Drug Discovery in Psychiatric Illness: Mining for Gold

Greg I. Elmer¹,² and Neri Kafkafi²

¹Department of Psychiatry, University of Maryland School of Medicine, Maple and Locust Streets, Baltimore, MD 21228

The discovery of truly efficacious treatments that lead to full recovery is a daunting task in psychiatric illness. A systems-based orientation to in vivo pharmacology has been suggested as a way to transform psychiatric drug discovery and development. A critical catalyst in the success of recent systems biology efforts has been the incorporation of data mining strategies. Our approach to the drug discovery problem has been to utilize the whole animal to provide a systems response that is subsequently mined for predictive attributes with known psychopharmacological value. Our in vivo data mining approach, termed Pattern Array, establishes a framework for screening novel chemical entities based upon a response that represents the net pharmacological effect on the system of interest, namely the central nervous system (CNS). Large scale screening of small molecules by non-conventional approaches such as this at a systems level may improve the identification of novel chemical entities with psychiatric utility. This type of approach will complement the more labor-intensive models based upon construct validity. It will take the collective effort of many disciplines and numerous strategies in close association with clinical colleagues to address quality of life issues and breakthrough treatment barriers in psychiatric illness.

Key words: Data mining/animal model/systems biology/exploratory behavior/Pattern Array/SEE

Schizophrenia is an illness characterized by positive (hallucinations, delusions, and thought disorder), negative (alopecia, blunted affect, avolition, and anhedonia), and cognitive symptoms (attention, executive, and memory deficits).¹ This textbook description does not do justice to the depth or breadth of the illness. Basic scientists sometimes do not have an opportunity to interact with patients at a level that would afford them some understanding of nuances in the illness. However, some insight into the devastating and highly complex nature of the illness is provided by First-Person Accounts of Schizophrenia Bulletin and invaluable interaction with clinicians. As a basic scientist, one cannot help but be a bit overwhelmed by the prospect of creating an animal model with sufficient face or construct validity to prove fruitful as a research platform. Other psychiatric conditions such as drug abuse at least have a core feature, such as drug self-administration, that runs relatively true across species.²⁻⁵ Fortunately, new perspectives on the psychopathological constitution of schizophrenia are slowly pushing clinical research from a disease entity paradigm with psychotic symptoms as the major targetable intervention point to a paradigm exemplified by domains of psychopathology that recognizes impaired cognition and negative symptoms as major impediments to an improved quality of life.⁶ The change in focus is beneficial to the animal research community in that it alleviates the burden to reproduce schizophrenia as a disease entity and makes available cognitive domains and endophenotypes that are more accessible across species (see for reviews Carpenter and Koenig⁷ and Markou et al⁸). Thus, while aspects of schizophrenia are thought to involve uniquely human disturbances, schizophrenia domains of psychopathology often sort independently and are amenable to independent investigation. With this in mind, an insightful guiding principle for developing animals models is that “we are not attempting to simulate the experiential aspects of schizophrenia, what we are attempting for our simulations is to model the constraints on information processing and behavior that underlie the experiential changes; the cognitive foundations of psychopathology rather than its overt experiential manifestations.”⁹ Instead of asking how we produce schizophrenia in a mouse, it may be more useful to ask what is it like for a mouse to have a cognitive domain undergo pathophysiological disruption similar to that found in schizophrenia.

Psychiatric Drug Development and Animal Models

Despite the advantages of a domain-oriented approach, the lack of a clear neuropathology in schizophrenia makes the use of animal models for drug discovery particularly challenging. For example, disturbances in reward processing can be induced at multiple levels and affect different interrelated components of the process.¹⁰⁻¹³ However, in order to most accurately model the reward deficits found in

¹To whom correspondence should be addressed; tel: 410-402-7576, fax: 410-402-6066, e-mail: gelmer@mprc.umaryland.edu

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schizophrenia, it is important to initiate the disturbance through similar mechanisms as that found in schizophrenia. Another example with pharmacological implications is the fact that the neurobiological disturbance and psychiatric profile of anhedonia and other primary or disease-based negative symptoms in schizophrenia is likely different than that involved in depression\textsuperscript{14,15}; as a consequence, anhedonia in schizophrenia is not ameliorated by antidepressants. It is difficult to construct animal models that represent blunted or flattened affect as opposed to a depressed or sad affect. A relatively significant degree of sophistication is required to develop appropriate and reliable behavioral assays to distinguish subtle characteristics that uniquely characterize deficits found in schizophrenia. To this end, animal model building is an iterative process as clinical research provides an increasing understanding of the psychopathological domains of interest. As we expand our knowledge of how the brain works and what might go wrong in psychiatric illness, we will likely reduce some mechanisms to realized points of intervention; however, we are just as likely to reveal significantly greater complexity. In this regard, the behavioral assays and animal models will have to grow increasingly sophisticated in their design to approach face or construct validity. Intensive efforts in assay development done in close collaboration with clinical colleagues are a significant priority in psychiatric drug discovery.\textsuperscript{8}

Predictive Pharmacological Models

Juxtaposed to sophisticated behavioral assays, animal models used in psychiatric drug discovery are often developed strictly for their high throughput and pharmacological predictive validity. The main purpose of these models is to predict the therapeutic potential of novel compounds with a moderate degree of sensitivity and specificity. The behavioral endpoint may or may not be developed with specific regard to the model’s face or construct validity. In some sense, we give in to the complexity of the illness and count on predictive validity to identify drugs of interest. For example, the potency of a drug to inhibit apomorphine-induced stereotypes\textsuperscript{16,17} or suppress a conditioned avoidance response\textsuperscript{18,19} is highly predictive of its antipsychotic potency. However, these endpoints do not have face or construct validity; stereotypy (apomorphine induced or otherwise) is not a cardinal feature in schizophrenia nor is the suppression of a response to avoid punishment a desirable treatment outcome. Nevertheless, the predictive pharmacological model has proved valuable in terms of its contribution to assessing the potential therapeutic value of novel compounds.\textsuperscript{19} A drawback of current types of predictive models is that they are restricted to the identification of drugs that antagonize a narrow pharmacology (apomorphine/dopamine antagonists), block a narrow behavior (suppression of punishment avoidance, not escape), or show utility for a single drug class. Novel compound discovery can be severely limited in most predictive animal models because they are generally geared to a single neurotransmitter system.\textsuperscript{20} The aforementioned limitations also restrict the high throughput for initial in vivo screening, because classifying a compound into one of $n$ psychopharmacological classes generally requires evaluating it with a battery of $n$ class–specific behavioral assays (eg, swim test for identifying antidepressants, elevated plus maze for anxiolytics, tail flick for identifying opioids, etc).

Systems Pharmacology

The focus on specific mechanistic interventions might prove unsatisfactory if the underlying pathology does not rest in a restricted neurotransmitter or transduction entity but rather in a “systems” response.\textsuperscript{19,21–23} The historical difficulty in psychiatric drug development may in fact rest, in part, on the overreliance on a few pharmacological mechanisms, the target-centric approach, and the overall implausibility of a single causal molecular abnormality.\textsuperscript{10,24,26} In contrast, the goal of systems biology is to understand physiology and disease from the level of molecular pathways, regulatory networks, cells, tissues, organs, and ultimately the whole organism.\textsuperscript{21} An example of a systems biology approach to drug discovery has been to utilize cell systems to interpret, classify, and predict the biological activities of drugs.\textsuperscript{27–29} However, high-throughput assays of this type are generally designed to isolate individual pathways and to minimize biological complexity, thus missing what may be critical interactions between pathways.\textsuperscript{21} An extension of the cell system approach has been to mimic physiological complexity by including one or more primary cell types engineered to incorporate critical pathway interactions that would have otherwise been missed.\textsuperscript{30–32} These aforementioned efforts have largely focused on physiological responses involved in cancer or inflammation. If one were to consider psychiatric drug discovery in this light, a critical component of the endeavor would be to study an experimental preparation that includes the appropriate components to provide critical pathways interactions in the central nervous system (CNS). A systems-based orientation to in vivo pharmacology and reinvigoration of in vivo pharmacology as a whole has been suggested as a way to transform psychiatric drug discovery and development.\textsuperscript{24,25} While the concept is enticing, its practical application is complicated by the difficulties involved in quantifying the behavioral system response at the necessary level and degree of proficiency.

Data-Mining Procedures Designed for Prediction

A critical catalyst in the success of systems biology has been the incorporation of data-mining strategies, an important ally in the discovery of interrelated components predictive of a specific outcome. For example, data mining
has been successfully applied to screen large-scale gene expression results from in vitro platforms for gene expression patterns predictive of a toxicological or carcinogenic response.33–35 An interesting twist to this approach has been used in a human neuronal precursor cell line as a means to discover expression patterns predictive of a drug’s psychoactive class. In this study, classification algorithms (classification tree and random forest) were used to discover gene expression profiles predictive of antidepressant, antipsychotic, and opioid drug action.36 Using the “leave-one-out” model in which one of the 36 drug profiles was left out from training for evaluation, approximately 90% of the drugs were correctly classified using the classification tree algorithm. While this approach represents a novel strategy, it is necessarily restricted in its ability to mimic a true systems pharmacology response to psychiatric drugs in that there are no astrocytes, limited neuronal variation, and no interacting neuronal pathways. Thus, while the data mining can be very successful at this level, it would be advantageous to extend the approach to an in vivo system.

Recently we have done just that. In our approach, termed pattern array (PA), we are essentially attempting to harness complexity by using the mouse brain as a processing entity in order to determine the system pharmacological properties of a drug; input (drug) $\rightarrow$ computation (system pharmacology) $\rightarrow$ output (behavior). The input portion of the process is relatively straightforward: We test a wide range of psychoactive drugs with known therapeutic and psychopharmacological properties. The second portion of the equation relies on the mouse brain. Because it is important to standardize the “computation” component, we use a highly inbred strain (C57BL/6J). In order to implement a data-mining approach in vivo, we determined that the behavioral output has to be (1) algorithmically defined and automatically measured, (2) common enough in natural behavior to supply large samples, (3) complex enough to provide a relatively detailed profile of a drug’s psychoactive properties, and (4) highly heritable and replicable thus likely reflecting “hard-wired” brain mechanisms. Extensive ethological, pharmacological, and behavior genetics studies in our laboratory...
and others have shown that exploratory behavior is a complex behavior that meets our criteria. Exploratory behavior in an open field is highly structured and amenable to algorithmic characterization in that it (1) is automatically measured as path coordinates amenable to mathematical description, (2) is high throughput, generating approximately 10^6 relevant data points per animal in a 1-hour unconditioned session, (3) is information rich, consisting of highly structured behavioral repertoire, and (4) includes some highly heritable and replicable aspects of behavior likely reflecting “hard-wired” brain mechanisms. We rely on this “hard-wired” system(s) to determine the constellation of pharmacological properties of novel chemical entities. Our approach follows the typical steps of constructing a classification model in data mining. Figure 1 shows an overview of PA’s approach to analyzing the path coordinates of an animal’s dynamic movement patterns in an open field arena. First, the behavioral units to be mined consist of a large number (approximately 100 000) of complex movement patterns, algorithmically defined as simultaneous combinations of several ethologically relevant “attributes” such as the distance from the arena wall, the speed and acceleration of movement, direction of movement, and turning. Second, the frequency of each of the 100 000 above patterns by each animal is measured. Third, a classification model is “trained” by mining for patterns that best predict each psychopharmacological class in a “training dataset,” and then only the discovered class predictors are tested in an independent “test dataset” measured in different animals. Finally, we validate our classification model by its ability to correctly classify additional drugs that were not encountered during the training process. The latter is a simulation of novel compound classification in drug discovery.

In a recent report, we used PA to characterize the psychopharmacological effects of 3 drug classes—psychomotor stimulant, opioid, and psychotomimetic. PA discovered a reliable drug classification scheme using behavioral predictors of all 3 classes. The discovered predictors showed orderly dose dependency despite being explicitly mined only for class differences, with the high doses scoring 4–10 SDs of the vehicle group. Furthermore, these predictors correctly classified in a dose-dependent fashion 4 “unknown” drugs (ie, that were not used in the training process) and scored a mixture of a psychomotor stimulant and an opioid as being intermediate between these 2 classes. The isolated behaviors were highly heritable (h^2 > 50%) and replicable as determined in 10 inbred strains across 3 laboratories. The advantage of the data-mining approach is that a large number of variables can be explicitly screened for prediction of any experimental factor of interest by customizing the comparisons to address specific research questions (eg, see PA application to an animal model of amyotrophic lateral sclerosis). In addition, the database can be stored and expanded as a repository. PA can in principle be applied for mining behaviors predicting additional properties such as within-class differences or be used to mine for predictors of properties across drug class, eg, mining for behavioral patterns that are predictive of the drug’s abuse potential in humans. It may be possible to reverse transcribe the effects of psychotomimetic drugs to discover behavioral patterns uniquely associated with drugs that precipitate psychotic symptoms in humans (ketamine or use anxiogenic drugs (pentylenetetrazol) to discover behavior patterns that are uniquely associated with anxiety.

Combined Efforts

Large-scale screening of small molecules by nonconventional approaches is suggested as a means to discover novel chemical entities (magic shotguns) with psychiatric utility. Our in vivo data-mining approach establishes a framework for screening novel chemical entities based upon a response that represents the net pharmacological effect on the system of interest, namely the CNS. Screening novel chemical entities may lead to the discovery of drugs that, through actions at known or unknown modulatory systems, have the same “net” desired effect, eg, on the dopamine-glutamate system but without direct dopamine D2 effects. One could expect that the spectrum of action, efficacy, and side-effect profile of these novel chemical entities would differ from traditional compounds. The next step in the process would be to utilize more traditional industrial assays to characterize the full profile of the drug. While many of the drugs may fail at subsequent steps in the process, it is worth the initial effort to explore the value of compounds that would otherwise sit on the shelf. The large-scale screening and data-mining approach is still partially limited by the reliance on gold standards. This type of approach will compliment the more labor-intensive models construct validity. Investment and development in the latter approach is the most promising way to discover neurobiological factors involved in psychiatric illness. Discovering truly efficacious treatment that leads to full recovery is a daunting task. It will take the collective effort of many disciplines and numerous strategies within each discipline in close association with clinical colleagues to address quality-of-life issues and breakthrough treatment barriers in schizophrenia.

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References


