI that could be readily translated into comparable human tests. Another example of translating an established animal paradigm into a human experimental tool is provided by the recent effort to develop the human counterpart to the rodent Behavioral Pattern Monitor, an established offshoot of the classical animal Open Field paradigm (Young *et al.*, 2007a). This effort was initiated primarily because of the difficulties in assessing the differential predictive validity of animal models for schizophrenia versus bipolar mania. Patients with either diagnosis exhibit both PPI deficits and perseverative behaviors and both are commonly treated with antipsychotic drugs. One marked difference between the two conditions is that mania, in contrast to schizophrenia, is characterized by motoric hyperactivity. Indeed, hyper-activity is a cardinal symptom of mania that is usually measured only by observer-rated scales. Given the importance of hyperactivity in many psychiatric disorders in general and in bipolar mania in particular, it is surprising that experimental approaches to measure locomotor behavior empirically in humans have not been more abundant in the literature (Einat, 2006; Cryan and Slattery, 2007). Our understanding of motor activity in rodents is quite sophisticated, due to extensive studies of the neurobiology and neuropsychopharmacology of this behavior. Exploratory locomotor behavior in rodents involves complex patterns of behavior that are not characterized sufficiently only by quantifying the amount of behavior (Geyer *et al.*, 1986; Drai and Golani, 2001; Eilam *et al.*, 2006). Instead, measures that quantify the temporal, spatial, and dynamic organization of the subject's movements and interactions with objects have proven to be valuable tools to differentiate the contributions of different neural transmitter systems on locomotor and exploratory behavior (Geyer and Paulus, 1996). Multivariate assessments of unconditioned locomotor behavior have shown that hyperactivity includes complex multifaceted behaviors, which has been effectively characterized using the rodent Behavioral Pattern Monitor. The Behavioral Pattern Monitor has been used to demonstrate differential effects of drugs on locomotor activity and exploratory behavior in rats and both normal and genetically modified mice (Risbrough *et al.*, 2007). Of relevance to the suggested relevance of psychostimulant effects to both schizophrenia and bipolar disorder, these studies in rodents have enabled clear distinctions to be made between various psychostimulants that have different primary mechanisms of pharmacological action, such as the dopamine releaser amphetamine, the direct dopamine agonist apomorphine, the serotonin releaser 3,4-methylenedioxymethamphetamine, and the NMDA antagonist phencyclidine (Geyer *et al.*, 1986; Callaway *et al.*, 1990). Clearly, detailed assessments of exploratory motor behavior can identify pharmacologically specific

and behaviorally differentiated forms of hyperactivity in rodents that are not detectable by simple measures of the amount of movement.

As an extension of the extensive work on patterns of locomotor and exploratory behavior in rodents, we developed the human Behavioral Pattern Monitor in order to characterize motor activity in manic patients (Young *et al.*, 2007a). Increased activity, object interactions, and altered locomotor patterns provide multidimensional phenotypes to model in the rodent Behavioral Pattern Monitor. This "reverse-translational" approach to modeling mania provides an opportunity to identify the neurobiology underlying bipolar mania and test novel antimanic agents. The current version of the human Behavioral Pattern Monitor has been established as a room on a locked inpatient psychiatry unit, equipped with a file cabinet, bookcase, desk, and no chair. Ten interesting and manipulable objects are placed around the room. Behavior is monitored by both a vest equipped with an accelerometer and physiological detectors and by a camera embedded in the ceiling that provides MPEG video files. The video images are then processed for spatial patterns of movements, as is done with video-tracking systems for rodents, and by visual scoring of object interactions and other observable behaviors. Preliminary findings using this approach have demonstrated that acutely ill bipolar manic patients exhibit dramatic increases in the amount of motor activity (Minassian *et al.*, 2007) and in interactions with objects in the room (Kincaid *et al.*, 2007). The normal habituation of activity exhibited by control subjects was diminished in manic patients (Minassian *et al.*, 2007; Paulus *et al.*, 2007). Additional analyses suggest that the spatial patterns of the movements of manic patients are similar in structure to those exhibited by rodents in which the dopamine transporter is disrupted either pharmacologically or genetically (Paulus *et al.*, 2007; Young *et al.*, 2007b). Groups of patients with other psychiatric disorders, such as schizophrenia or attention deficit hyperactivity disorder, do not exhibit profiles of behavior in this paradigm that match that of bipolar manic patients. Thus, this simple objective measurement of specific behaviors in patients has the potential to discriminate between different diagnostic groups and parallel the profiles of activity associated with specific psychostimulant treatments in rodents. It is noteworthy that the profiles of behavior seen in bipolar mania and not in schizophrenia patients are similar to those produced by manipulations that induce hyperdopaminergia in rodents. Although rodent hyperactivity is often used to assess potential models related to schizophrenia, it does not appear that schizophrenia patients are motorically hyperactive as are bipolar manic patients. Hence, rodent models of hyperactivity may be generally more relevant to mania than schizophrenia.

## CONCLUSIONS

Animal models have long been used to explore hypotheses regarding the neurobiological substrates of and treatments for psychiatric disorders. Early attempts to develop models that mimic the entirety of the diagnostic syndromes in psychiatry have evolved into more appropriate efforts to model specific symptoms. Such an approach reflects the facts that even in patients, clinical symptoms transcend diagnostic categories and the specific etiologies of psychiatric disorders are unknown. An animal model can only be identified adequately by specifying both the manipulation (drug, lesion, strain) used to induce abnormalities and the measure(s) used to characterize them. Many different pharmacological, lesion, and developmental manipulations have been combined with various measures of information processing to develop useful animal models that parallel human tests. The further development of cross-species models is critically important, given the new opportunities for the development and registration of specific treatments for the cognitive disorders of schizophrenia that are not ameliorated by available drugs. In moving beyond the focus on psychotic symptoms to the cognitive symptoms of schizophrenia, animal models that provide translational equivalents across species are receiving increased attention. Prepulse inhibition of startle, ERP measures of auditory gating, and Cambridge neuropsychological test automated battery (CANTAB)

measures of cognition are examples of measures that can be used in both rodents and humans and that are robustly altered in both psychiatric disorders and animals manipulated with appropriate drugs or lesions. The use of enriched populations of normal subjects, such as volunteers having low levels of gating, may enable proof of principle studies to be accomplished early in the drug development process using behavioral measures that mirror those used in the preclinical phases of the drug discovery process. Following such examples provided by the gating paradigms, recent efforts have begun to develop and evaluate the use of human equivalents of the established open field and behavioral pattern monitor paradigms used in rodents. In rodents, such multivariate assessments are able to differentiate among a variety of psychostimulants that have been used to assess various neurochemical hypotheses regarding the substrates of and treatments for disorders such as schizophrenia and bipolar mania. New parallel studies in which the exploratory motor behavior of humans is measured objectively may enable similar distinctions to be made among subgroups of psychiatric patients. If successful, this approach would further demonstrate the value of bi-directional development of objective behavioral tests that assess similar responses in both rodents and humans to facilitate the process of drug development and validation.

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