nature neuroscience

Using model systems to understand errant plasticity mechanisms in psychiatric disorders

Bruno B Averbeck[1] & Matthew V Chafee[2,3]

In vivo **model systems are a critical tool for gaining insight into the pathology underlying psychiatric disorders. Although modern functional imaging tools allow study of brain correlates of behavior in clinical groups and genome-wide association studies are beginning to uncover the complex genetic architecture of psychiatric disorders, there is less understanding of pathology at intervening levels of organization. Several psychiatric disorders derive from pathological neural plasticity, and studying the mechanisms that underlie these processes, including reinforcement learning and spike-timing-dependent plasticity, requires the use of animals. It will be particularly important to understand how individual differences in plasticity mechanisms at a cellular level confer resilience on some but lead to disease in others.**

Understanding the neurobiology of psychiatric disorders requires the use of animals. Functional MRI in patient groups has opened a window into the human brain that provides insight into the networks that may be disrupted in various disorders, and positron-emission tomography can show differences in neurotransmitter systems between patient groups and comparison participants[1]. However, this work only suggests gross anatomical correlates of disorders and provides little insight into the neural mechanisms that are disrupted in patient groups. Some psychiatric disorders are likely due to disordered learning caused by pathology in cellular plasticity mechanisms. Insight into disordered plasticity mechanisms at the cellular and synaptic levels requires experiments in model systems.

While it is clear that animals are necessary to gain an understanding of the mechanistic underpinnings of psychiatric disorders, model systems can be used in many ways[2]. One approach to using animals in psychiatric research, which has failed to yield progress, is to develop an animal model of the disease using a behavior thought to be relevant to the disease in conjunction with a manipulation that affects this behavior. The model is then used as a screen in drug discovery by showing that a drug can ameliorate a behavioral deficit in the model[3,4]. In this approach the model's translational utility is assessed with face, construct and predictive validity[5]. Face validity refers to similarity between behavioral or neural features of a disease and the animal model. As there are no well-validated biomarkers of psychiatric disorders[5], behaviors are usually used to achieve face validity in animal models. However, reducing psychiatric disorders to a single or even a few behaviors is problematic for multiple reasons, including heterogeneity among patients with a single diagnosis.

[1]Laboratory of Neuropsychology, National Institute of Mental Health, National Institutes of Health, Bethesda, Maryland, USA. [2]Department of Neuroscience, University of Minnesota, Minneapolis, Minnesota, USA. [3]Brain Sciences Center, Virginia Medical Center, Minneapolis, Minnesota, USA. Correspondence should be addressed to B.B.A. (bruno.averbeck@nih.gov).

Received 6 June; accepted 13 September; published online 26 October 2016; doi:10.1038/nn.4413

Construct validity refers to the technique used to generate the animal model. If the neuropathological process that gives rise to the disease was understood, and if that process could be recapitulated in an animal model, this would provide strong construct validity. The advent of transgenic rodent models suggested an approach to generating a model system with good construct validity[6]. Specifically, if a candidate gene existed for a psychiatric disorder, the disease-causing allele could be knocked into a rodent. However, it is now clear that psychiatric disorders result from both a large number of common alleles with low penetrance and a much smaller number of very rare alleles with high penetrance[7,8]. In schizophrenia, each mechanism contributes similarly to disease liability in the population[9] and therefore any single gene accounts for a limited fraction of disease cases. Studying the highly penetrant low-frequency alleles[10] may provide insight into general disease mechanisms. However, expression of a gene that leads to disease in the human brain often recapitulates only a subset of disease features in animal models[11], therapies that ameliorate deficits in animal models often fail to translate to humans[12] and genes that have clear phenotypes in animal models[3] often have weak penetrance in human populations.

Predictive validity is the ability of the model to predict whether a new treatment will prove effective in the clinical setting. This is often assessed by determining whether current state-of-the-art treatments are effective in the animal model, although effectiveness is often relative to a behavior that itself lacks sufficient validity. Overall, the validity framework appeared plausible but has been ineffective: the clinical efficacy of antipsychotic medications has not improved over the past 50 years of drug development[13,14].

Identifying mechanisms in model systems

Animal models can also be used to study the neural mechanisms that underlie behavior or behavioral dimensions[3,15,16]. A detailed understanding of pathology in neural mechanisms relevant to psychiatric disorders can give rise to treatments. Going from an understanding of mechanism to treatment is a difficult step in itself, because tools currently available to treat psychiatric disorders are blunt instruments. For example, even in disorders caused by single

gene mutations like Huntington's disease[8], discovery of the gene has led to increased understanding of the underlying pathology but not improvements in treatment. In addition, for this approach to work there needs to be a close collaboration between clinicians and basic scientists, so that highly similar behaviors that are mediated by very similar neural circuits and dynamics within those circuits are studied across species.

Understanding mechanism can, however, lead to improvements in clinical practice. For example, the use of deep-brain stimulation to treat Parkinson's disease was developed from an understanding of how the basal ganglia drives movements[17,18]. Specifically, increased activity in the excitatory subthalamic nucleus (STN) drives increased activity in the inhibitory globus pallidus internal segment (GPi), and this leads to decreased activity in thalamocortical circuits[19], which drive movements. Although current understanding of this system is more complex[20], this simple model does predict the effects of manipulations of this circuit on behavior[21]. Lesions of the STN were shown to ameliorate motor deficits in the macaque MPTP model (which results in loss of dopamine neurons) of parkinsonism[22]. Subsequent work in patients examined stimulation of either GPi or the STN and found that both could alleviate symptoms[23]. While deep-brain stimulation is clinically effective, its specific mechanism of action is still not clear[24]. Although this example shows that understanding disease mechanisms can lead to improvements in treatment, the pathophysiology that underlies Parkinson's disease has been understood since the beginning of the 20th century[25]. In psychiatric disorders we still lack understanding of the pathophysiology[26].

Neuropsychiatric diseases as pathological learning

Understanding pathogenesis in psychiatric disorders is difficult because it requires establishing causal relationships between events that take place at different levels of scale in the brain. Fully understanding the causal chain of events leading to pathology requires understanding how genetic mutations[7,27] produce changes in development[28–30] that interact with the environment[31] to alter the physiology of neurons and synapses[32], changing the patterns of activity generated by networks[33–35] and leading to distortions of perception and cognition[36,37]. We know most about disease at the two extremes of this sequence. What is lacking is a mechanistic understanding of events at intervening levels of scale, where pathogenesis proceeds by changing how neurons and synapses work.

Evidence at genetic and behavioral levels suggests that psychiatric disorders may be disorders of learning. For example, many of the genetic loci associated with schizophrenia are related to synaptic plasticity[7]. In addition, at a behavioral level, drug addiction follows from a pathological association of drug cues and motivational systems, and post-traumatic stress disorder (PTSD) develops when the fear and anxiety driven by a traumatic event does not extinguish. Furthermore, across several disorders, treatments currently being put forward from a mechanistic point of view target NMDA receptors, which are closely related to synaptic plasticity. What is missing, however, is an understanding of the pathology in cellular mechanisms that link genetic predispositions, when they exist, to the deficits in learning at a behavioral level. Disorders in dopamine-driven reinforcement learning[38] and spike-timing-dependent plasticity[39] may underlie pathology in, for example, addiction and schizophrenia. Therefore, close links between genetics, plasticity at a cellular level driven by one of these learning mechanisms, and behavior need to be worked out. Below we consider where studying learning and plasticity in model systems has led to suggestions for novel therapeutics and also consider areas where additional research on these mechanisms is needed. In particular, understanding of how individual differences in plasticity mechanisms confer resiliency on some and lead to disease in others is just beginning in addiction but has been little explored in other disorders.

Relevance of fear learning and extinction to anxiety disorders

Fear conditioning or, more specifically, threat conditioning[40], and its extinction is one of the better-understood behaviors with relevance to psychiatric disorders in systems neuroscience. In the fear conditioning model, a neutral conditioned stimulus (CS) is paired with an unconditioned stimulus (US), which often takes the form of a foot shock[41]. Following a few pairings, the animal forms an association between the CS and the US, such that when the animal is brought back in a subsequent session, presentation of the CS leads to freezing. Considerable work has shown that circuits within the amygdala play a critical role in the association of the CS and the US[42–44]. For example, before the association between the CS and the US, cells in the lateral nucleus of the amygdala (LA) respond only weakly to the CS. However, after the association, the CS drives a robust response in LA neurons[45,46]. Furthermore, the increased response to the CS is largely driven by plasticity in the LA, rather than being inherited from other structures[47,48]. The LA projects directly to the central nucleus (CN) of the amygdala, as well as to the basal nucleus, which also projects to the CN[49]. Freezing following presentation of the CS is driven by descending outputs from the CN of the amygdala to the periaqueductal gray.

Fear extinction is the process of extinguishing the behavioral response to the CS. In the extinction paradigm, once a fear association has been formed, it is extinguished by exposing the animal to the CS in the absence of the US. Following a sufficient number of trials, the freezing response to the CS disappears. While extinction learning has often been thought of as unlearning or erasing the original fear association[50], it is now accepted that most extinction learning (but see[51] and below) is the learning of a new inhibitory association between the CS and no-US, which competes with the original CS–US association[52,53]. This is based on several findings in extinction experiments. Specifically, under renewal, when the CS is extinguished outside of the original context, a return to the original context leads to a return of freezing. Under reinstatement, if the US is delivered by itself following extinction, the CS will subsequently drive freezing. Under recovery, the simple passage of time leads to the reemergence of the fear memory. In addition, after extinction, reassociation of the CS and US in a subsequent conditioning session occurs more quickly, a process referred to as savings. Thus all of these conditions show that the original CS–US association was still present in some form following extinction training.

This work has also been translated to human subjects and clinical studies of anxiety disorders[54–58]. Using functional MRI in healthy human participants, it was shown that the neural circuitry underlying fear learning and extinction is shared across humans and rodents[59]. This work has not, however, translated into a useful biomarker for anxiety. In addition, fear conditioning and extinction in animal models differ from the more complex clinical picture of anxiety disorders. For example, participants with diagnosed PTSD that resulted from a single discrete trauma are hyper-responsive to acoustic startle, consistent with the fear conditioning model, whereas patients with PTSD that resulted from cumulative trauma have decreased response to acoustic startle[60]. Discrete-trauma PTSD patients also respond more readily to exposure therapy than cumulative-trauma patients[61]. In addition to this clinical distinction, fear is an emotional state that can only be assessed in human participants, and fear as an emotion

differs from physiological responses to threat assessed in animals[40]. Meta-analyses suggest that patients with anxiety disorders have a modest increase in acquisition of fear associations, particularly a generalization to safety cues (i.e., CSs not associated with aversive USs) as well as a modest increase in expression of fear during extinction[54]. Like functional imaging data, however, behavioral studies of fear learning are not diagnostic of anxiety disorders because there is a large overlap in behavior across groups. In addition, and perhaps most importantly, individual differences in synaptic plasticity at a cellular level that may underlie resilience in some but result in anxiety disorders in others are not known.

Exposure therapy, derived from fear extinction, is an important component of cognitive behavioral therapy in anxiety disorders[57,62]. Similarly to extinction in rodents, extinction in anxiety disorders leads to temporary relief from symptoms, but often fear returns after the passage of time due to renewal or recovery[63]. This has led to a search for ways to improve exposure therapy by enhancing learning. Two ideas for improvement have come from basic science studies of extinction learning[64]. Specifically, the use of D-cycloserine (refs. 65,66) and reconsolidation–extinction to enhance extinction learning[67,68].

Early experiments showed that blocking NMDA receptors in the amygdala, which interferes with plasticity mechanisms, decreased extinction learning in rodents[69]. It was subsequently shown that D-cycloserine, a noncompetitive NMDA agonist, administered systemically or in the amygdala, could enhance extinction[70]. Follow-up studies showed that D-cycloserine administered to human participants with acrophobia in combination with exposure therapy led to increased extinction learning[71]. Subsequent results have been mixed and current meta-analyses suggest that results are inconclusive, but additional studies should be done to clarify effects and mechanism[72]. Better understanding of the cellular mechanisms that underlie extinction may lead to better treatments to improve extinction learning.

The second approach that has emerged from basic research to increase the effectiveness of exposure therapy is the reconsolidation–extinction paradigm. As discussed above, standard extinction protocols do not lead to erasure of fear memory. Rather they lead to the creation of a new CS–no-US memory that inhibits the original CS–US association. However, when memories are retrieved they become labile and must be reconsolidated[73], a process that requires protein synthesis. This was first exploited in an extinction paradigm in which, during extinction, rats were given a single CS with either anisomycin, which blocks protein synthesis, or artificial cerebrospinal fluid as a control. Freezing to the single CS did not differ by group. However, on the day after the CS was given with anisomycin, presentation of the CS led to less freezing by the rats that had received anisomycin. Unfortunately, anisomycin is toxic in humans. Therefore, a behavioral procedure was developed in an attempt to achieve the same end. In this study, it was shown that if rats were given a single CS presentation either 10 min or 1 h before extinction training, but not 6 or 24 h before extinction training, the return of fear by recovery, reinstatement or renewal was substantially decreased (**Fig. 1**)[67]. This was taken as evidence that, following the reconsolidation–extinction model, the fear memory was permanently attenuated. Subsequent studies suggested that this approach also worked in healthy human subjects, in a fear-learning model[68]. Considerable additional work has followed this finding[51,74]. Current meta-analyses suggest that reconsolidation extinction reduces the return of fear in healthy human participants but not in rodents[75]. Efficacy of this procedure has not yet, however, been examined in clinical groups. These results suggest that bottom-up work in basic science focused on understanding the neural mechanisms that underlie a relevant behavior can drive treatments based on novel mechanisms.

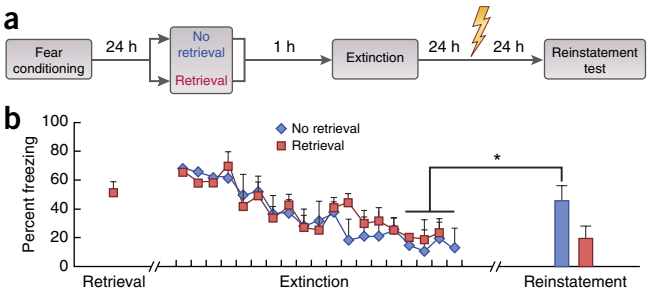

Figure 1 Reinstatement of fear following the retrieval–extinction procedure. (**a**) Conditioning paradigm used to induce and extinguish fear under either a standard extinction protocol or a retrieval–extinction protocol in which a fear memory is retrieved and rendered labile 1 h before extinction. (**b**) Behavioral performance following extinction and reinstatement. Images adapted from ref. 67, AAAS. Error bars are s.e.m.; $*P < 0.05$.

Neural circuits underlying compulsive drug taking

The neural circuitry that underlies addiction has considerable overlap with the circuitry that underlies fear learning[76]. Addiction can be considered a pathological association between cues and appetitive USs (i.e., drugs of abuse) just like fear is a pathological association between cues and aversive USs. The amygdala plays an important role in addiction[77]. However, the dopamine system and the striatum are also heavily implicated. Many drugs of abuse either directly or indirectly increase dopamine signaling[78,79]. There is considerable evidence that dopamine codes reward prediction errors (i.e., the difference between the received and expected reward)[80] and that reward prediction errors are an important component of reinforcement learning, or associating stimuli with prediction of reward[81]. This theory predicts that when outcomes are more rewarding than expected, dopamine is released and the estimate of reward associated with cues, actions or the current context are increased. In explicit versions of this model the dopamine signal drives synaptic plasticity on cortical–striatal synapses, and it is these synapses that encode expected reward[82]. In addition, temporal-difference learning models predict that the first cue that predicts reward drives dopamine release[83]. In a simple appetitive Pavlovian experiment, when a CS is first shown, it will not lead to dopamine release because the CS does not predict reward. If a reward (US) is then delivered following the CS, there will be a dopamine response to the reward. However, following learning, when the CS comes to predict the reward, the dopamine response will shift to the CS because it is the first cue that predicts reward. When the reward is subsequently delivered there will be no dopamine response because the reward has been predicted.

Drugs may drive pathological levels of learning because they drive dopamine release and therefore a constant reward prediction error[84]. Under normal physiological conditions, after learning, the reward prediction would equal the received reward (for example, the sight of a food pellet is a cue that predicts the actual reward obtained when the food pellet is consumed) and the reward prediction error would be zero. With no reward prediction error there would be no dopamine release and no additional learning. However, with drugs of abuse that cause an artificial increase in dopamine levels, there would always be a positive reward prediction error and therefore learning. This would cause value estimates to be driven to pathological levels. Although several general aspects of this model have been

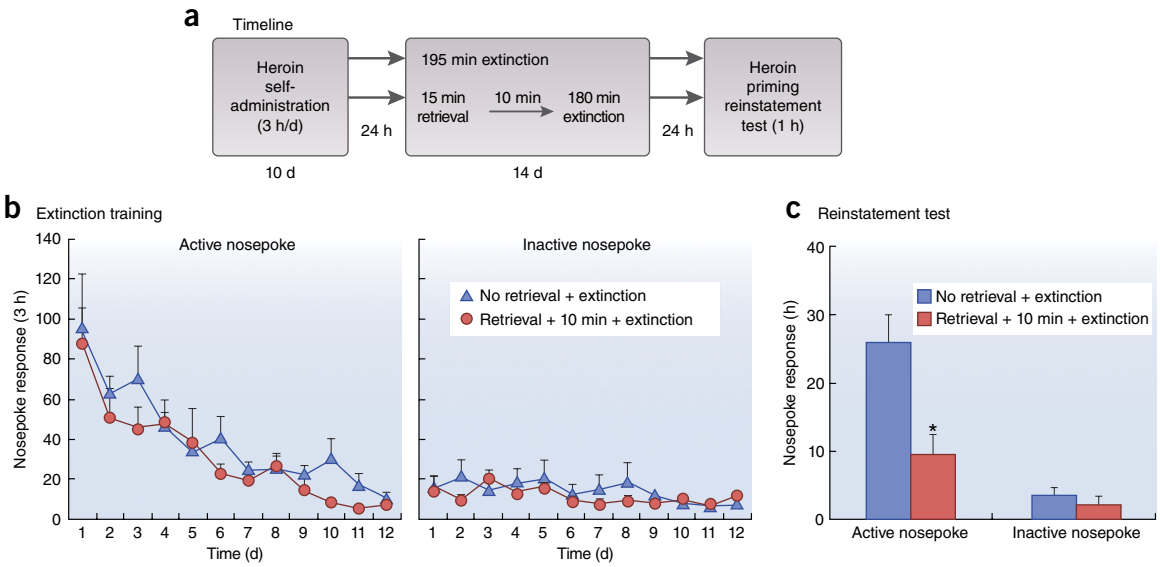

Figure 2 Reinstatement of nose-poke behavior following acquisition and extinction. (**a**) Behavioral procedure used to extinguish heroin self-administration using either a standard extinction protocol or a retrieval–extinction procedure. (**b**) Behavioral response during extinction. (**c**) Active nose-poke behavior following reinstatement driven by heroin delivery. Images adapted from ref. 100, AAAS. Error bars are s.e.m.; $*P < 0.05$.

well-supported by data, some specific predictions of this model have not been supported by subsequent experiments[85].

This model has been used to account for dopamine responses in addiction. Positron-emission tomography work has shown that in addicts, there is a large dopamine response in the striatum to drug cues, which are CSs[86]. However, there is decreased dopamine response to the actual delivery of the drug, which is the US. In addition, it has been shown that the dopamine released in response to the drug cues causes craving in addicts[87].

In addition to dopamine, amygdala-dependent processes have also been implicated in addiction[77,88]. Studies have shown that the amygdala underlies appetitive learning[89,90] in addition to fear learning[42,44]. Recent circuit analyses suggest that it may be the basolateral amygdala projections to the ventral striatum that are important for appetitive learning[90–92], which argues for an interpretation of amygdala contributions to addiction within the dopamine reward prediction error framework. Specifically, this would predict that dopamine is modifying amygdala–ventral striatal synapses, instead of cortical–striatal synapses. However, there is also work that shows plasticity specifically within the amygdala during appetitive learning[90,93].

Drug self-administration, in which animals learn to press a lever to receive drug, has often been used to mechanistically understand drug taking that, in humans, may lead to addiction[94]. However, self-administration does not account for drug seeking or craving. More recent behavioral paradigms have required animals to complete a random interval schedule on a seeking lever before being presented with a different, 'taking' lever, which delivers drugs on a fixed response schedule[95,96]. In variants of this task, rats are extensively trained using the chained seeking–taking schedules. In subsequent sessions the rats are probabilistically punished in some trials after completing the seeking schedule, instead of being presented with the taking lever. A subset of rats continues to respond compulsively on the seeking lever, obtaining the taking lever in some trials and punishment in others. A complimentary approach uses second-order conditioned reinforcement schedules[72,73]. In these procedures rats are reinforced only with drug-associated cues, which are able to maintain responding over long intervals. Both of these procedures better capture the compulsive seeking aspect of drug abuse than self-administration, although they have not yet directly led to changes in treatment. In addition, there is some work on individual differences in rats that predispose animals to compulsive drug taking[97], and a few recent studies have examined differences in plasticity mechanisms that may underlie behavioral differences[98,99]. Additional work on individual differences in plasticity may better reveal treatment targets or at least lead to a better understanding of why some individuals become addicts while others do not, given the same drug exposure.

Two learning manipulations originally proposed to affect aversive learning, driven by studies in the amygdala, have also been explored in appetitive learning. Specifically, both retrieval–extinction behavioral procedures[100] and pharmacological manipulations of reconsolidation[101] have been examined. Similarly to the effects previously explored in fear extinction, a retrieval–extinction procedure has been developed to extinguish the appetitive associations tied to drug cues in addicts[100]. This study found that in animals, presenting appetitive cues 10 min or 1 h before a subsequent extinction session led to decreased renewal, reinstatement (**Fig. 2**) and spontaneous recovery of conditioned place preference. Similarly, in human drug addicts, extinction training of drug cues following retrieval led to less spontaneous recovery up to 184 days after extinction training. This suggests that retrieval–extinction training can be effective in appetitive learning as well. The appetitive extinction effects have also been found to be significant in a meta-analysis in rodents[75].

In addition to these behavioral procedures, postretrieval pharmacological manipulations have also been used to alter learning. In these experiments, rats are conditioned to CSs paired with drugs. Following the conditioning, they are given an extinction session that serves to recall the CS memory. Either just before or just after the extinction session, they are given various drugs including NMDA antagonists or beta-adrenergic antagonists, as both have been shown to interfere with reconsolidation. They are subsequently tested behaviorally. Meta-analyses have shown that both NMDA antagonists and beta-adrenergic antagonists can affect reconsolidation and enhance extinction[101].

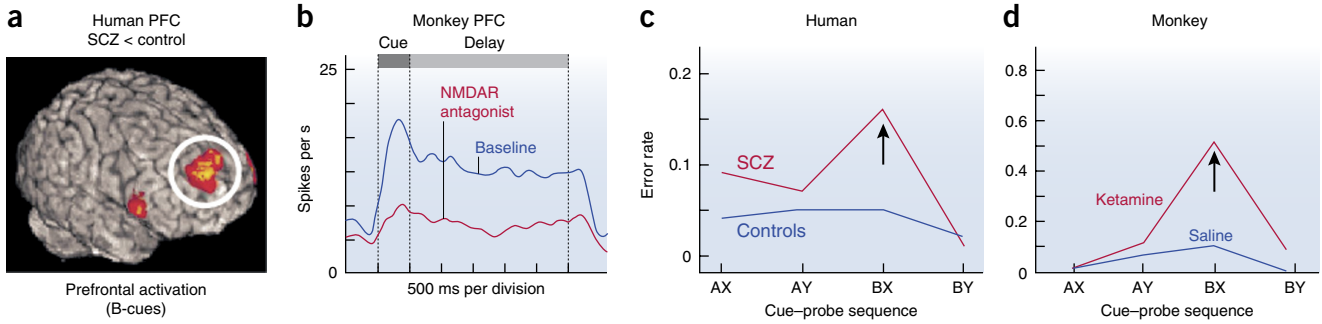

Figure 3 NMDAR antagonists in monkeys replicate both behavioral and neurophysiological features of cognitive deficits in patients with schizophrenia. (**a**) Blood-oxygen-level dependent (BOLD) signal reflecting maintenance of the B-cue (which countermands the habitual response to subsequent X-probes) in working memory is reduced in prefrontal cortex of schizophrenia patients relative to controls performing the AX-CPT. (**b**) Focal iontophoretic application of an NMDAR antagonist in prefrontal cortex of monkeys performing the ODR task reduces the spatially selective persistent firing of a prefrontal neuron associated with maintenance of the cue location in spatial working memory. (**c**) Patients with schizophrenia (red) make selectively more errors on BX-trials relative to controls (blue) on the AX-CPT task. (**d**) In monkeys performing the AX-CPT, systemic injections of ketamine (an NMDAR antagonist) induce the same error pattern: a selective increase in errors on BX-trials (red line) relative to control (saline injections; blue)[140]. Images in **a** and **c** adapted from ref. 34, American Psychiatric Association; images in **b** adapted from ref. 132, Elsevier; images in **d** adapted from ref. 140, Nature Publishing Group.

Model systems for understanding cortical network dysfunction in schizophrenia

Schizophrenia is a more complex disorder to study than anxiety or addiction. In anxiety there are better-developed models of the circuitry that gives rise to defensive or avoidance behaviors and in addiction there is a reasonable understanding of the pathogenesis. The gap between understanding and disease is larger in schizophrenia. Nonetheless substantial advances have been made in understanding the neurobiology of the disease. Functional imaging[34,35], magnetoencephalography[102] and electroencephalography[103] have shown changes in brain activity and synchrony patterns[104,105] in patients. These studies provide important insight into pathophysiological signatures of schizophrenia. However, they cannot resolve brain activity in patients at the level of action potentials in neurons. This is a significant limitation because accumulating evidence suggests that one aspect of disease pathogenesis in schizophrenia may involve the molecular mechanisms of activity-dependent synaptic plasticity[106]. Specifically, some risk mutations in schizophrenia involve a cluster of genes that play a role in NMDA receptor (NMDAR)-mediated synaptic transmission[107]. NMDA receptors play a crucial role in triggering activity-dependent synaptic plasticity[108], and the plasticity mechanism mediated by NMDARs is exquisitely sensitive to the precise timing of action potentials in pre- and postsynaptic neurons[39]. Additional risk mutations involve genes that play a role in the immune system[7], and new evidence suggests these genes support molecular signaling pathways that target synapses for elimination during development, a process which itself is activity-dependent[109]. This suggests that schizophrenia pathogenesis could involve a disturbance in the linkage between activity patterns at the level of spiking neurons and the strength of synaptic connections in cortical networks. Support for this class of theories could significantly redirect strategies to identify novel treatments. However, because pathogenic mechanisms of this type depend crucially on the timing of action potentials in synaptically coupled neurons and the disruption of this timing in the disease state, testing them requires resolving electrical activity at the cellular level, which requires the use of animals.

To effectively model the interaction between activity patterns and synaptic plasticity mechanisms, it is necessary to first try to replicate pathophysiogical activity patterns likely to occur in the human disease in the model system. This will be more likely if behavior is well matched between patients with schizophrenia and the model system. Consequently, the two species should perform the same behavioral task. In addition, a manipulation should be identified that causes the emergence of the same behavioral error pattern in the animal model that is evident in patients. Second, because neural activity patterns are constrained by patterns of anatomical connectivity in cortical networks, it is optimal if the neural system mediating performance in the animal is as similar in organization as possible to the corresponding network in the human brain. As behavioral and neurophysiological deficits in schizophrenia often preferentially involve the prefrontal cortex[110,111], this places particular weight on the necessity to optimize homology of prefrontal networks across species, and this criterion favors primate over rodent models[112,113].

This raises the question of which behavioral features of schizophrenia provide the most promising targets for successful translation to animals. The clinical symptoms of schizophrenia, which include hallucinations, delusions and flatness of affect[114] present obvious challenges for translation to animals (not least of which is that these symptoms are typically evaluated clinically by talking to patients). However, patients with schizophrenia also exhibit deficits in cognitive functions that are measurable using automated behavioral tasks that can be translated to animal models. Understanding the neural basis of cognitive deficits rather than clinical symptoms of schizophrenia has therefore been the focus of translational research[31,115]. Several multi-investigator consortia have identified behavioral models that most reliably measure specific cognitive deficits reflecting genetic risk in schizophrenia, including deficits in executive control, working memory, attention and sensory gating[116–119]. As with the other psychiatric disorders, reducing a disease as complex as schizophrenia to one or a few cognitive deficits in an animal model will likely lead to a model with limited validity, and therefore results from these studies should be interpreted carefully.

Patients with schizophrenia, and to a lesser degree their first-degree relatives, exhibit deficits in tasks that require spatial working memory[120]. A deficit in spatial working memory can be demonstrated in patients performing the oculomotor delayed response (ODR) task[121]. In this task, subjects direct a saccadic eye movement to the location of a peripheral visual cue several seconds after it disappears. Working memory for the location of the cue is associated with the persistent activation of spatially selective neurons in the dorsolateral prefrontal cortex in monkeys[122,123]. Dorsolateral prefrontal lesions[124], inactivation[125] or injection of D1 dopamine receptor antagonists

into monkey prefrontal cortex[126] induce spatially restricted deficits in working memory. Importantly, performance on the ODR task is preserved after insult to prefrontal cortex if the target remains visible through the delay, providing a visual target for the saccade at the time it is executed. This establishes the specificity of the deficit for working memory. The ODR task was successfully back-translated from monkeys to patients with schizophrenia and first-degree relatives to demonstrate a specific impairment in spatial working memory[127]. It has been repeatedly documented, using functional imaging in patients, that reduced performance on the ODR and other working memory tasks is associated with reduced activation of prefrontal cortex[128,129] (**Fig. 3a**).

Most efforts to model behavioral and neurophysiological features of schizophrenia in nonhuman primates have been based on administration of noncompetitive NMDAR antagonists such as ketamine or phencyclidine[130]. Blocking NMDAR in human control subjects replicates positive and negative symptoms as well as some cognitive deficits of schizophrenia[131]. In monkeys, local iontophoretic application of NMDAR antagonists disrupts the persistent activation of prefrontal neurons associated with spatial working memory[132] (**Fig. 3b**). Other studies have shown that systemic administration of ketamine to monkeys induces errors in a rule-based antisaccade task similar to those produced by patients, and neural recording has characterized concomitant reduction in the encoding of task-related information by prefrontal neurons[133–135]. Collectively, these studies provide important insight into how prefrontal circuits computationally fail in response to loss of NMDAR function. However, some robust findings in patients are not replicated by the NMDAR model[136].

The AX-CPT (continuous performance task) is a task that measures specific deficits in executive control in patients with schizophrenia[34,137–139] and has been successfully translated to monkeys[140,141]. In this task, a cue stimulus modifies the response required to a subsequent probe. On some trials (BX trials), the cue stored in working memory countermands a habitual or prepotent response to the probe, and it is specifically on this subset of trials that patients with schizophrenia commit the most errors (**Fig. 3c**)[117,137,138]. Administration of ketamine to monkeys performing the AX-CPT induces the same error pattern (**Fig. 3d**)[140]. This is one example of a strong behavioral match between the error pattern of patients and an animal model.

However, the fact that a drug in monkeys is able to mimic the symptoms of a disease in humans is not evidence that the drug and disease work through the same neural mechanism. Testing causal theories at the cell and circuit levels requires neural recordings to evaluate the impact of mutations on neural function. The *Df(16)A*$^{+/-}$ mouse[142] is engineered to mimic the 22q11.2 chromosomal microdeletion (DiGeorge syndrome), which confers a 30-fold increase in risk of developing schizophrenia and is among the strongest genetic risks for the disease[142]. This mouse exhibits behavioral deficits similar to those seen in schizophrenia, including reduced sensory gating[143] and impaired spatial working memory[143,144], as well as reduced gamma band synchrony between prefrontal cortex and hippocampus[144]. Deletion of a single gene (*Dgcr8*) in this region that is involved in microRNA processing confers much of the phenotype and has been shown to produce deficits in short-term synaptic plasticity in slice recordings[145]. MicroRNA are involved in the post-transcriptional regulation of other genes. Genome-wide association studies indicate that the large majority of single nucleotide polymorphisms increasing risk of schizophrenia, as with other psychiatric disorders, do not occur in coding regions of genes[8], suggesting protein structure may be largely normal in the disease. Both observations point to the possibility that a defect in gene regulation could trigger pathogenesis in schizophrenia, potentially via activity-dependent gene regulatory pathways.

CONCLUSIONS

It has proven difficult to use animal models to screen for new drugs with therapeutic potential. While models have been generated that satisfy face, construct and predictive validity, they have not facilitated drug discovery. Animals are, however, the only available tool for mechanistic studies of the neural circuitry that drives behavior. More importantly, animals provide the only tool available to study learning driven neural plasticity at a cellular level, and pathology in these plastic processes likely underlies many psychiatric disorders. Understanding individual differences in plasticity mechanisms may further lead to insights into why, given similar genetic backgrounds or behavioral experiences, some individuals develop disorders while others are resilient. This understanding may then lead to better treatments.

ACKNOWLEDGMENTS

This work was funded in part by the intramural research program of the National Institute of Mental Health and NIH grants ZIA MH002928-01 (B.B.A.) and 1R01MH107491 (M.V.C.).

AUTHOR CONTRIBUTIONS

B.B.A. and M.V.C. wrote the paper.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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