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COMMENTARY

Revitalizing Psychiatric Therapeutics

Steven E Hyman*,[1]

[1]*Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, Cambridge, MA, USA*

Despite high prevalence and enormous unmet medical need, the pharmaceutical industry has recently de-emphasized neuropsychiatric disorders as 'too difficult' a challenge to warrant major investment. Here I describe major obstacles to drug discovery and development including a lack of new molecular targets, shortcomings of current animal models, and the lack of biomarkers for clinical trials. My major focus, however, is on new technologies and scientific approaches to neuropsychiatric disorders that give promise for revitalizing therapeutics and may thus answer industry's concerns.
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INTRODUCTION

The term 'revolution' in science and medicine is often used hyperbolically, but the period from 1949 to 1957 can fairly be described as revolutionary for psychopharmacology. A remarkable burst of discovery began with John Cade's recognition of the therapeutic potential of lithium in 1949 (Cade, 1949). Henri Laborit first administered chlorpromazine for preoperative sedation in 1952, but quickly recognized its possible utility for the treatment of psychotic patients (Laborit *et al*, 1952). Iproniazid, the first monoamine oxidase inhibitor (MAOI) antidepressant, failed in its intended use as a treatment for tuberculosis in the early 1950s, but in clinical trials, significant elevation of patients' moods was noted. Imipramine, the prototype monoamine reuptake inhibitor antidepressant, was synthesized as a candidate antipsychotic drug based on modifying the tricyclic molecular structure of chlorpromazine. Imipramine failed to treat psychosis but was recognized to have antidepressant effects. By 1957, both the MAOI iproniazid and the tricyclic drug imipramine were recognized as antidepressants (Deverteuil and Lehmann, 1958).

These serendipitously recognized drugs gave rise to a large number of related compounds in each therapeutic class that in aggregate produced enormous benefit to patients while fundamentally changing the scientific and clinical landscape of psychiatry. For the first time, there were pharmacologic interventions that targeted specific symptoms clusters within psychiatric syndromes: lithium for mania and mood stabilization, antipsychotic drugs for the hallucinations and delusions of schizophrenia and severe mood disorders, and antidepressants for depression and anxiety disorders. Later, beginning with clomipramine, serotonin-selective antidepressants were found to exhibit a degree of efficacy for obsessive-compulsive disorder. These discoveries not only improved many lives but also motivated significant advances in both basic science and clinical investigation.

Unfortunately for individuals with psychiatric disorders, the astonishing developments of the 1950s have been followed by a similarly improbable half-century of stagnation. This period has been characterized by failure to improve the efficacy of pharmacologic treatments for established clinical indications or to extend effective treatments to additional significant symptom clusters. The most significant success during the past five decades has been in the domain of toxicity. Thus, for example, antidepressants approved since the late 1980s (eg, the selective serotonin reuptake inhibitors) are far safer and more tolerable than the older tricyclic drugs and MAOIs. A second generation of antipsychotic drugs exhibits decreased liability to cause serious motor side effects, including tardive dyskinesia, compared with first-generation drugs—but carries its own serious side effects including significant risk of weight gain and associated metabolic derangements.

What has not happened for five decades across the range of psychiatric drug classes is any significant improvement in efficacy. No antidepressant drug has proven more effective than imipramine or the first MAOIs (Rush *et al*, 2006; Trivedi *et al*, 2006; Khin *et al*, 2011). Second-generation antipsychotic drugs are, in general, no more efficacious than the first (Lieberman *et al*, 2005), and no antipsychotic drug is as efficacious as clozapine (Kane *et al*, 1988), a drug that was discovered in the early 1960s. In the 1980s some anticonvulsants were found to have therapeutic benefits as mood stabilizers, but none has proved so effective as to

*Correspondence: Dr S Hyman, Stanley Center for Psychiatric Research, Broad Institute of MIT and Harvard, 7 Cambridge Center 5015, Cambridge, MA 02142, USA, Tel: +1 617 714 7061,
E-mail: seh@harvard.edu
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obviate the need for lithium, despite its side effects and difficulty of use. Many individuals with schizophrenia and related disorders have significant residual psychotic symptoms despite current treatments, and there are no significantly effective treatments for the highly disabling cognitive or deficit symptoms of schizophrenia (Keefe *et al*, 2007). Many patients with depression (most notably bipolar depression) and anxiety disorders have substantial residual symptoms despite optimal use of current treatments (Rush *et al*, 2006; Sachs *et al*, 2007). Moreover, no effective pharmacologic treatment has been developed for the core social deficits of autism. In short, the unmet medical need of patients with psychiatric disorders remains vast. The failure to improve efficacy or extend therapies to additional serious syndromes is mirrored by the fact that the molecular targets of all of today's widely used psychiatric medications are the same as the targets of their 1950s prototypes (Table 1).

TABLE 1 Molecular Targets of Major Classes of Psychiatric Drugs

Drug class	Prototype compound	Molecular target(s)
Mood stabilizer	Lithium (Li^+)	GSK3β, inositol 1-phosphatase[a]
Antipsychotic drugs	Chlorpromazine	Dopamine D_2 receptor
Antidepressants	Iproniazid Imipramine	Monoamine oxidase NE and 5-HT transporters
Benzodiazepine receptor agonists	Chlordiazepoxide	$GABA_A$ receptor, benzodiazepine site

Abbreviations: GABA, γ-aminobutyric acid; GSK3β, glycogen synthase kinase β; NE, norepinephrine; 5-HT, 5-hydroxytryptamine, serotonin.
[a]GSK3β is thought to be the most likely therapeutic target of Li^+, but it interacts with other possible targets at therapeutic levels.
Adapted from Hyman (2012).

Given the significant unmet need, the high prevalence of psychiatric disorders (Kessler *et al*, 2005), and their outsized negative effects on disability worldwide (Vos *et al*, 2011), psychiatric drugs would seem to be compelling focus for the biotechnology and pharmaceutical industries. Instead, the past 4 years have seen the industry significantly decreasing its investment in psychiatric disorders while investing in other areas (Hyman, 2012). Recent commercially successful antidepressants have included a metabolite of an existing drug (desvenlafaxine) and the active enantiomer of another (escitalopram). Clinically these drugs differed from their parent compounds only by relatively modest improvements in side effects as well as longer patent life. Payers and regulatory agencies have begun to balk at the marketing of expensive new treatments that fail to advance efficacy. Faced with payer demand for greater efficacy or at least a companion biomarker to identify likely responders, companies have retreated from psychiatry because they can identify no clear path to satisfying such requirements. Upper level management at many pharmaceutical companies recognizes the large markets and unmet need. However, given what they perceive as less mature scientific underpinnings than in competing areas of medicine, they are, for the most part, unwilling to renew their once substantial investments in psychiatry. In short, given the choice between investing in psychiatry *vs* cancer, autoimmunity, or metabolism where more is known about disease mechanisms combined with a seeming plethora of molecular targets, companies are opting for the latter (Hyman, 2012). These decisions have enormous negative consequences for patients with psychiatric disorders and their families. Notwithstanding discoveries that may come from academic labs in the near term, without the engagement of companies that possess the scientific and financial resources to develop new drugs, patients and families may have to wait for years or even decades for better pharmacologic treatments. Progress continues in the development of cognitive- and computer-based psychotherapies, especially for schizophrenia (Subramaniam *et al*, 2012), and in the investigation of devices that modulate neural circuit activity (Holtzheimer *et al*, 2012). However, concomitant advances in drug therapy would seem absolutely necessary if we are to have an adequate range of treatments across the diversity of psychiatric disorders.

In the sections that follow, I address two major areas of concern that have been identified by companies in their retreat from psychiatry: (1) poor understandings of disease mechanisms and thus a dearth of compelling molecular targets, and (2) poor model systems, indeed significant disillusionment with animal models, that would be needed for target validation and for prediction of treatment efficacy. Ironically, during these recent years in which industry has been moving away from psychiatry, powerful new technologies have emerged that will likely answer many important doubts. It is must be admitted, however, that the contribution of the resulting new science to therapeutics may occur over a longer time period than is comfortable for many industrial investment decisions today. Specific technologies that may contribute to revitalization of psychiatric therapeutics include genomics (Shendure and Ji, 2008), stem cell technologies (Takahashi and Yamanaka, 2006; Takahashi *et al*, 2007 (Along with Takahashi and Yamanaka (2006), this Nobel prize winning work described the discovery of a method to produce stem cells from adult cells, such as skin fibroblasts. These methods are of central importance to the creation of *in vitro* cellular models to test hypotheses about the pathogenesis of brain disorders.); Zhang *et al*, 2013), and diverse advances in systems neurobiology (Gradinaru *et al*, 2009; Chung *et al*, 2013; Fox *et al*, 2005), all based on technologies or discoveries less than a decade old.

A third area that has contributed significantly to industry's skepticism about psychiatric therapeutics is a phenomenological diagnostic system and a lack of biomarkers for diagnosis or ascertainment of treatment response. I have written extensively about the vicissitudes of psychiatric diagnosis and the need for new approaches; thus, I will only comment briefly at the end (Hyman 2007, 2010). Newer technologies combined with growing momentum for a 'cognitive jailbreak' from the fictive DSM categories that have captured grant making, journal editing, and regulatory decisions for the past several decades suggest that progress may be in the offing for biomarkers as well.

TARGET DISCOVERY

The pharmacologic revolution of the 1950s highlighted an important role in psychiatric therapeutics for molecules and biological processes involved in neurotransmission. The basic research that followed these early discoveries elucidated such processes as neurotransmitter synthesis, storage, release, reuptake, metabolism, receptor binding, and post-receptor signaling. Such work produced truly foundational findings for neurobiology, including discoveries that led to Nobel Prizes for Julius Axelrod in 1970 and Arvid Carlsson in 2000. In parallel with such basic science, insights from pharmacology were applied to investigations of disease pathogenesis. Beginning in the 1960s, inspired by the action of recently discovered drugs, measurements were made of monoamine neurotransmitter release and metabolism in animals and in both healthy and ill human subjects. From the outset, concern was expressed about the potential for excessive diversion of scientific effort based on the *post hoc ergo propter hoc* fallacy. In the case of psychopharmacology, this type of risky syllogism took the form that if increased synaptic monoamine levels treated depression, the pathogenesis of the disorder might involve low levels of production or release, and if dopamine receptor antagonists treated psychotic symptoms, schizophrenia might result from excessive dopamine function. Perspicacious early warnings (Schildkraut and Kety, 1967) were not always heeded, and arguably, an overly exuberant focus on monoamines (extending even to recent 'biological candidate' gene studies of monoamine transporters and receptors) has narrowed the focus of psychiatric research to its detriment.

More generally, compounds that release neurotransmitters, deplete their stores, or act as neurotransmitter receptor agonists or antagonists have historically been used as probes of disease mechanisms, often with experimental end points based on the production of symptoms reminiscent of a disorder (Myers and Veale, 1968; Javitt and Zukin, 1991). Pharmacologic provocation studies have produced some important findings, for example, when combined with positron emission tomography to study dopamine release in schizophrenia (Abi-Dargham *et al*, 1998), as well as some fruitful hypothesis, for example, that NMDA receptor glutamate receptors dysfunction might have a role in schizophrenia (Javitt and Zukin, 1991). Nonetheless, pharmacologic provocation studies face significant challenges as an approach to studying pathophysiology. Because the human brain is a highly complex biological system with branching and recurrent 'causal paths' and extraordinary levels of adaptation, both within a given level of analysis (eg, molecular, cellular, synaptic, circuit, cognitive, and behavioral) and across these levels, the administration of a probe drug cannot, by itself, identify underlying mechanisms with any certainty. The effects of manipulating a neurotransmitter system produce such a multiplicity of downstream effects and adaptations that attempts to identify key causal mechanisms of disease or of their treatments have often been frustrated by the absence of significant independent information about the genetic or neural substrates of the disorder. Thus, we know a great deal about the neurobiology of addictive disorders because pharmacologic research has been grounded in substantial knowledge of reward circuits. In contrast, even with respect to understanding the action of antidepressants, antipsychotic drugs, and lithium, the ultimate therapeutic mechanisms (beyond the first few molecular interactions) remain scientific mysteries.

Similarly, it has also become increasingly apparent, both in animal models and human subjects, that multiple mechanisms can converge on a given cognitive or behavioral output. Thus, there are significant limitations to use of behavioral phenomenology as a sole end point for preclinical investigation. Studies that rely on the 'face validity' of a behavioral result risk taking phenocopies for disease-related phenotypes. Perhaps, as a result, many treatments that appear efficacious in terms of behavioral end points in animal models have lacked the predicted beneficial effects in human disease (van der Worp *et al*, 2010; Nestler and Hyman, 2010). The implication is that the translatability of behavioral end points in animal models requires greater attention to evolutionary conservation, and significant connections with molecular, cellular, and circuit mechanisms (Insel *et al*, 2013).

A large fraction of the approaches to psychiatric pathophysiology and molecular target identification during the past half century has been driven by a limited number of hypotheses, many that trace their intellectual pedigrees to pharmacologic agents or the effects of stress. The limited progress in therapeutics since 1960 would seem to cry out for new and broader approaches to hypothesis generation. Given our relatively narrow understanding of brain development, structure, and function, what would seem to be of greatest value are unbiased methods that are not dependent on current hypotheses. Fortunately, we find ourselves at a time in history when technological advances make large-scale unbiased inquiry possible. Specifically, given the high heritabilities of some of the most serious neuropsychiatric disorders, including autism, schizophrenia, and bipolar disorder, unbiased genetic studies may yield for psychiatry the kind of useful pathophysiologic clues that they have produced for other fields of medicine, such as cardiovascular disease (Cohen *et al*, 2006), inflammatory bowel disease (Rossin *et al*, 2011), and various cancers (Cancer Genome Atlas Network, 2012). Because of advances in genomic technologies, psychiatry is at the threshold of gaining information about molecular mechanisms of disease. That said, putting genetic findings to work in the service of understanding the pathogenesis on psychiatric disorders and revitalizing therapeutics poses very difficult challenges.

The Promise of Genetics for Psychiatry

Extensive evidence from family and twin studies has confirmed that genes have a highly influential role in the pathogenesis of many neuropsychiatric disorders. This means that significant clues to disease mechanisms have

lain hidden, albeit inaccessible, within patient genomes. With few exceptions, notably rare monogenic forms of autism, the high heritabilities of these disorders result from the aggregate effects of a very large number of genes, likely many hundreds, each contributing only a small increment of risk. However, most cases of autism, and essentially all of schizophrenia and bipolar disorder, appear to be polygenic (Sullivan *et al*, 2012). Given the large amount of DNA sequence variation that characterizes the human genome (1000 Genomes Project Consortium, 2012), it is very easy to find sequence variants, but very difficult to determine whether any particular variant influences disease risk. In short, there is a daunting 'signal-to-noise' problem for psychiatric genetics that has proven to be statistically tractable only with the study of tens of thousands of patients and a roughly equal number of healthy comparison subjects. Genetic research at this scale was simply not possible without recent technological advances in genotyping (determination of specific variants at a given locus in the genome) and sequencing of DNA. For genotyping, the advent of DNA microarrays and their steady improvement has made genome-wide association studies (GWAS) remarkably inexpensive and increasingly accurate. In the near future, a microarray (currently in late design stages) will be available that includes every known marker or mutation associated with psychiatric disorders (a 'psych' chip in analogy with the useful existing 'immuno' chip), with the plan that it be updated at intervals. There have also been remarkable advances in DNA sequencing. During the past decade, the cost of sequencing DNA has declined approximately a millionfold while increasing in speed and accuracy. As a result, it has been possible to progress from zero loci known to be associated with schizophrenia in 2007 to approximately one hundred loci at genome-wide levels of significance in the spring of 2013. As samples are collected from larger populations, progress is accelerating in the genetic dissection of schizophrenia, bipolar disorder, and autism (Lee *et al*, 2012).

For polygenic disorders, the benefits of GWAS to identify a large number of allelic variants that exert small effects on risk are often misunderstood. The most significant near-term goal is not so much to account for all of the heritability, but to gain clues to the biology of disease mechanisms. Discovery of risk-conferring variants through unbiased genetic studies such as GWAS represents the most powerful method we possess to identify the genes involved in disease processes. The association of a disease phenotype with a sequence variant by GWAS points to nearby genes or, in some cases, a single gene that may harbor the variant.

GWAS arrays, which carry a finite number of markers (eg, one million), can detect only relatively common allelic variants, which are, given their widespread nature, ancient in origin. Rare variants are identified by sequencing the DNA of the gene-containing regions of the genome ('the exome') of affected and unaffected individuals. Very rare variants may have higher penetrance than common variants because they represent recent mutations have not yet been subject to rounds of natural selection that would tend to weed out highly deleterious alleles. Sequencing of whole exomes has been proceeding in schizophrenia and autism using different designs (case–control and parent–child trios). Interestingly, it appears that a significant fraction of rare variants that might be disease associated occur in genes already identified by GWAS. The generation of large genetic data sets has not only provided the statistical power to identify disease-associated alleles against background variation but also has helped advance biology. As large numbers of risk-associated genes are identified, they can be assembled into biological pathways (eg, signaling pathways), functional protein networks (eg, postsynaptic specializations or synaptic release mechanisms), and developmental processes (eg, chromatin regulation) involved in pathogenesis. These pathways and protein networks can, in turn, be exploited to select or to help validate molecular targets for potential therapies (Jonsson *et al*, 2012).

The genetic analysis of schizophrenia, bipolar disorder, and autism have begun to identify multi-subunit protein complexes and protein networks involved in pathogenesis, notably postsynaptic specializations within excitatory synapses (autism and schizophrenia) and L-type calcium channels in which genes encoding four different subunits have been identified as being associated with bipolar disorder or schizophrenia (Kirov *et al*, 2012; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Other proteins, many previously unsuspected, have also been identified from genetic studies such as the sodium channel type II, α-subunit identified as a risk gene for autism by a mutation in its gene, SCN2A, and proteins involved in chromatin modification, and also implicated in autism (Neale *et al*, 2012; Sanders *et al*, 2012). The point here is not to review particular recent results, but to show that large-scale unbiased genetic studies are already providing useful clues for biochemical and neurobiological analysis of several neuropsychiatric disorders.

A Comment on Diagnosis

In addition to illuminating the neurobiology of disease, genetic information will contribute to the deconstruction of the chimeras that currently populate the DSM system and thus to better diagnostic schemata (Hyman, 2007, 2010). The contribution of genetics to better diagnoses will proceed slowly, however (despite the premature claims of some diagnostics companies). This partly reflects the need to achieve reasonable completeness of genetic data in multiple human populations to avoid false-negative results. More importantly, it has been found that psychiatric disorders share genetic risk factors. Thus, for example, the risk for schizophrenia conferred by common genetic variants is approximately 70% shared with bipolar disorder (Purcell *et al*, 2009; Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013). Even damaging mutations, such as gene deletions, duplications, and translocations that

might have been expected to act in a more Mendelian manner, produce multiple disease phenotypes even within families, or no disease at all (Blackwood *et al*, 2001; Sahoo *et al*, 2011), presumably depending on interactions with other genes, epigenetic effects, and environmental influences. Limited penetrance of risk-associated variants, variable expressivity, and shared genetic risk across disorders is turning out to be the rule not only in psychiatry (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013) but also in other fields of medicine (Cotsapas *et al*, 2011). The upshot is that for diagnostic uses, genetic data will have to be integrated with non-genetic information. However, long before genetic information is used for clinical diagnoses, it can provide important hypotheses pertaining to intermediate phenotypes (eg, that might result from abnormalities of ion channels or excitatory synapses) as well as possible treatment-responsive biomarkers.

TARGET VALIDATION: CELLS, ANIMALS, AND HUMAN STUDIES

The discovery of disease risk genes and the pathways through which they act is an epochal development that is beginning to provide psychiatry with its first molecular target candidates based on the knowledge of disease processes rather than serendipity or weak inference based on pharmacologic models. However, even when genetic findings are used to identify pathways and networks, they will not by themselves elucidate disease mechanisms or lead easily to new therapeutics: biological model systems are also required. A critical step in selecting promising molecular targets and in their validation is interrogation of their biological function within relevant cell types, and an understanding of how disease-associated variants confer risk. Learning, for example, that in relevant cell types a risk allele changes levels of expression of a resulting protein or produces (partial or full) gain or loss of function, or alteration of function dictates what the action of a drug treatment must be. Understanding the pathway in which a risk-associated gene functions can suggest alternative targets even if the gene product associated with risk proves difficult to modify with a drug. Finally, clues to efficacy come from the modification of phenotypes within model systems. The validation of molecular targets for therapeutic development is not based on any single datum. Rather, validation represents a process of gaining increasing confidence in the target based on biological research, reaching an end point, perhaps only with a convincing proof-of-concept clinical trial.

Model systems, whether cellular or animal models, are critical for target selection and target validation. However, the development of good translational models represents a very high hurdle for human brain disorders, especially those that affect higher cognition, emotion regulation, and executive function. The challenge of developing cellular or animal models for psychiatry can be illustrated by comparison with cancer biology. In cancer research, the diseased cells are obtained directly from patients following surgical procedures; moreover, most fundamental disease processes in cancer are cell autonomous. The availability of cancer cells permits sequencing of their genomes, which has led to enumeration of 'driver' somatic mutations, as well as biochemical studies, development of cell lines that can be used, *inter alia*, for chemical screens, and implantation into mice. Moreover, cellular phenotypes of interest for therapeutics may be relatively straightforward, such as cell division *vs* cell death. In contrast, the living human brain can be examined only indirectly under most circumstances. Even where biopsies or resections might be performed, the information provided by the tissue would be limited, as psychiatric illnesses, far from being cell autonomous, depend on the development, structure, and function of distributed neural circuits involving multiple cell types and diverse synapses.

The inaccessibility of the human brain for study would seem to underscore the importance of animal models for psychiatric research. However, recent years have brought significant disillusionment with animal-based pharmacologic screens performed in healthy animals and animal models of psychiatric disorders. The question raised at a recent workshop at the Institute of Medicine is: Why do many therapeutics show promise in preclinical animal models but then fail to elicit predicted effects when tested in humans (Institute of Medicine, 2013)? To be sure, this is not a problem unique to psychiatry. For example, in inflammatory disorders there have been repeated failures of human clinical trials after drugs had appeared effective in mouse models. These failures are now thought to reflect the lack of conservation of murine cytokine responses in humans (Seok *et al*, 2013). Adequate evolutionary conservation of molecular pathways, cells, and circuits would appear to represent a substantial concern when attempting to model aspects of psychiatric disorders, given, for example, that rodents are lissencephalic, and have a particularly underdeveloped prefrontal cortex compared with humans.

It is important to recognize crucial differences between the role of models in basic neuroscience and in translational research. Animals are absolutely critical for studies of basic biological mechanisms. Without them important research on areas such as brain development, synaptic biology, and neural circuit function would essentially come to a halt. Basic science succeeds by understanding particular biological systems in detail and attempting to derive general principles; thus, the system under investigation can be freely chosen. In contrast, a disease model, especially if it is to be used to predict responses to therapeutics, must be highly constrained. The model is useful only insofar as it closely or identically reproduces underlying mechanisms of the human illness or treatment response it is meant to portray. In many fields of medicine treatment development has repeatedly been led astray by the mistaken study of phenocopies in which the underlying mechanisms differ from the human diseases they were meant to model (Nestler and Hyman, 2010; van der Worp *et al*, 2010; Seok *et al*,

2013). An additional problem across all of medicine is the use of one inbred laboratory mouse strain, or at most a few inbred laboratory mouse strains to test therapies that will be administered to highly heterogeneous human populations.

Given the early state of the relevant science, psychiatry has often had to rely on behavioral assays in healthy animals or on putative disease models that, on the surface, mimic symptoms of disorder, but where the underlying mechanisms remain unknown. Indeed, lacking of knowledge of the mechanisms by which psychiatric drugs produced their therapeutic effects, pharmacologists developed rodent assays, beginning as early as the 1950s, based on the behavioral effects of drugs that were known to be efficacious in humans. The hope was that the behavioral responses of healthy (although sometimes stressed) laboratory rodents in such assays as the forced swim test (based on the action of prototype tricycle antidepressant drugs) or the elevated plus maze (based on prototype benzodiazepines) would predict antidepressant or anxiolytic efficacy across diverse drug mechanisms. The explicit fear concerning reliance on such assays is that they would detect little more than the mechanism of the prototype drugs on which they were based, and might thus screen out potentially efficacious new drugs acting by different mechanisms. Unfortunately, the fearful negative prediction has proven to be the case with ruthless certainty: the molecular targets of all of today's commonly used psychiatric drugs are the same as those of their 1950s prototypes. On the basis of a 100% failure rate to bring new therapeutic mechanisms to regulatory approval and clinical use, industry has progressively eschewed these black-box behavioral assays, or exited psychiatry altogether (Institute of Medicine, 2013). Disconcertingly, assays such as the forced swim continue to be used in academic research to phenotype genetically engineered mice and inexplicably to be used as proxies for depression, anxiety, and other disorder phenotypes—uses for which they were never intended.

Despite recent successes in gene identification, the development of useful disease models of neuropsychiatric diseases is no easy matter. The greatest opportunity comes from rare psychiatric syndromes that are caused by single highly penetrant mutations, such as syndromal forms of autism. In such cases, it has been possible to replace the orthologous mouse gene with the human disease gene and to gain useful biological information from the resulting transgenic animals (Peça *et al*, 2011; Földy *et al*, 2013). Some of the monogenic autism mouse models such as those involving mutations in the *SHANK* genes produce abnormal synaptic function as well as abnormal social behavior and avoidance of novel objects (Peça *et al*, 2011). For treatment discovery and development, biochemical or physiological characteristics of animal models such as abnormal synaptic function are likely to prove more useful than behaviors by virtue of permitting at least intermediate throughput assays in primary neuronal culture, and because biochemical and physiological functions are biologically closer to the actions of the causative gene than are behavioral outputs. Genetic mouse models have also been developed based on moderately penetrant copy number variants, such as the 22q11.2 microdeletion that in humans is associated with schizophrenia (25% of carriers) and autism (20% of carriers), as well as significant learning disabilities, and palatal, facial, and cardiac defects (Xu *et al*, 2013). A challenge in dissecting the neurobiological effects of copy number variants such as 22q11.2 is that, in contrast to monogenic disorders exemplified by SHANK mutations, copy number variants alter gene dosage at a large number of contiguous loci. Nonetheless, the resulting genetic mouse models are useful tools to study molecular, cellular, and synaptic phenotypes (Xu *et al*, 2013). Unfortunately, even when important aspects of a human disease are reproduced in a genetic mouse model of a monogenic disorder, such as fragile X syndrome, there is no guarantee that treatments that rescue aspects of the disease phenotype in the animal model (Henderson *et al*, 2012) will prove efficacious in humans with the disorder (Berry-Kravis *et al*, 2012).

The hurdles for translating therapeutics in genetic mouse models of monogenic disorders only become steeper when thinking about the common polygenic forms of autism, schizophrenia, and bipolar disorder. As described, risk genes are rapidly being discovered for these disorders and are beginning to be assigned to functional protein networks (Neale *et al*, 2012; Sanders *et al*, 2012; Kirov *et al*, 2012; Lee *et al*, 2012; Sullivan *et al*, 2012). Moreover, technologies to engineer single or multiple genetic variants into the mouse genome have improved vastly lowering barriers to model construction (Wang *et al*, 2013). Nonetheless, selection of genes for investigation (among the myriads now emerging), selection of relevant species and strains for the questions being asked, and the unknown generalizability of animal-based evidence for treatment efficacy to heterogeneous human populations all remain daunting questions. For heterogeneous, polygenic disorders of, lower heritability such as unipolar depression, putative genetic mouse models have no 'construct validity' at the present time, leaving the field without potentially important investigative tools. Despite many underpowered 'biological candidate gene' studies of unipolar depression, no variants have yet reached adequate levels of confidence (Sullivan *et al*, 2012; Wray *et al*, 2012; Ripke *et al*, 2013).

As a result of many failures in translation from animal models across medicine, a widely asked question concerning target validation is under what circumstances therapies that appear efficacious in animal models will prove similarly effective in human patients (Institute of Medicine, 2013). One important response is to recast genetic mouse models and other compelling animal model systems as important investigative tools that should not be considered determinative (assuming adequate safety data) of what compounds should enter human trials. Put another way, even for monogenic disorders, there is increasing skepticism that animal models should be treated as 'efficacy gates' before initiation of clinical trials. Instead, animal models are likely to represent part of the evidence for target validation along with human cellular (neuronal) models *in vitro* and perhaps

earlier stage investigation of compounds (assuming adequate safety data) in humans with the disorder.

An important consideration, already alluded to, in considering the utility of animal models for translational research is the degree of evolutionary conservation of molecular pathways, cells, and circuits proposed for investigation in the chosen species. For circuits that underlie basic emotional and motivational processes such as fear and reward, there is much evidence for reasonably good conservation across the approximately 90 million years since humans and rodents shared a common ancestor. As a result, important information relevant to mechanisms of human psychiatric symptoms in anxiety disorders and addictions has been gleaned from studies of rodents (although therapeutics has lagged). In contrast, the lateral prefrontal cortex, an evolutionarily recent brain region that is most highly developed in humans, is poorly developed or absent in rodents. This brain region is among the most significantly affected in schizophrenia, partly explaining its significant cognitive impairments (Barch *et al*, 2001). Indeed, the human brain exhibits significant evolutionary differences not only from rodents but also from non-human primates. At the genomic level, the most significant DNA sequence differences between humans and other primates occur in regulatory rather than protein coding sequences. It has been found that the transcriptional networks that control gene expression in the prefrontal cortex exhibit little correlation between human and chimpanzee, compared with the evolutionary older basal ganglia, which shows reasonably high levels of conservation, at least with our nearest primate relative (Konopka *et al*, 2012). Findings of this sort, which are also emerging in other fields of medicine (Seok *et al*, 2013), highlight the importance of taking evolutionary conservation into account when attempting to model molecular, cellular, circuit level, cognitive, or behavioral aspects of a human disease and certainly when testing therapeutic interventions. The implication is that animal models will have utility for some translational purposes, but not others, and that investigation of disease mechanisms and the processes of target validation and efficacy testing will likely have to depend on combinations of animals, human cellular models *in vitro*, and human experimental biology.

Cellular Models

Diverse experimental findings have pointed to the need to develop human cellular models *in vitro* for nervous system disorders. One pragmatic issue is that with the recognition that hundreds of genes and a larger number of allelic variants within those genes contribute to risk of psychiatric disorders, high-throughput systems are needed to study their action and to screen their RNA or protein products for value as potential therapeutic targets. As it may prove important to study some risk genes in combination (eg, based on low individual penetrance), the number of possible experiments could be very large indeed, making it infeasible to rely entirely or even largely on genetic animal models.

Beyond this pragmatic issue, a critical scientific issue derives from considerations of evolutionary conservation discussed above. The greatest differences in DNA sequences across species, including mouse–human (Church *et al*, 2009), tend to be in non-protein coding RNA genes and in regulatory regions of the genome. The resulting differences in gene regulation likely explain more of the divergence in brain size, complexity, and connectivity across species than amino-acid substitutions in important proteins (which tend to be under strong selective constraint). Thus, for example, differences in timing or levels of gene expression that might represent the effects of the many non-coding DNA sequence variants found in GWAS studies of schizophrenia would best be investigated in cell types expressing appropriate human transcriptional networks. Beyond the functional examination of non-coding disease-associated variants, the examination of gene function and comparison of the actions of risk and non-risk variants would likely benefit from *in vitro* systems that come as close as possible to representing relevant neural cell types in the brain. For schizophrenia, for example, the most useful cells in which to study gene function and gene regulation, including regulation by epigenetic mechanisms, would include models of human pyramidal neurons and parvalbumin-expressing interneurons, both implicated by post-mortem studies (Lewis and Sweet, 2009).

Recent advances in stem cell biology have made it possible to produce human neurons *in vitro*. Three different approaches are now in use across many laboratories: (1) the differentiation of human embryonic stem cell lines into relevant neuronal subtypes; (2) differentiation of induced pluripotent cells derived from human skin fibroblasts using a defined set of transcription factors (Takahashi and Yamanaka, 2006; Takahashi *et al*, 2007); and (3) direct differentiation of pluripotent stem cells into neurons (Zhang *et al*, 2013). What remains a work in progress is the ability to differentiate the resulting neural precursors or 'generic' neurons into specific mature cell types that are implicated in specific diseases. At the time of this writing, it is possible to make a mix of forebrain neurons, but not yet possible to make individual cell types. Most advanced is the ability to make midbrain dopamine neurons to study Parkinson's disease and motor neurons to study amyotrophic lateral sclerosis (Son *et al*, 2011).

The ability to produce human neurons *in vitro*, when combined with highly efficient methods of genome engineering (Cong *et al*, 2013), makes it possible to test the function of disease-associated genes in a variety of cell-based assays. For example, several groups are introducing schizophrenia- and autism-associated mutations into isogenic human stem cell lines (derived from individuals free of the disease under study). These lines can be differentiated into increasingly appropriate neural cell types as the science advances, but in the mean time, much can be learned about these risk associated genes. Analogous experiments are going on in other areas of medicine, with their appropriate

cell types, such as cells involved in metabolism (Ding *et al*, 2013). A complementary strategy is to culture fibroblasts derived from small skin biopsies of patients with the disorder under study. These patients (or their cells) will have been genotyped and/or had their exomes or whole genomes sequenced. The resulting fibroblasts can be made into stem cells and then genetic engineering can be used to 'rescue' disease-associated mutations. Also promising is the ability to perform chemical screens in neurons made from patient fibroblasts as has been reported for amyotrophic lateral sclerosis (Yang *et al*, 2013).

As exciting as these technologies are, many challenges remain. For autism, schizophrenia, bipolar disorder, and other neuropsychiatric disorders, we are a long way from knowing precisely what neural cell types are involved in pathogenesis. Even when there are good candidate cell types, as there are for schizophrenia, the technology is not yet at the point of producing good models of mature neurons (recognizing that there will always be significant differences between brain-embedded neurons and neurons in culture.) For disorders like autism and schizophrenia, where synaptic structure and function have been implicated by genetics, it will not be adequate to produce 'good enough' neurons. It will also be important to be able to make replicable small circuits with synapses that can be investigated. One of the most challenging problems will be to identify and validate disease-relevant phenotypes using some combination of human post-mortem tissue, studies of human peripheral organs where possible, and animal models. Despite these hurdles, the technology is so promising and seems so central to development of novel human therapeutics that it must be pursued vigorously. Of course, it should be clear that for phenotypes that require complex multicellular interactions or intact circuits, *in vitro* models will not replace animal models or human experimental biology, at least not any time soon.

Human Studies

Given the evolutionary limitations on the information that can be gleaned from rodent and other animal models, as well as limitations of *in vitro* cellular models with respect to circuits, there is substantial need to advance human experimental biology. As the discovery of risk-associated genes progresses, new hypotheses are likely to emerge concerning measurable human phenotypes (intermediate phenotypes) that can contribute to the development of biomarkers. In addition, advances in cognitive neuroscience, human brain imaging, new approaches to post-mortem studies (Chung *et al*, 2013), and research associated with progress in therapeutic neuromodulation (Holtzheimer *et al*, 2012) are likely to improve understanding of human brain circuit function in health and in neuropsychiatric disease.

There is great need for identification of objective biological measures of psychiatric disorders, ideally related to disease mechanism. The symptoms of many psychiatric disorders fluctuate over time and with context, making biomarkers critical for both proof of concept and larger registration trials. At present, the need to rely on subjective rating scales is well recognized to contribute to costly failures in clinical trials, as has been well illustrated for antidepressant trials—even for drugs that ultimately achieve approval (Khin *et al*, 2011). Unfortunately, DSM system, based on the descriptive psychiatry of the 1960s and 1970s, promulgates a large number of discontinuous diagnostic categories that are poor mirrors of nature (Hyman, 2007, 2010). DSM diagnoses exhibit the remarkable properties that they are at the same time too narrow, resulting in substantial clinical comorbidity, and too broad, meaning that diagnosed patients remain highly heterogeneous. Thus, if DSM-5 diagnoses are taken as the gold standard against which biomarkers are to be validated, it is difficult to imagine significant progress. Fortunately, some efforts have been made in recent years to circumvent the limitations of the DSM system. These include Cognitive Neuroscience Research to Improve Cognition in Schizophrenia (CNTRICS; Carter *et al*, 2012), which is searching for cognitive and imaging biomarkers, and more recently the NIMH Research Domain Criteria (RDoC) project aimed at developing a new approach to diagnosis centered on neural circuit function (Insel *et al*, 2010). These and similar efforts will likely be aided by advances in genetics and diverse areas of brain science, but what is most important is the willingness to eschew DSM categories that no longer serve.

There is also a need to study promising therapeutic candidates in patients even if we must forego animal behavioral assays that once seemed reassuring as putative demonstrations of efficacy. Serious discussions have begun concerning both ethical and pragmatic issue related to earlier stage administration of potential therapeutics to patients. These have included a workshop held at the Institute of Medicine on Accelerating Therapeutic Development for Nervous System Disorders towards First-in Human Trials in April 2013 that involved industry, academics, patient groups, FDA, and NIH. Clearly, the choice of living systems for the study of psychiatric therapeutics is in a complex state of reflection and transition that will ultimately require a judicious use of cellular and animal models as well as human studies. Without progress in developing better model systems, however, advances in genetics of psychiatric disorders may produce little more than sterile lists. That would be an intolerable situation.

Additional Areas of Concern, Now Receiving Attention

Several additional areas that are scientifically tractable are already receiving attention with the goal of enhancing drug discovery and development in neuropsychopharmacology. These include synthesis of chemical libraries with more brain penetrant compounds; tools (including but not limited to positron emission tomography ligands) to establish target engagement in the human brain and to

aid in dose finding; and methods to assess whether compounds produce appropriate pathway engagement (modification) in human brain (http://www.nimh.nih.gov/research-priorities/research-initiatives/fast-fast-fail-trials.shtml). Measurement of target and pathway engagement is needed to know whether a clinical trial has tested the hypothesis that each molecular target represents. When a clinical trial fails for lack of efficacy, it is clearly better to know whether a new compound should be tested or whether it is time to move on to a new target.

CONCLUSION

It is important to view the stasis of the past five decades with clear eyes, rather than defensively. The disorders of higher brain function that neuropsychopharmacology is concerned with have greater associated challenges than those that face many other fields of medicine. Nonetheless, the difficulties inherent in confronting polygenicity, disease heterogeneity, and limitations of current animal models appear more similar than different across medical disciplines. The pace of technology development seems only to be accelerating, and should thus give us hope. Despite the challenges, there is a substantial opportunity to win back industry and to revitalize psychiatric therapeutics by embracing clear thinking and by putting technologies to work.

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