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REVIEW

Animal models of neuropsychiatric disorders

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Modeling of human neuropsychiatric disorders in animals is extremely challenging given the subjective nature of many symptoms, the lack of biomarkers and objective diagnostic tests, and the early state of the relevant neurobiology and genetics. Nonetheless, progress in understanding pathophysiology and in treatment development would benefit greatly from improved animal models. Here we review the current state of animal models of mental illness, with a focus on schizophrenia, depression and bipolar disorder. We argue for areas of focus that might increase the likelihood of creating more useful models, at least for some disorders, and for explicit guidelines when animal models are reported.

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Neuropsychiatric disorders such as schizophrenia, major depression, bipolar disorder and autism are highly prevalent[1], begin early in life[2] and contribute substantially to disease burden worldwide[3]. Despite the profoundly negative effects of these disorders on public health, progress in understanding their pathophysiology has been frustratingly slow and the discovery of new therapeutic mechanisms is at a near standstill. The molecular targets of current major classes of psychotherapeutic drugs[4] (**Supplementary Table 1**) were all reverse engineered from drugs discovered before 1960 by clinical observation. What factors have impeded progress? Arguably, the most important are the exceedingly challenging neurobiology of higher brain function and the ethical and practical difficulties of examining the living human brain. Although the last two decades have seen rapid progress in the development of noninvasive technologies to study human brain structure and function, there remain substantial limitations in our ability to investigate details of the physiology and molecular biology of the human brain.

Given these limitations, it is hard to imagine substantial progress in pathophysiology or therapeutics without good animal models. Unfortunately, current animal models have substantial limitations, ranging from weak validation to poor predictive power for drug efficacy in human disease[5]. As discussed in this review, the generation of convincing and useful animal models of neuropsychiatric disorders represents a major set of challenges that will not have easy answers.

Challenges for producing animal models of mental illness

The increasing ease of developing rodent and invertebrate models by genetic manipulation or other means has not obviated the difficulties of modeling disorders that often seem uniquely human. Many of the symptoms used to establish psychiatric diagnoses in humans (for example, hallucinations, delusions, sadness and guilt) cannot be convincingly ascertained in animals. When there are reasonable correlates in animals (for example, abnormal social behavior, motivation, working memory, emotion and executive function), the correspondence may only be approximate.

A further complication is determining how symptoms in an animal add up to a recognized human disorder, a seemingly critical issue if the animal is to be used for the development of therapeutics. For the vast majority of pathological states contained in the *Diagnostic and Statistical Manual of Mental Disorders*, *4th edition* (DSM-IVTR)[6], knowledge of pathophysiology remains scant and objective diagnostic tests are lacking. Consequently, diagnoses are based solely on phenomenology, that is, on symptoms, signs and course of illness (**Box 1**). As a result, the boundaries between DSM-IVTR disorders and the boundaries between disorder and normal variation are often arbitrary or hazy[7]. This state of affairs creates enormous hurdles for the development and validation of animal models. Investigators and reviewers alike must rely on judgment rather than slavish devotion to meeting all DSM-IVTR criteria for the disorder being modeled.

With the exception of some neurodegenerative disorders, DSM-IVTR diagnoses do not currently map onto objectively ascertainable abnormalities of molecules, synapses, cells or neural circuits. For familial Alzheimer's disease, insertion of disease-causing alleles has produced useful rodent models[8,9] that produce amyloid plaques similar to those of human disease. In contrast, for virtually all of the remaining disorders in DSM-IVTR, there are no molecular or cellular abnormalities in the human disease that could validate potential phenomenology in an animal. Instead, reversing the direction of 'validation', pathology in genetic animal models might usefully be sought in human patients, either in postmortem tissue or via noninvasive imaging[10].

These considerations do not mean that useful animal models are impossible to develop; instead, they suggest that animal models are unlikely to mirror the full extent of a given human neuropsychiatric disorder, especially as currently defined in DSM-IVTR. In addition, individual symptoms observed in animal models may not have a simple, straightforward correspondence to human symptoms. For

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BOX 1 DIFFICULTY IN USING DSM CRITERIA TO CONSTRUCT A MOUSE MODEL OF MENTAL ILLNESS

To illustrate the challenges involved in using DSM criteria to construct animal models, consider two individuals with the same DSM-IVTR diagnosis of major depression (see criteria at right). The first individual might have depressed mood, weight loss, insomnia, psychomotor agitation and suicidal thoughts, whereas the second individual might have markedly diminished pleasure, weight gain, hypersomnia, psychomotor retardation and fatigue. There are no symptoms in common! Some of these symptoms (for example, depressed mood and suicidality) cannot be assessed in mice and the multiple symptom combinations means that different mouse models of depression would have little in common. Similar problems exist for most other DSM-IVTR diagnoses. This early and inexact state of psychiatric diagnosis in humans creates an enormous obstacle and complex judgments are needed when deciding when an animal model of a neuropsychiatric disorder has achieved an acceptable level of face validity.

DSM criteria for major depressive episode

A. At least five of the following are present simultaneously for at least 2 weeks (symptom 1 or 2 is necessary):
   1. Depressed or irritable mood
   2. Markedly diminished interest or pleasure in all, or almost all, daily activities
   3. Substantial weight loss or weight gain
   4. Insomnia or hypersomnia nearly every day
   5. Psychomotor agitation or retardation nearly every day
   6. Fatigue or loss of energy nearly every day
   7. Feelings of worthlessness or inappropriate guilt nearly every day
   8. Diminished ability to think or concentrate nearly every day
   9. Recurrent thoughts of death or suicide

B. It cannot be established that an organic factor is the cause and the disturbance is not a normal reaction to the death of a loved one (abstracted from DSM-IVTR[6]).

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example, compulsive grooming (that is, grooming to the point of self-injury) in genetically engineered mice has been plausibly argued to correspond to behaviors that occur in obsessive-compulsive disorder in humans[11,12], but even this hypothesis remains something of an intellectual leap, as the related cognitive and emotional context cannot be determined.

Even more than with other types of human disease, the scientific community may have difficulty deciding when a particular animal model is adequately validated to warrant further investment, either as a tool to illuminate pathophysiology or as a basis for treatment development. Unsurprisingly, there is often disagreement on what counts as a good disease model as opposed to a tool to investigate the neurobiology of behavior. Here, we propose some guidelines by which to judge putative animal models of neuropsychiatric illness and illustrate the obstacles by discussing animal models of schizophrenia, depression and bipolar disorder. We have selected these illnesses because of slow progress in therapeutics, despite their substantial contribution to disease burden. Also, clinical features of these disorders are more difficult to model in animals than disorders of fear and reward, for which more robust models exist. Finally, the unsettled state of the human genetics and pathophysiology of schizophrenia, depression and bipolar disorder underscore the challenges with which the field is struggling. In contrast, genetic studies of autism spectrum disorders have begun to identify several Mendelian forms and other highly penetrant mutations that are beginning to yield convincing genetic models in mice[13–20]. As we will discuss, such mutations are more likely to produce meaningful disease-related phenotypes in animal models than disease-associated genetic variants of small effect (**Box 2**). The greater difficulty and controversy lie in diseases that currently lack such tools.

Evaluating animal models of neuropsychiatric disorders

By disease model, we refer to more than a useful tool for probing abnormal neurobiology and behavior. Disease models should be derived from plausible risk factors or causative agents of human disease or else exhibit a substantial degree of neural or behavioral pathology that corresponds convincingly to human disease. Animal models of neuropsychiatric disorders have been generated through diverse means, including selective breeding, genetic engineering, brain lesions and environmental manipulations (**Table 1**). Optogenetic manipulations of specific circuits[21] promise a useful new approach.

Given these diverse approaches and the challenges of validation, it is useful for the scientific community to share criteria for judging whether a particular disease model is good enough to warrant further investments. A longstanding framework posits three types of validators: construct, face and predictive validity. This framework would benefit from greater agreement on how stringently to judge validators. Validity is too often asserted in published papers rather than systematically discussed in terms of strengths and weaknesses.

Construct (or etiologic) validity refers to the disease relevance of the methods by which a model is constructed. In the ideal situation, researchers would achieve construct validity by recreating in an animal the etiologic processes that cause a disease in humans and thus replicate neural and behavioral features of the illness[22]. A straightforward way of accomplishing this would be knocking a known disease-causing (Mendelian) genetic mutation into a mouse or, with somewhat less certainty, inserting a highly, but not fully, penetrant genetic variant that markedly increases vulnerability for a human disease. However, this is currently not possible for most mental illnesses, as such disease-causing genes have not been established with certainty and most disorders exhibit highly complex genetic architecture[23]. Moreover, most reported genetic associations represent common variants of small effect, which makes their utility for animal models highly questionable (**Box 2**).

In addition to genetic manipulation, disease models can be generated by altering the expression or function of particular proteins, biochemical pathways or neural circuits that are hypothesized to be involved in disease pathogenesis (**Table 1**). The challenge for interpreting such approaches in the absence of relevant human genetic evidence is whether they represent legitimate disease models rather than interesting phenocopies. There is an important chasm between the claim that disruption of some biochemical pathway regulates behavior and the claim that it models a particular human disorder with useful implications for pathophysiology or treatment development.

Construct validity might also be achieved through exposure of an animal to a well-validated environmental risk factor or known disease-causing agent. An example would be a pathogenic prion inducing Creutzfeldt-Jakob disease in rodents[24]. However, beyond this

BOX 2 DIFFICULTIES IN ACHIEVING CONSTRUCT VALIDITY OF GENETIC MODELS OF MENTAL ILLNESS

Given the substantial contribution of genetic factors to virtually all major neuropsychiatric disorders, an obvious way of developing animal models with good construct validity would be insertion of human disease–associated alleles into mice. However, there are several problems with this approach.

A first consideration is how penetrant a given genetic variant is in producing a disorder. The more penetrant (ideally Mendelian) a disease-associated (or disease-causing) allele is in humans, the more likely it is to produce a reliable phenotype in a mouse. Examples include knockin mouse models of Fragile X and Rett syndrome[13,17] and mouse and invertebrate models of familial Alzheimer's disease[8,9]. These models show some behavioral and biochemical abnormalities that correspond to the human disease, but replicating the genetic lesion in mice does not recapitulate all of the robust phenotypes seen in humans. Knockin mouse models constructed from single human familial Alzheimer's disease–causing mutations exhibit some cognitive impairment and amyloid plaques; however, the cognitive impairments are relatively mild and little neuronal death is seen. More robust phenotypes have been constructed by increasing the dosage of human alleles. However, for most of the disorders listed in the DSM-IVTR, few highly penetrant alleles, if any, have been identified.

A second consideration is how clearly the chosen genetic variant correlates with a specific disorder. Unfortunately, even highly penetrant mutations are associated with different syndromes, even in the same family. The same *Disc1* mutation gives rise to schizophrenia, bipolar disorder and depression with psychosis, even in a single extended family, whereas several autism-associated genes are also associated with schizophrenia[11,16,18,23,37,69,70]. The mechanisms by which a given genetic variant produces different phenotypes in different individuals may depend on other genes, on stochastic developmental events producing epigenetic modifications or on unknown environmental factors. This greatly complicates the fidelity of any mouse model made with that genetic variation for a given syndrome.

Third, the slippery nature of construct validity for animal models based on genetic manipulation reflects the current state of human genetics, even for autism, schizophrenia and bipolar disorder, which are highly genetically influenced and are among the best studied of genetically complex neuropsychiatric disorders[71]. These syndromes are associated with both large numbers of common genetic variants of small effect and rare, more highly penetrant mutations. Thus, different affected individuals likely have different genetic pathways to each of these disorders.

Fourth, construct validity becomes difficult to defend *per se* when transgenic animals are produced using common genetic variants, often single nucleotide polymorphisms, that contribute small increments of risk for a disorder. Variants that have not been shown to be statistically significantly associated with human disease in large enough studies or by meta-analysis should be approached with caution. Even for intrepid investigators who are willing to assume significant association in the face of suggestive, but uncertain, human genetics data, it is still important to retain skepticism about the magnitude of effect that the variant under study can produce. In this regard, we disagree with researchers who too readily accept assertions of construct validity for models expressing common genetic variants of small effect. Indeed, with common polymorphisms of small effect, it is highly likely that the genetic background of the mouse will dominate the effects of the transgene.

Finally, across all of medicine, not limited to neuropsychiatric disorders, it is often asked whether studies of familial forms of illness caused by rare mutations shed light on common, genetically complex forms of the disorders. This question has, for example, been raised about such mouse models of autism spectrum disorders, of schizophrenia resulting from chromosome 22q11.2 microdeletions and of Alzheimer's disease. The ultimate answers concerning broad relevance are ultimately empirical matters that may well differ from disorder to disorder. Given our present state of knowledge, however, it seems far more prudent from a biological point of view to focus, where possible, on highly penetrant mutations rather than on variants that exert only small effects on human disease risk.

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straightforward case, there is much room for disagreement in selecting thresholds for construct validity of environmental insults, given their frequent lack of specificity; virtually all environmental contributions to mental illness, such as stress or childhood adversity[25], are associated with multiple disorders and most often normal outcomes. Given the pleomorphic effects of genes in the brain, the shallow and phenomenological nature of current disease classification for mental disorders[7], and the still evolving understanding of how disease-associated genes correlate with disease phenotypes[23], it is critical to be circumspect about when construct validity is achieved and, if so, how best to use the resulting model.

Face validity indicates that a model recapitulates important anatomical, biochemical, neuropathological or behavioral features of a human disease. As stated earlier, however, there are few, if any, neurobiological abnormalities that are known with certainty to be hallmarks or biomarkers of common mental illnesses. Consequently, behavioral features reminiscent of a human disorder are still required to achieve face validity. Unfortunately, it is not likely that any animal model of a neuropsychiatric disorder would recapitulate all of the behavioral features observed in humans or even that single behaviors will precisely model the human situation. Moreover, the diagnosis of a given disorder can be highly variable and inexact (**Box 1**). Thus, judgments of face validity will often be contested, putting the onus on authors to make explicit arguments for and against face validity in a proposed animal model.

Predictive (or pharmacological) validity signifies that a model responds to treatments in a way that predicts the effects of those treatments in humans. For neuropsychiatric disorders, however, predictive validity is a highly vexed concept. As stated earlier, the targets of the major classes of drugs that treat neuropsychiatric disorders were identified *post hoc* by studying the mechanism of action of drugs identified by serendipity[4]. To discover new drugs, several behavioral screens were developed (**Supplementary Tables 2–4**) that used the animal nervous system as a black box, with behavior as its readout, to detect drugs that act in similar fashion to existing reference compounds. These screens were not developed as mechanistic models of drug action, nor have they been shown to reflect either the pathophysiological processes of human disease or the therapeutic mechanism of action of the reference compounds. These screens also may not detect potential efficacy of compounds that interact with distinct molecular targets. A frequent failing of the literature is the use of such screens as if they were based on validated pathophysiological models.

Table 1 Approaches to constructing animal models of neuropsychiatric disorders

General approach	Specific method	Strengths	Weaknesses
Genetics	Selective breeding	Focus on phenotypes of interest	May produce a phenocopy of human disorder
	Random mutation and screening	Focus on phenotypes of interest	May produce a phenocopy of human disorder
	Transgenic animals (for example, knockouts, knockins, overexpression)	Recapitulates genetic abnormality in human disorder; focus on gene of interest	Variable penetrance of genetic abnormality in rodents
			Human relevance of phenotype may be difficult to establish
	Virally mediated gene delivery to brain	Spatial and temporal control over genetic change; focus on gene of interest	Does not recapitulate genetic cause of human disorder
Pharmacological	Administration of neurotransmitter agonist or antagonist	Temporal and some spatial (with intracranial delivery) control; focus on neurotransmitter system of interest	Lack of evidence that common mental disorders involve selective lesions of a single neurotransmitter system
Environmental	Chronic social stress (adult or during development)	May recapitulate risk factors in humans	Lack of specificity for a given human disorder
	Chronic physical stress	Easy to administer	Lack of construct validity for most human disorders
Electrical stimulation and lesions	Brain stimulation, including optogenetic approaches	Spatial and temporal control over neural circuit function; may recapitulate some findings in humans with DBS	Current limitations in knowledge of neural circuit abnormalities in human disorder
	Anatomical lesions	May produce behavioral abnormalities reminiscent of human disorder	Lack of evidence for anatomical lesions as cause of human disorder

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Animal models of schizophrenia

Schizophrenia is a devastating disorder with typical onset between late teen years and early thirties[26]. Twin and adoption studies have confirmed that schizophrenia is highly genetically influenced, but the genetics have proven to be markedly complex[23], with risk resulting from the interplay of diverse genetic variants with stochastic and environmental factors. The fundamental pathophysiology is likely neurodevelopmental, but, given the etiologic complexity, there are probably multiple variations on that pathophysiological theme. Three major symptom clusters, positive, negative and cognitive symptoms, have been identified in schizophrenia, which presumably reflect diverse downstream consequences of the initiating developmental abnormalities[4,27]. Positive symptoms include hallucinations and delusions, experiences that are not characteristic of normal mental life. Negative symptoms represent deficits in normal functions, such as blunted affect, impoverished speech, asocial behavior and diminished motivation. Cognitive symptoms include deficits in working memory and conscious control of behavior. Current antipsychotic drugs are efficacious for positive symptoms, but, with small exceptions, lack efficacy for negative and cognitive symptoms[28].

Additional abnormalities have been observed among individuals with schizophrenia in laboratory settings that may not be experienced by individuals as symptoms. One example, a deficit in prepulse inhibition (PPI), is germane to the present discussion, because it can readily be studied in animals[29]. PPI describes the phenomenon in which a weak initial stimulus (the prepulse) inhibits the startle response that is elicited by a strong stimulus. Deficient PPI is thought to demonstrate impaired sensorimotor gating that occurs in schizophrenia and in several other neuropsychiatric disorders.

Much research, still inconclusive, has focused on the neurobiological abnormalities that might underlie the symptoms of schizophrenia. Among the best-replicated neural abnormalities is thinning of the cerebral cortex, most severely in prefrontal and temporal regions[30,31]. This is thought to result from impoverishment of the dendritic arbors of cortical neurons rather than from cell death. In addition, there is reduced synthesis of GABA, the brain's major inhibitory neurotransmitter, in parvalbumin-expressing cortical interneurons. Both abnormalities have been hypothesized to underlie the cognitive symptoms of schizophrenia[32]. Positive symptoms have been hypothesized to reflect a different set of neural abnormalities, involving excessive dopamine release in ventral and perhaps dorsal striatal projections of midbrain dopamine neurons[33]. Negative symptoms have heterogeneous neurobiological underpinnings. Despite promising leads, the causal relationship between neural abnormalities and the three main symptom clusters remains uncertain. Developmental mechanisms that might tie different neurobiological abnormalities together remain largely hypothetical.

Generating animal models of schizophrenia

Genetic animal models developed from highly penetrant human mutations[34,35] are, arguably, good candidates for satisfying construct validity. For example, chromosome 22q11.2 microdeletions that produce velocardiofacial syndrome are associated with a schizophrenia-like syndrome in roughly 30% of cases[36]. Mice that lack genes in homologous regions of the mouse genome have been generated. However, even here, caution is required, as many individuals with the deletion are diagnosed, not with schizophrenia, but with bipolar disorder or any of several other psychiatric syndromes, and work is ongoing to identify which of the deleted genes produce the relevant behavioral abnormalities in mouse models[36,37]. Another example is a translocation that disrupts the gene *Disrupted in schizophrenia-1* (*Disc1*), which was first associated with schizophrenia in a Scottish family. Several studies have generated mice with *Disc1* mutations and some of these mice show behavioral abnormalities reminiscent of schizophrenia[38]. However, as described in **Box 2**, mutations of *Disc1* have been associated with multiple disorders, even in the index family[39]; thus, the construct validity of these mice as models of schizophrenia *per se* is open to debate.

As emphasized in **Box 2**, genetic animal models based on common variants of small effect should be treated with skepticism. This is illustrated by a common valine/methionine (Val/Met) polymorphism in the gene encoding catechol-O-methyltransferase (COMT)[40], an enzyme that degrades catecholamine neurotransmitters. Associations between the Val/Met polymorphism and schizophrenia have both been reported and disconfirmed, as is common for variants that exert small, if any, effects on risk[41]. It appears unlikely that this polymorphism is associated with schizophrenia and it is uncertain whether it is associated with human cognitive phenotypes[42]. However, even if the Val/Met polymorphism is associated with schizophrenia, it would contribute a very

small increment of risk and would not likely produce a disease-relevant phenotype on its own if expressed in mice. Genetic animal models made with polymorphisms of small effect may exhibit interesting neurobiological properties, but we would argue that it is premature to accept such animals as exhibiting construct validity as disease models.

Similarly, although environmental risk factors for schizophrenia have been studied extensively, even the best replicated to date are not adequately specific nor of large enough effect size to achieve construct validity when used to generate animal models. For example, one group of putative environmental models uses prenatal viral infection (for instance, influenza) to induce behavioral and neural abnormalities, but the role of viral infection in schizophrenia[43] remains a matter of contention. Consequently, efforts to claim construct validity must be seen as highly speculative.

Other attempts have used pharmacology, genetic tools or lesions to recapitulate symptoms of schizophrenia. The efficacy of D_2 dopamine receptor antagonist drugs in treating positive symptoms of schizophrenia historically gave rise to various dopamine hypotheses. Subsequently, the observation that NMDA glutamate receptor antagonists, such as phencyclidine (PCP) and ketamine, produce psychotic symptoms and cognitive disturbances reminiscent of schizophrenia gave rise to glutamate hypotheses. Diverse animal models have thus been based on manipulations of dopamine or glutamate function. The construct validity of these models requires strong argument, however, as the putative dopaminergic or glutamatergic abnormalities in schizophrenia are not precisely established.

For example, transgenic mice were recently developed to examine the hypothesis that some symptoms of schizophrenia result from hypofunction of NMDA glutamate receptors expressed by cortical GABAergic interneurons[44]. In these mice, the NMDA receptor NR1 subunit was selectively eliminated in about half of cortical interneurons early in postnatal development. These mice exhibit deficits in mating, nest building and novelty-induced hyperlocomotion[44]. The mice are undoubtedly a useful tool for examining the biological and behavioral consequences of NMDA receptor hypofunction. The important question is whether the resulting disruption of cortical interneuron function supports an NMDA receptor hypothesis of schizophrenia with implications for pathophysiology and treatment development. The case for construct validity seems weak, given the lack of compelling human genetic evidence to implicate genes encoding NMDA receptor subunits in schizophrenia, and there is no consensus on altered subunit levels in postmortem human brain studies. Without supporting human genetic or proteomic evidence, it would be circular to argue that inactivation of NR1 is a validator. Thus, the degree to which such a mouse can be considered to be a disease model that tests the glutamate hypothesis depends on the degree to which the behavioral abnormalities can be seen as rodent analogs for symptoms of schizophrenia or another major neuropsychiatric disorder (face validity) and whether appropriate symptoms are ameliorated by drugs known to treat schizophrenia (predictive validity). Given the neurobiological heterogeneity of negative symptoms, such as social deficits, and their occurrence in other neuropsychiatric disorders, this argument would seem challenging. As a general matter, it would be useful for researchers to state the goals of their model; for example, for schizophrenia, whether they are modeling underlying developmental pathologies, positive, negative or cognitive symptom clusters, or some other clearly delineated aspect of the disorder. Greater conceptual clarity (for example, see refs. 45,46) would offer referees and readers alike a framework in which to judge both the validity and utility of the proposed model.

Validating animal models of schizophrenia

Diverse behavioral assays have been developed to assess the face validity of animal models of schizophrenia (**Supplementary Table 2**). Historically, screens were developed to identify new antipsychotic drugs on the basis of the behavioral effects of early drugs such as chlorpromazine. With the recognition that all efficacious antipsychotic drugs are antagonists (or weak partial agonists) of D_2 dopamine receptors, it was recognized that drug screens, such as apomorphine-induced cage climbing and catalepsy, detect motor deficits associated with Parkinson-like side effects of these drugs and not their antipsychotic efficacy *per se*[4]. Deficits in motor behavior represent 'on target' toxicities of antipsychotic drugs, given that they result from blockade of the same molecular target (D_2 receptors) involved in efficacy for this class of drugs. Such older drug screens have, for the most part, appropriately been supplanted in the literature as putative validators of animal models. A possible exception is amphetamine- and NMDA glutamate receptor antagonist–induced locomotor activation and sensitization. Amphetamine causes synaptic dopamine release by acting directly on presynaptic terminals of dopamine neurons[4]. NMDA receptor blockers also cause dopamine release, but do so indirectly[4]. Not surprisingly, current antipsychotic drugs (that is, D_2 antagonists) inhibit the dopamine-mediated locomotor effects of these drugs. Animal models exhibiting excessive amphetamine-induced locomotor activation have arguably gained some measure of face validity given findings from single photon and positron emission tomography that individuals with schizophrenia have excessive striatal dopamine release in response to an amphetamine challenge compared with healthy controls[33]. That said, locomotor activation does not correspond convincingly to any of the cardinal symptoms of schizophrenia.

More recently, cognitive deficits characteristic of schizophrenia (but missing from DSM-IVTR) have been used to evaluate animal models[44–46]. Although deficits in attention, working memory and executive function are not individually specific to schizophrenia, they are important and disabling features of the disorder; thus, animal models that reproduce such symptoms have some claim on face validity. Given advances in studies of both human and animal cognition, this is likely a promising area for animal models.

Dopamine, glutamate and other mechanisms have also been examined for their effects on PPI. PPI deficits can be induced in normal rodents by amphetamine or NMDA receptor antagonists and can be alleviated by D_2 antagonists in several animal models of schizophrenia[29]. An advantage of PPI is that deficits are documented in many individuals with schizophrenia. A limitation is that PPI deficits are not specific; they occur in other conditions, including Alzheimer's disease. Thus, PPI can contribute to establishment of face validity, but does not, by itself, make the case.

Although negative symptoms of schizophrenia, such as asociality, amotivation, anhedonia and blunted affect, can be modeled in animals, such symptoms also occur in other disorders (for example, autism and depression) and little is known of their neural underpinnings. Consequently, models based largely on negative symptoms are, for now, best seen with skepticism.

Animal models of depression

Although much has been learned about the neural circuitry of mood on the basis of brain imaging studies, and a host of neurochemical and neuroendocrine disturbances have been described in depressed individuals, no abnormality has proven sufficiently robust or consistent enough to either diagnose depression in humans or validate an animal model[10]. In addition, highly penetrant genetic variants that cause depression have not yet been identified. These considerations highlight the challenge in constructing and validating animal models of depression.

Depression is diagnosed on the basis of a cluster of highly variable symptoms (DSM-IVTR; **Box 1**). In addition to depressed or irritable

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mood, depression includes cognitive symptoms (guilt, ruminations and suicidality), emotional symptoms (anhedonia), homeostatic or 'neurovegetative' symptoms (for example, abnormalities in sleep, appetite, weight and energy), and psychomotor agitation or retardation. Only a subset (homeostatic symptoms, anhedonia and psychomotor behavior) can be measured objectively in rodents (**Supplementary Table 3**).

In addition, depression is often characterized by excessive activity of the hypothalamic-pituitary-adrenal (HPA) axis that regulates stress responses[4]. Such abnormalities are not universally observed in human depression, nor are they adequately specific to provide diagnostic criteria. Nonetheless, they are robust enough to be usefully exploited both in producing and testing animal models.

Generating animal models of depression

In the absence of known highly penetrant genetic causes of depression, much work in animal modeling has relied on the observation that stress and emotional losses are potent risk factors. Several chronic stress procedures have been employed, seeking to achieve a measure of construct validity. Chronic mild or chronic unpredictable stress involves subjecting normal rodents to a series of repeated physical stresses (for example, restraint, foot shock and cold temperature) over a period of weeks or longer[47]. At the end of the stress, the animals show signs of anhedonia (for example, reduced sucrose preference; face validity), which can be reversed by chronic, but not acute, administration of antidepressant medications (predictive validity).

Chronic social defeat stress involves subjecting rodents to repeated bouts of social subordination, after which the rodents show a range of depression-like symptoms, including anhedonia and social withdrawal, which can be reversed by chronic, but not acute, antidepressants[48]. Chronic social defeat also induces a metabolic syndrome in mice characterized by weight gain and insulin and leptin resistance[49], consistent with homeostatic abnormalities observed in depression. A further advantage of chronic social defeat is that it can be used to study 'resilience', as a subset of mice, subjected to the same stress, fail to develop behavioral and metabolic disturbances. Thus, the social defeat procedure exhibits features of construct, face and predictive validity, although the intensity of the stress used is more severe than that seen in most humans. Similar validity has been established for early life stress, such as maternal separation, which induces life-long behavioral and neuroendocrine abnormalities in the pups, some of which can be reversed by antidepressant medications[50]. In contrast with all of these forms of 'active' stress, it was recently found that prolonged exposure (weeks to months) of adult rodents to social isolation induces anhedonia that can be treated effectively with chronic antidepressants[51].

Finally, several procedures have disrupted an animal's glucocorticoid homeostasis, based on derangements in the HPA axis in depression. In some models, animals are treated chronically with glucocorticoids[52]. In others, genetic mutant mice express abnormal levels of glucocorticoid receptors in the brain to disrupt the normal feedback inhibition that occurs[53]. These models display anhedonia that is reversible with antidepressants. However, abnormalities in the HPA axis are highly variable in human depression, which means that researchers using HPA axis abnormalities to argue for construct or face validity should explicitly defend these choices and ideally rely on additional validators.

Validating animal models of depression

Unfortunately, widely used behavioral tests, the forced swim and tail suspension tests[54,55], are not models of depression at all (**Supplementary Table 3**). Instead, they are rapid, black box tests developed decades ago to screen compounds for antidepressant activity. In both tests, normal rodents are subjected to an acute, short-duration (minutes) stress and the time during which they respond actively versus passively is measured. Currently used antidepressant medications, after single doses, increase the time of active responding, often described as reducing behavioral despair. This enormous anthropomorphic leap has not been convincingly related to pathophysiology.

The learned helplessness test can be viewed as analogous to the forced swim and tail suspension tests, although the former involves a series of stresses and antidepressant treatments, albeit only over a few hours or days[56]. A major weakness of all three tests is that they involve short-term stress applied to normal rodents, which is very different from human depression, in which an underlying genetic vulnerability combines with stochastic and chronic environmental exposures to produce long-lasting behavioral pathology. Similarly, the ability of antidepressants to produce a rapid response after single doses in these tests contrasts markedly with the well-established need to use antidepressants chronically (weeks to months) to obtain a clinical response in humans. It also remains unknown whether these tests are sensitive to non-monoaminergic mechanisms of antidepressant action[57]. Despite these weaknesses, the forced swim, tail suspension and learned helplessness tests are used, all too often without comment, to argue that a genetic mutation or other experimental manipulation has produced a depression- or antidepressant-like effect in rodents.

A second major class of tests of depression-related behavior involves measuring anhedonia or homeostatic symptoms[47,48]. This approach has the advantage of being based on symptoms of depression, and therefore yielding more convincing face validity, rather than on properties of current antidepressants. Most frequently examined is an animal's interest in pleasurable activities, such as preference for a sucrose solution over water or engaging in social or sexual behavior. Models with decreased sucrose preference, not resulting from a motor or sensory deficit, are interpreted as demonstrating anhedonia and thus depression-like behavior. Although anhedonia is not specific to depression (it is also seen in schizophrenia and stimulant withdrawal), it is a core symptom of depression about which there are testable neurobiological hypotheses, making it an attractive target for investigation in animal models.

Another confounding issue for current behavioral tests of depression is the interpretation of anxiety-like phenomena. Although it is true that many individuals with major depression also exhibit anxiety, the underlying neural circuitries are thought to be distinct[4]. Many stress-based rodent models exhibit anxiety-like behavior in a range of assays, such as the elevated plus maze, dark-light test and open field test, all of which were developed to detect benzodiazepine-like anxiolytic drugs. These tests exploit the balance between the preference of rodents for avoiding open exposure to predators versus exploration for possible rewards. Novelty-suppressed feeding, in which rodents placed in a novel environment show a latency to consume food, responds to chronic, but not acute, doses of antidepressant drugs (the result being decreased latency to feed). It is unclear whether this result demonstrates what is already known in humans, that is, that chronic antidepressant administration treats anxiety disorders as well, or another observation that is well known in humans, the frequent intermixture of symptoms of depression and anxiety. In sum, depression and anxiety-like symptoms both occur in some, but not all, animal models[48,51,58]. Our ability to make sense of these observations in rodents is hindered by our lack of understanding of the boundaries between several depression and anxiety syndromes in humans.

In our view, assays based on acute stress procedures or anxiety-like behavior might be useful in initial screens, but such screens should not be used as definitive evidence of a depression phenotype. We also suggest a greater focus on anhedonia and homeostatic symptoms and broadening the scope of these assays. For example, in addition to sucrose preference, measures of other reward-related behavior (for

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example, social interaction and sexual behavior) or direct assessments of the sensitivity of the brain's reward circuitry (for example, intracranial self-stimulation[59,60]) might be considered. In addition, a range of homeostatic symptoms (alterations in sleep, circadian rhythms and feeding with attendant metabolic parameters) that are common in depressed humans, but only infrequently examined in animal models, would add a useful objective dimension to rodent studies.

Animal models of bipolar disorder

Bipolar disorder is diagnosed by episodes of mania, with or without depression. Although bipolar disorder is highly genetically influenced, the identification of genetic risk factors is still in early stages[61]. Lacking well-replicated, highly penetrant mutations or deep understanding of pathophysiology, the field has struggled to develop rodents that exhibit mania-like symptoms and has been unable to develop rodent models exhibiting spontaneously alternating episodes of mania- and depression-like behaviors[55].

The most often used model of mania-like behavior involves treating normal rodents with psychostimulants, such as cocaine or amphetamine[62]. Repeated administration of psychostimulants causes sensitization of the acute locomotor-activating effects of the drugs, which in some studies can be blunted by Li^+ or valproate, two important treatments for mania in humans, thus arguing for predictive validity. The weakness of this model is that there is no evidence that the molecular and cellular adaptations underlying psychostimulant-induced sensitization have anything in common with the pathophysiology of mania. Several seizure-based models have also been used, including amygdala kindling and lithium-pilocarpine induced seizures[63], however, these models too lack both construct and face validity.

More recently, some transgenic mice have been reported to exhibit manic-like behavior[64]. Overexpression of glycogen synthase kinase-3β (GSK3β) was found to induce hypophagia, hyperlocomotion, reduced immobility in the forced swim test and reduced anxiety-like behavior in several standard assays (inferred to represent risk-taking behavior)[65]. This study was based on the knowledge that Li^+ inhibits GSK3β. However, Li^+ has numerous molecular actions and there is still no information as to which is responsible for its anti-manic effects in humans[4,66,67]. As another example, mice with a loss-of-function mutation in the *Clock* gene exhibit a similar range of mania-like symptoms, which in this case could be reversed by chronic Li^+ administration[68]. This is an intriguing finding, as circadian abnormalities are prominent in bipolar individuals; however, there is no evidence for circadian gene mutations in the vast majority of cases of bipolar disorder. The GSK3β and *Clock* mutants thus meet some criteria for face and predictive validity, but not construct validity.

In this context, we suggest that studies aimed at investigating mania or manic-depressive illness use a broad range of behavioral tests (**Supplementary Table 4**), including predictive validation with commonly used mood stabilizing medications, and that researchers interpret such data with caution and skepticism. The hope is that placing bona fide bipolar-causing mutations in mice will produce better models of this illness, particularly in the occurrence of both depressive and manic episodes.

Conclusions

The development of convincing and useful animal models for neuropsychiatric disorders represents a major challenge. However, despite the hurdles, such models appear to be necessary for understanding disease pathophysiology and for hastening the development of treatments based on new molecular targets. We have illustrated some of the difficulties and have suggested approaches to thinking about generating and validating such models. Most importantly, we think it highly unlikely that animal models, especially in organisms as neurobiologically different from humans as rodents, can be expected to recapitulate all of the salient features of a human mental illness or even to have perfect correspondence with respect to individual behavioral symptoms. Above all, models are meant to serve as investigative tools. Thus, most important in developing, examining and reporting on animal models of disease is to be clear about the goals of the model and, in that context, to critically judge construct, face and predictive validity (**Box 3**).

Given the current uncertainties related to genetic and nongenetic risk factors, pathophysiology, and even the nosology of the human disorders, and given the lack of objective medical tests or biomarkers for virtually all mental illnesses, there will be reasonable disagreement concerning judgments of construct, face and predictive validity of different models. That said, we would argue that some generalizations can be made.

With current technology, transgenic animals produced with common genetic variants of small effect should not ordinarily be considered to achieve construct validity. At this point in time, effort would be better focused on rare Mendelian forms of disorders or highly penetrant mutations where they have been demonstrated to exist. The lack of currently known mutations of high penetrance that might cause depression or bipolar disorder does not make animals produced with single polymorphisms of small effect any more convincing or useful.

We would now eschew the all too common practice of using black box behavioral tests developed as drug screens as if they confer face validity. A corollary of this is that tendentious anthropomorphizations, such as describing responses in the forced swim test as behavioral despair, should be avoided in the scientific literature. In reporting symptoms that appear in animal models, it is most helpful if they were discussed in terms of

BOX 3 RECOMMENDATIONS TO RESEARCHERS

Recommendations for describing animal models of neuropsychiatric disorders

1. State the goal. Is this a neurobiological tool or a disease model?
2. State the hypothesis to be tested.
3. List the specific aspects of the illness meant to be modeled.
4. State the type(s) of validators (for example, construct, face and predictive) applied to the model.
5. State the evidence for and against the validity of the model in the context of the validator(s) used.

Currently recommended areas of focus for animal models of neuropsychiatric disorders

1. Construct validity is generally the most compelling and useful approach.
2. To maximize construct validity, focus, where possible, on replicated risk alleles with high penetrance.
3. Studies of depression and bipolar disorder models produced by environmental manipulations and validated by treatment response should focus on chronic, rather than acute, environmental manipulations and chronic responses to treatment.
4. All putative animal models should be evaluated with the broadest range possible of behavioral assays.

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hypothesized pathophysiology, including situations in which symptoms are clustered on the basis of shared neurobiological mechanisms (for example, positive or cognitive symptoms of schizophrenia; mood, anxiety, homeostatic or cognitive symptoms of depression). Such information can help to determine whether behavioral phenotypes in a putative model may be connected by neural mechanisms relevant to the human disorder as opposed to chance findings that are reminiscent of human symptoms.

Perhaps the greatest disappointment with existing animal models of neuropsychiatric disorders is that they have failed, over several decades, to predict treatment efficacy in humans for previously unknown mechanisms of action. Of course, such failures also reflect the current state of clinical knowledge with a lack of objective diagnostic tests and validated biomarkers of these highly heterogeneous illnesses. Our hope is that clinical advances driven by progress in genetics, which may await full sequencing of the genomes of large numbers of affected individuals, combined with human experimental neurobiology ranging from neuroimaging to deep brain stimulation will facilitate the development of better validated and more useful animal models. We look forward to models with clearly stated rationales and sober discussions of validity as disease models as opposed to simple neurobiological tools. Given the fact that human genetics is ultimately an observational, rather than an experimental, science, and given the ethical and practical limitations to human experimental biology, animal models will almost certainly be a necessary aspect of progress in both pathophysiology and treatment development.

Note: Supplementary information is available on the Nature Neuroscience website

COMPETING FINANCIAL INTERESTS

The authors declare competing financial interests: details accompany the full-text HTML version of the paper at www.nature.com/natureneuroscience/.

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1. Kessler, R.C. *et al.* Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch. Gen. Psychiatry* **62**, 593–602 (2005).
2. Kessler, R.C. *et al.* Age of onset of mental disorders: a review of recent literature. *Curr. Opin. Psychiatry* **20**, 359–364 (2007).
3. World Health Organization. *World Health Report 2001* (World Health Organization, Geneva, 2001).
4. Nestler, E.J., Hyman, S.E. & Malenka, R.C. *Molecular Neuropharmacology: a Foundation for Clinical Neuroscience,* 2nd edn (McGraw-Hill, New York, 2009).
5. Markou, A., Chimmulera, C., Geyer, M.A., Tricklebank, M. & Steckler, T. Removing obstacles in neuroscience drug discovery: the future path for animal models. *Neuropsychopharmacology* **34**, 74–89 (2009).
6. *Diagnostic and Statistical Manual of Mental Disorders.* 4th edn, text revision (American Psychiatric Association Press, Washington, DC, 2000).
7. Hyman, S.E. The diagnosis of mental disorders: the problem of reification. *Annu. Rev. Clin. Psychol.* **6**, 155–179 (2010).
8. Götz, J. & Ittner, L.M. Animal models of Alzheimer's disease and frontotemporal dementia. *Nat. Rev. Neurosci.* **9**, 532–544 (2008).
9. Morrissette, D.A., Parachikova, A., Green, K.N., & LaFerla, F.M.. Relevance of transgenic mouse models to human Alzheimer disease. *J. Biol. Chem.* **284**, 6033–6037 (2009).
10. Krishnan, V. & Nestler, E.J. Molecular neurobiology of depression. *Nature* **455**, 894–902 (2008).
11. Welch, J.M. *et al.* Cortico-striatal synaptic defects and OCD-like behaviors in *Sapap3*-mutant mice. *Nature* **448**, 894–900 (2007).
12. Chen, S.-K. *et al.* Hematopoietic origin of pathological grooming in *Hoxb8* mutant mice. *Cell* **141**, 775–785 (2010).
13. Shahbazian, M. *et al.* Mice with truncated MeCP2 recapitulate many Rett syndrome features and display hyperacetylation of histone H3. *Neuron* **35**, 243–254 (2002).
14. Tabuchi, K. *et al.* A neuroligin-3 mutation implicated in autism increases inhibitory synaptic transmission in mice. *Science* **318**, 71–76 (2007).
15. Jamain, S. *et al.* Reduced social interaction and ultrasonic communication in a mouse model of monogenic heritable autism. *Proc. Natl. Acad. Sci. USA* **105**, 1710–1715 (2008).
16. Morrow, E.M. *et al.* Identifying autism loci and genes by tracing recent shared ancestry. *Science* **321**, 218–223 (2008).
17. Moy, S.S. & Nadler, J.J. Advances in behavioral genetics: mouse models of autism. *Mol. Psychiatry* **13**, 4–26 (2008).
18. Buxbaum, J.D. Multiple rare variants in the etiology of autism spectrum disorders. *Dialogues Clin. Neurosci.* **11**, 35–43 (2009).
19. Etherton, M.R., Blaiss, C.A., Powell, C.M. & Sudhof, T.C. Mouse neurexin-1 alpha deletion causes correlated electrophysiological and behavioral changes consistent with cognitive impairments. *Proc. Natl. Acad. Sci. USA* **106**, 17998–18003 (2009).
20. Silverman, J.L., Yang, M., Lord, C. & Crawley, J.N. Behavioral phenotyping assays for mouse models of autism. *Nat. Rev. Neurosci.* **11**, 490–502 (2010).
21. Gradinaru, V. *et al.* Molecular and cellular approaches for diversifying and extending optogenetics. *Cell* **141**, 154–165 (2010).
22. Chadman, K.K., Yang, M. & Crawley, J.N. Criteria for validating mouse models of psychiatric diseases. *Am. J. Med. Genet. B Neuropsychiatr. Genet.* **150B**, 1–11 (2009).
23. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748–752 (2009).
24. Aguzzi, A., Sigurdson, C. & Heikenwaelder, M. Molecular mechanisms of prion pathogenesis. *Annu. Rev. Pathol.* **3**, 11–40 (2008).
25. Green, J.G. *et al.* Childhood adversities and adult psychiatric disorders in the national comorbidity survey replication I. *Arch. Gen. Psychiatry* **67**, 113–123 (2010).
26. Saha, S., Chant, D., Welham, J. & McGrath, J. A systematic review of the prevalence of schizophrenia. *PLoS Med.* **2**, e141 (2005).
27. Tamminga, C.A. The neurobiology of cognition in schizophrenia. *J. Clin. Psychiatry* **67** Suppl 9, 9–13 (2006).
28. Keefe, R.S.E. *et al.* Neurocognitive effects of antipsychotic medications in patients with chronic schizophrenia in the CATIE trial. *Arch. Gen. Psychiatry* **64**, 633–647 (2007).
29. Swerdlow, N.R., Weber, M., Qu, Y., Light, G.A. & Braff, D.L. Realistic expectations of prepulse inhibition in translational models for schizophrenia research. *Psychopharmacology (Berl.)* **199**, 331–388 (2008).
30. Cannon, T.D. *et al.* Cortex mapping reveals regionally specific patterns of genetic and disease-specific gray-matter deficits in twins discordant for schizophrenia. *Proc. Natl. Acad. Sci. USA* **99**, 3228–3233 (2002).
31. Lewis, D.A. & Sweet, R.A. Schizophrenia from a neural circuitry perspective: advancing toward rational pharmacological therapies. *J. Clin. Invest.* **119**, 706–716 (2009).
32. Lewis, D.A. & Moghaddam, B. Cognitive dysfunction in schizophrenia: convergence of gamma-aminobutyric adic and glutamate alterations. *Arch. Neurol.* **63**, 1372–1376 (2006).
33. Kegeles, L.S. *et al.* Increased synaptic dopamine function in associate regions of the striatum in schizophrenia. *Arch. Gen. Psychiatry* **67**, 231–239 (2010).
34. Arguello, P.A., Markx, S., Gogos, J.A. & Kraiorgou, M. Development of animal models for schizophrenia. *Dis. Model Mech* **3**, 22–26 (2010).
35. Walsh, T. *et al.* Rare structural variants disrupt multiple genes in neurodevelopmental pathways in schizophrenia. *Science* **320**, 539–543 (2008).
36. Green, T. *et al.* Psychiatric disorders and intellectual functioning throughout development in velocardiofacial (22q11.2 deletion) syndrome. *J. Am. Acad. Child Adolesc. Psychiatry* **48**, 1060–1068 (2009).
37. Karayiorgou, M. Simon, T.J., & Gogos, J.A. 22q11.2 microdeletions:linking DNA structural variation to brain dysfunction and schizophrenia. *Nat. Rev. Neurosci.* **11**, 402–416 (2010).
38. Pletnikov, M.V. *et al.* Inducible expression of mutant human DISC1 in mice is associated with brain and behavioral abnormalities reminiscent of schizophrenia. *Mol. Psychiatry* **13**, 173–186 (2008).
39. Brandon, N.J. *et al.* Understanding the role of DISC1 in psychiatric disease and during normal development. *J. Neurosci.* **29**, 12768–12775 (2009).
40. Diaz-Asper, C.M. *et al.* Genetic variation in catechol-O-methyltransferase: effects on working memory in schizophrenic patients, their siblings, and healthy controls. *Biol. Psychiatry* **63**, 72–79 (2008).
41. Allen, N.C. *et al.* Systematic meta-analyses and field synopsis of genetic association studies in schizophrenia: the Sz database. *Nat. Genet.* **40**, 827–834 (2008).
42. Barnett, J.H., Scoriels, L. & Munafo, M.R. Meta-analysis of the cognitive effects of the catechol-O-methyltransferase gene Val158/108Met polymorphism. *Biol. Psychiatry* **64**, 137–144 (2008).
43. Patterson, P.H. Immune involvement in schizophrenia and autism: etiology, pathology and animal models. *Behav. Brain Res.* **204**, 313–321 (2009).
44. Belforte, J.E. *et al.* Postnatal NMDA receptor ablation in corticolimbic interneurons confers schizophrenia-like phenotypes. *Nat. Neurosci.* **13**, 76–83 (2010).
45. Kellendonk, C. *et al.* Tranient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron* **49**, 603–615 (2006).
46. Simpson, E.H., Kellendonk, C. & Kandel, E. A possible role for the striatum in the pathogenesis of the cognitive symptoms of schziphrenia. *Neuron* **65**, 585–596 (2010).
47. Willner, P. Chronic mild stress (CMS) revisited: consistency and behavioural-neurobiological concordance in the effects of CMS. *Neuropsychobiology* **52**, 90–110 (2005).
48. Krishnan, V. *et al.* Molecular adaptations underlying susceptibility and resistance to social defeat in brain reward regions. *Cell* **131**, 391–404 (2007).
49. Chuang, J.C. *et al.* A b_3-adrenergic-leptin-melanocortin circuit regulates behavioral and metabolic changes induced by chronic stress. *Biol. Psychiatry* **67**, 1075–1082 (2010).
50. Meaney, M.J. Maternal care, gene expression and the transmission of individual differences in stress reactivity across generations. *Annu. Rev. Neurosci.* **24**, 1161–1192 (2001).
51. Wallace, D.L. *et al.* CREB regulation of nucleus accumbens excitability mediates social isolation–induced behavioral deficits. *Nat. Neurosci.* **12**, 200–209 (2009).

52. Gourley, S.L., Kiraly, D.D., Howell, J.L., Olausson, P. & Taylor, J.R. Acute hippocampal brain-derived neurotrophic factor restores motivational and forced swim performance after corticosterone. *Biol. Psychiatry* **64**, 884–890 (2008).
53. Müller, M.B. & Holsboer, F. Mice with mutations in the HPA-system as models for symptoms of depression. *Biol. Psychiatry* **59**, 1104–1115 (2006).
54. Cryan, J.F., Markou, A. & Lucki, I. Assessing antidepressant activity in rodents: recent developments and future needs. *Trends Pharmacol. Sci.* **23**, 238–245 (2002).
55. Nestler, E.J. *et al.* Preclinical models: status of basic research in depression. *Biol. Psychiatry* **52**, 503–528 (2002).
56. Maier, S.F. & Watkins, L.R. Stressor controllability and learned helplessness: the roles of the dorsal raphe nucleus, serotonin and corticotropin-releasing factor. *Neurosci. Biobehav. Rev.* **29**, 829–841 (2005).
57. Berton, O. & Nestler, E.J. New approaches to antidepressant drug discovery: beyond monoamines. *Nat. Rev. Neurosci.* **7**, 137–151 (2006).
58. Carlezon, W.A. Jr., Duman, R.S. & Nestler, E.J. The many faces of CREB. *Trends Neurosci.* **28**, 436–445 (2005).
59. Markou, A. Animal models of depression and antidepressant activity. *Neurosci. Biobehav. Rev.* **29**, 501 (2005).
60. Carlezon, W.A. Jr. & Chartoff, E.H. Intracranial self-stimulation (ICSS) in rodents to study the neurobiology of motivation. *Nat. Protoc.* **2**, 2987–2995 (2007).
61. Craddock, N. & Sklar, P. Genetics of bipolar disorder: successful start to a long journey. *Trends Genet.* **25**, 99–105 (2009).
62. Einat, H. & Manji, H.K. Cellular plasticity cascades: genes-to-behavior pathways in animal models of bipolar disorder. *Biol. Psychiatry* **59**, 1160–1171 (2006).
63. Belmaker, R.H. & Bersudsky, Y. Lithium-pilocarpine seizures as a model for lithium action in mania. *Neurosci. Biobehav. Rev.* **31**, 843–849 (2007).
64. Malkesman, O., Austin, D.R., Chen, G. & Manji, H.K. Reverse translational strategies for developing animal models of bipolar disorder. *Dis. Model Mech.* **2**, 238–245 (2009).
65. Prickaerts, J. *et al.* Transgenic mice overexpressing glycogen synthase kinase 3beta: a putative model of hyperactivity and mania. *J. Neurosci.* **26**, 9022–9029 (2006).
66. Shaldubina, A., Agam, G. & Belmaker, R.H. The mechanism of lithium action: state of the art, ten years later. *Prog. Neuropsychopharmacol. Biol. Psychiatry* **25**, 855–866 (2001).
67. Beaulieu, J.M. *et al.* A beta-arrestin 2 signaling complex mediates lithium action on behavior. *Cell* **132**, 125–136 (2008).
68. Roybal, K. *et al.* Mania-like behavior induced by disruption of CLOCK. *Proc. Natl. Acad. Sci. USA* **104**, 6406–6411 (2007).
69. International Schizophrenia Consortium. Rare chromosomal deletions and duplications increase risk of schizophrenia. *Nature* **455**, 237–241 (2008).
70. O'Donovan, M.C. *et al.* Identification of loci associated with schizophrenia by genome-wide association and follow-up. *Nat. Genet.* **40**, 1053–1055 (2008).
71. Hyman, S.E. A glimmer of light for neuropsychiatric disorders. *Nature* **455**, 890–893 (2008).

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