12

From Rodent Behavioral Models to Human Disorders

Trevor W. Robbins

Abstract

To what extent is it feasible to generalize behavior in rodents to complex cognitive functions in humans via rodent models of neurodegenerative diseases or neuropsychiatric disorders? This chapter takes the view that prudent application of rodent models is actually essential to drug development in these areas, but has been hampered by what has been at times their naïve and inaccurate application. Some behavior in rodents may constitute building blocks of more complex cognitive or affective domains in humans. Many of the underlying neural systems, together with their chemical modulation and mechanisms of neuronal plasticity, appear to have been conserved across species. Tests of the validity of models should incorporate their underlying neural substrates to triangulate possible homologies in humans. The ultimate validity of the models depends crucially on the way in which the biological bases of the disorder are modeled, for example, in terms of contributory genetic, neurodevelopmental, experiential, or neuropharmacological factors.

Introduction

For pharmaceutical companies, the huge expense of Phase III trials and relative lack of success of developing effective new compounds in clinical neuroscience, including psychiatry, has raised questions over the utility of animal models of complex neurological or neuropsychiatric human disorders. A reasonable case can be made that the pathway to effective and useful back-translation of such models has not always been facilitated by multicenter clinical trials with heterogeneous patient groups, resulting from sometimes imperfect nosology, coupled with insensitive outcome measures based on clinical scales and compounds of limited efficacy with adverse side effects. Nevertheless, in a climate where some have debated the need for any animal models, we should review what constitutes and limits them, and what aspects may and may not be useful in future attempts at effective translation. This article seeks to synthesize elements of my recent previous reviews with colleagues, which focused

on animal models of cognition (Keeler and Robbins 2011) and psychiatric disorders (Fernando and Robbins 2011).

What Is a Model?

This issue has been discussed by many authors who rehearse the several criteria employed to validate animal models: face validity, predictive validity, etiological validity, and construct validity. Most of these are self-explanatory, except perhaps the latter, which refers to theoretical plausibility based on an integrated neurobehavioral explanation of a disorder which thus essentially subsumes the other forms of validity and includes behavioral, neural systems, cellular, and even molecular components.

Essentially, animal models depend on two separate elements: the "disease" (or "plausible perturbation") aspect, in which, for example, the molecular pathology of a disease is reproduced, sometimes via monogenetic inheritance; and the "symptomatic" aspect, in which the symptoms (e.g., behavioral or neurophysiological) are enacted and quantified. Both of these depend to some extent on comparability with humans; molecular pathology may show subtle cross-species differences that bear on the model's validity. However, when the underlying molecular pathology of a condition is well-known (e.g., in terms of the "huntingtin" protein of the autosomal dominant Huntington disease), there is obviously some form of comparability with the human condition, even if other aspects of the phenotype do not approximate the human disorder. The precise causal role of the pathology in the disease or the mechanism by which the pathology causes neurodegeneration may, of course, be more difficult to unravel. More problematic are those examples where (a) there are multiple forms of molecular pathology, as occurs for the amyloid plaques and neurofibrillary (tau) tangles in Alzheimer disease, and when (b) the molecular pathology of human disease does not occur in experimental animals, necessitating strategies for producing, for example, "humanized" disease-bearing mutants. Nevertheless, it is difficult not to believe that animal disease models bearing these forms of pathology will play important roles in elucidating disease mechanisms, as well as screening new therapeutic strategies.

I also suggest that further attention to the "construct" validity of such models may also be important. For example, if a therapeutic agent was found that potently blocked the formation of amyloid, but did not prevent neurodegeneration in relevant brain regions or remediate a dysfunctional outcome, such as a memory deficit or even an impairment in long-term potentiation found in those animals, then one would be more skeptical of its likely therapeutic efficacy. In other words, it may still be desirable to subject such "disease models" to tests of memory appropriate for those brain regions at risk in Alzheimer disease.

In the case of neuropsychiatric disorders such as depression and schizophrenia, we are rather far from identifying the molecular pathology that causally

leads to symptoms. It is undoubtedly true that genetic analysis may change this situation in years to come, but it is still likely that multiple genes (generally of small effect) will contribute—most likely additively, or via epistasis—to the complex heterogeneity, for example, of schizophrenia; thus it will be difficult to specify precisely what aspects of the disorders will be a consequence of particular genes or, more likely, the converging products of massive gene clusters. Moreover, there are also the complexities of epigenetic factors to consider, as well as the importance of relevant environmental factors gleaned, for example, from human epidemiological studies. Hence, most of the other "plausible perturbations" used in animal models of psychiatric disorders have a developmental or "stress"-related basis, reflecting perhaps a declining tendency to employ pharmacological interventions, such as intracerebral 6-hydroxydopamine or MPTP (Parkinsonian movement disorder), amphetamine or ketamine/phenylcyclidine (psychosis), or scopolamine (cognitive deficit) to "short-cut" etiological considerations. Of these, the production of striatal dopamine loss to model Parkinson disease has produced perhaps the most successful models; however, they still fail to simulate in rodents the same qualitative motor deficits that are seen in human patients with Parkinson disease, and they are unable to reproduce the chronic progression of the disease.

Environmental factors such as "stress" are also difficult to control, partly because of the likelihood of different forms—physical stressors, social (e.g., isolation or "social defeat") stressors, "learned helplessness"—and the difficulties of modeling specific human stressors (e.g., "urban alienation"). Developmental events also vary widely according to their timing and nature, and it is sometimes unclear whether they impact the brain in a disorder-relevant manner. Moreover, our understanding of how best to combine environmental manipulations with genetic factors to optimize the models is weak.

Thus for psychiatric disorders, the task of modeling becomes far more difficult and inevitably focuses, to a much greater extent, on behavioral and cognitive aspects and their neural underpinning. These aspects themselves hinge controversially on the extent to which animal behavior can be said to bear any reasonable approximation to the complexities of human cognition and upon the interpretation of possible neural homologies. One way of addressing this difficulty is to invoke again the concept of construct validity. If the animal behavior in question can be shown to be the product of homologous brain systems, controlled by similar physiological interactions as occur in humans, and subject to the same sorts of environmental conditions or interventions (e.g., stress, therapeutic drug effects), then it becomes more plausibly a "model" of what occurs in humans.

An inherent limitation of the construct validity approach is the importance and utility of the mouse mutant models for molecular genetics. A very real difficulty has been that, compared with rats and primates, mice have hitherto been far from the ideal species for neuroscientific and behavioral (e.g., based on learning theory and operant methods) investigations. This has partly been for

historical reasons, but there are also mundane practical considerations, such as brain size. Hence, currently it is simply not feasible to provide optimal models, if the goal is construct validation. This situation is slowly changing due to excellent innovation in this area; see, for example, the elegant review on the application of mouse models to psychiatry by Arguello and Gogos (2006) as well as new behavioral approaches for the mouse (e.g., Bussey et al. 2012). I predict that it will remain a major obstacle to progress until molecular genetic approaches can also be applied more comprehensively to rats and nonhuman primates.

Another limitation of the construct validation approach is the controversy that often surrounds the identification of neural homology. Although there are major differences in size, and sometimes evolution, of brain structure in the parietal, temporal, and prefrontal cortices between humans and other animals, there is also considerable conservation, encompassing structures of the limbic system, basal ganglia, midbrain, and brain stem. For example, the human "reward" or value systems appear to have very similar neural representation in other animals, including rodents with a focus on the ventral striatum and ventromedial prefrontal cortex (PFC) (Haber and Knutson 2010). The classical ascending neurotransmitter systems such as dopamine, which is often identified with reinforcement and motivational functions in humans and rodents, as well as serotonin, noradrenaline, and acetylcholine all exhibit remarkable phylogenetic conservation (and correspondingly similar functions in behavior). At a different level of investigation, it is intriguing to consider whether the molecular basis of different forms of plasticity (especially learning and memory) involve fundamental differences across species. While this is to some extent an open question, it seems likely that the same molecular "building blocks" hold across species.

There are obvious and often impossible hurdles to surmount in animal models of human behavior, including largely unique human characteristics (e.g., the capacity for language and moral reasoning). Even nonhuman primates fail many tests of "social cognition," such as the tendency to reject unfair offers in variants of the "ultimatum game" (Jensen et al. 2007). Moreover, it is dubious that even monkeys entertain a "theory of mind," at least according to all of the main criteria (Penn and Povinelli 2007). Animals appear to lack the capacity for subjective thought, although this, of course, is in part a function of their inability to express it. Doubtless, with this in mind, many have reasoned that it is impossible for animals to experience such complex symptoms as depression or the hallucinations or delusions associated with psychosis. But this may be taking things slightly too far. Subjective symptoms are undoubtedly an important component of psychiatric disorders, but they can mislead and in fact only form part of the symptomatic picture, which is also somatic and behavioral in nature. The latter point is important as, for example, monkeys chronically treated with amphetamine have been described to exhibit behaviors that would be difficult to explain without invoking the notion "hallucinations" (Nielsen et

al. 1983). Moreover, operational measures of concepts such as "reward threshold" (Paterson and Markou 2007), "negative feedback bias" (Bari et al. 2010), and the ability to discriminate between different internal states (e.g., drug cue discrimination learning, which can be generalized to emotional states such as anxiety; Vellucci et al. 1988) provide a basis for inferring altered motivational states in animals in a manner that could be used more routinely in human patients to approximate their subjective status.

A related general stratagem is to "triangulate" animal findings in a way that is relevant for human disorders. A major discovery of recent years has been that fast phasic firing of the midbrain dopamine neurons encodes a "prediction error" that represents the difference between expected and obtained outcome (e.g., reward), thus corresponding to an essential parameter of reinforcement learning (Schultz and Dickinson 2000). Translation of this notion to the functional magnetic resonance imaging (fMRI) setting confirms that similar activity in regions homologous to the midbrain ventral tegmental region is found during causal learning in humans. Moreover, ketamine, the NMDA receptor antagonist and well-known psychotogen, disrupts the formation of prediction errors in a way that predicts its capacity to produce delusional phenomena in human volunteers (Corlett et al. 2007). Therefore, by measuring prediction errors and their disruption in experimental animals (including rodents), it may be feasible to gain predictive data relevant to aspects of psychosis.

There is an increasing trend not to model psychiatric syndromes in their entirety, but to focus instead on modeling well-defined symptoms or symptom clusters. This is especially exemplified by schizophrenia, which has major cognitive and motivational symptoms, in addition to the positive symptoms of psychosis. In fact, there is an argument for considering most of the symptoms of schizophrenia, depression, or any of the other major neuropsychiatric disorders as being "cognitive" or "motivational" in nature one way or another. For example, we have seen above how the fundamental basis of delusions may possibly derive from aberrant prediction errors in learning. However, it is much easier to model fundamental units of cognition (such as learning, working memory, or executive control) that also occur in schizophrenia in experimental animals because of the considerable literature that has accrued on the neural mediation of these processes. In parallel, understanding the neural basis of motivation in humans has gained immeasurably from animal studies of drug-related reward processes in the nucleus accumbens (Wise 2004) and learned fear in the amygdala (LeDoux 2000), to name but two obvious examples.

This realization has informed current initiatives to rework or even replace the current DSM-IV/5 nosology in terms of "dimensional criteria" that depend on underlying neuroscience concepts such as the "reward system" (e.g., Research Domain Criteria; Cuthbert 2014) as well as to the possibility that some common deficits may occur across different psychiatric disorders. In terms of the latter, the new classifications may depend on a mosaic of features,

some of which may be similar and some different, thus accounting in part for pervasive comorbidities.

A combined neurobehavioral approach to understanding symptoms may also enable the definition of intermediate endophenotypes that represent intermediate markers between top-level symptoms and bottom-level genetic contributions (Gottesman and Gould 2003) to mental disorders. Endophenotypic markers are believed to be closer to the underlying neuropathology than top-level symptoms of a clinical phenotype. Thus, "neurocognitive endophenotypes" could be used to enhance the power of psychiatric genetic studies, to produce purer cohorts of patients for clinical trials, to tailor potentially effects of new treatments more effectively in accordance with burgeoning pharmacogenomic principles, and to identify prodromal states for which it is possible to treat "before the damage is done" (for mild cognitive impairment is prodromal to Alzheimer disease and at-risk psychosis possibly heralds first episode psychosis).

Modeling Cognition

Cognition refers to the set of processes that manipulate representations in the brain in various ways to produce thinking or behavior. These processes include perception, attention, working memory, episodic and semantic memory, symbolic and propositional functions such as language, and executive control processes which coordinate these modular functions to effect decision making and planning. Such mechanisms interact with motivational and emotional processes, and include social aspects of cognition. Cognitive processes are mediated by different, frequently overlapping neural networks that include wide regions of the neocortex, such as the temporal, parietal and frontal lobes, as well as the subcortical brain. Remarkably, the elements of many of these processes can be studied in experimental animals and have been used or could be used for drug discovery. I will illustrate this by surveying some aspects of cognition; an overview of behavioral constructs, animal models, and clinical applications is given in Table 12.1. If one adopts, as here, a "modular" approach that recognizes the existence of separate aspects of cognition under control by different neural systems, in other words assuming that cognition is not unitary, the logical conclusion is that it has to be assessed with a battery of tests. This "battery" approach mirrors similar batteries for testing cognition in humans, such as the Wechsler Adult IQ Scale (WAIS) which extracts a "general" measure of IQ, the MATRICS battery[1] for schizophrenia, and the CANTAB battery[2] which utilizes some tests that can be given to both humans, including clinical patients, and experimental animals, nonhuman primates or, with suitably modified tests,

[1] http://www.matricsinc.org (accessed March 3, 2015)

[2] http://www.cambridgecognition.com/academic/cantabsuite/battery (accessed March 3, 2015)

rodents. Human test batteries, however, differ greatly in how they are administered: the WAIS is mainly a set of paper and pencil tests which incorporates tests of verbal intelligence; the MATRICS battery recapitulates many classical neuropsychological tests under separate cognitive domains; the CANTAB battery employs largely nonverbal tests using a touch-sensitive screen to emulate tests of cognition in experimental animals.

The use of touch screens to test cognitive function in humans and other animals is a relatively recent development. The requirement to make actual contact with discriminative stimuli is a considerable aid to ensure rapid learning, as the task contingencies are rapidly discerned, probably because of the elicitation of fundamental Pavlovian approach tendencies toward the discriminative stimuli. The use of touch screens was originally introduced for the testing of nonhuman primates (Gaffan et al. 1984), but was extended to humans (e.g., via the CANTAB battery) and most recently to rodents (Bussey et al. 1994, 2012) with the aim of enhancing translational potential. A recent application of CANTAB has been to show the relationship between a hierarchy of different behavioral capabilities as a function of gene variants of Dlg mutant mice, with implications for the evolution of cognition, conservation of cognitive "building blocks" in evolutionary terms, and for certain neuropsychiatric disorders (Nithianantharajah et al. 2013).

Whether considering human or animal cognition, such functions are generally componential: impairment in perception, attention, or motivation caused, for example, by sedation or satiety might lead secondarily to learning and memory problems. The ideal test of memory would therefore incorporate basic behavioral controls to show that any effects of a putative cognitive-enhancing compound could not be ascribed to such other factors. General sensory, motor, or motivational factors which may affect cognitive function only indirectly (and thus lead to possible artifacts or mistaken reasoning) must also be tested. Sensorimotor functions, for example, in transgenic mice are often tested in a neurological battery (e.g., Irwin 1968). Primary motivation can be assessed in terms of ingestive behavior (eating or drinking), including high- or low-incentive or high- or low-calorie foods, as well as the propensity to work or exert effort; for example, in terms of instrumental (or operant) behavior directed toward a particular reinforcer, as on a progressive ratio schedule where the amount of work required to gain the reward becomes progressively greater and motivation is measured in terms of the "break-point" (i.e., the number of lever-presses a rat is prepared to make to gain the reinforcer). Unfortunately, the use of similar objective tests for human motivation is poorly developed, although modern paradigms employ relevant parameters of performance to assess this, including measures of latency and force of responding. The better designed tests of cognition incorporate a condition or measures that provide internal controls for motivational effects, and several examples of this will be exemplified below. Overall, it is important to note that although animals may vary widely in their motor capacities or their dependence on different sensory

Table 12.1 Summary of behavioral constructs, animal models, and some clinical applications (see text for details). OCD: obsessive-compulsive disorder; 5-CSRTT: 5-choice serial reaction time task; ADHD: attention-deficit/hyperactivity disorder; PTSD: posttraumatic syndrome disorder; CANTAB PAL: CANTAB paired associate learning.

Behavioral process	Behavioral paradigm	Animal equivalent?	Relevant to which neuropsychiatric or neurological disorder
Perception	Gain control Integration	Yes for gain control (cat, monkey)	Schizophrenia
Attention			
Preattentive gating	Prepulse inhibition	Yes (rodent, monkey)	Schizophrenia, Huntington disease, OCD
Covert attention	Posner's spatial attention	Yes (rodent, monkey)	Parietal lobe damage
Habituation	Latent inhibition	Yes (rodent)	Schizophrenia?
Sustained attention, vigilance	Continuous performance	Yes (e.g., 5-CSRTT) (rodent, monkey)	Schizophrenia, ADHD, dementia
Attentional set-shifting	ID/ED shift test, Wisconsin Card Sort	Yes: digging test (rodent), visual (marmoset, macaque)	Schizophrenia, OCD, frontal lobe injury
Associative learning (Pavlovian, action-outcome, habit learning)	Under development	Yes (rodent)	Psychosis, OCD, addiction, autism

Table 12.1 (continued)

Behavioral process	Behavioral paradigm	Animal equivalent?	Relevant to which neuropsychiatric or neurological disorder
Memory			
Consolidation, reconsolidation, extinction	Under development	Yes (rodent)	Anxiety, addiction, PTSD
Recognition memory, recall, declarative memory	Warrington Faces Hopkins Verbal Memory, REY Auditory-Verbal Test, CANTAB PAL	Yes: delayed matching to sample object recognition, paired associates (rodent, monkey)	Dementia, schizophrenia, temporal lobe/hippocampal damage, depression
Reference memory	Virtual water maze	Yes: Morris water maze, Olton maze (rodent)	Dementia, schizophrenia
Working memory	One-back task; spatial	Yes: spatial delayed response (primate), delayed alternation (rodent)	Dementia, schizophrenia, basal ganglia disorders
Executive functions (e.g., cognitive inhibitory control, planning)	Stop-signal task, Stroop test, Tower of London	Yes: stop-signal (rodent, monkey); Stroop but less developed (rodent) No: Tower of London (rodent)	ADHD, schizophrenia, OCD, binge eating, bipolar disorder, basal ganglia disorders, frontal dementia, frontal lobe injury
Cognitive-motivational interface: "hot" cognition	Iowa Gambling Task Delayed discounting Response to faces, words or feedback	Yes (rodent) Yes (rodent, monkey) Only to feedback (rodent, monkey)	Depression, addiction
Social cognition	Trust game, Ultimatum game, "theory of mind"	Not readily modeled in animals	Social interaction/recognition, autism, negative symptoms in schizophrenia

modalities, this most likely does not affect the fundamental principles of learning theory, such as the Rescorla-Wagner rule (an equation that captures the concept of learning through the "surprise" generated by a deviation of actual from expected outcomes, defined as prediction errors) or cognitive representation. Thus, it is possible to generalize findings on cognition from animals to humans despite basic differences in sensorimotor performance.

Testing Specific Aspects of Cognition from Rodents to Humans (and Vice Versa)

Perception

Perception arises from "online" representation of the world by the sensory systems and is ultimately used to make decisions about how to perform. Perceptual capacity is often tested in experimental animals and humans by what appear to be similar methods. Thus, perceptual assessment in rats generally involves the capacity for discrimination, whereby responding in the presence of one stimulus is rewarded or reinforced (e.g., with food for food-restricted rats) while the other is not. Stimuli are presented randomly across two locations to avoid the task being solved incorrectly by the animal on the basis of spatial factors. For humans, perceptual testing is less often accompanied by obvious reinforcing feedback (e.g., by points, money, or praise), although such factors would come into play in the case of training or rehabilitation. Human psychophysical methods, such as titrations of stimulus threshold, determination of contrast sensitivity functions, and application of signal detection theory to separate perceptual sensitivity from motivational bias (as in pain perception), can all be readily applied in rodents. However, an overriding consideration is, of course, that the dominant modality in humans and other primates is visual, whereas in rodents it is olfactory, which clearly limits the utility of rodent models involving perceptual ability.

In the CNTRICS (cognitive neuroscience treatment research to improve cognition in schizophrenia) process, two constructs in perception were identified as being possibly relevant to perceptual disturbance on schizophrenia: gain control and visual integration (Green et al. 2009). The former is defined as processes enabling sensory systems to adapt and optimize their responses to stimuli within a surrounding context. Integration is defined as processes enabling local attributes (e.g., of a scene) to be encoded globally. Of the two, only gain control is readily modeled in experimental animals. The contrast-contrast effect (CCE) task derives from the common illusion that contrast sensitivity is modulated by the properties of adjacent or surrounding stimuli. CCE has been well characterized in terms of its psychophysical and neural underpinning, and has been studied in macaque monkeys and cats (for a review, see Green et al. 2009).

Attention

Attention generally depends on fluctuations in asymptotic test performance that cannot be attributed to changes in motivational state (see Lustig et al. 2013; Robbins 2014). Several forms of attention identified in humans can be modeled in experimental animals: selective attention (focusing on one input or feature, while ignoring the rest), sustained attention (maintaining attention over a long period), vigilance (detecting rare inputs), and divided attention (maintaining attention to more than one input or task). Attentional deficits occur in such disorders as attention-deficit/hyperactivity disorder (ADHD), schizophrenia, addiction, and mania, as well as after brain damage. It is important to take possible attentional deficits into account when considering possible changes in memory and learning; without appropriate input, these processes cannot easily occur.

Preattentive gating. Attention involves both conscious (explicit, overt) and unconscious (implicit, covert) aspects. Moreover, "preattentive" filtering or "gating" processes have been postulated that are also assumed to be unconscious. Within this domain, the prepulse inhibition (PPI) paradigm is the most well-developed test because of its enormous translational validity across species, including rodents, and has been of considerable use in experimental studies of schizophrenia, where implicit measures of cognition are useful. (PPI has also been suggested to be an example of perceptual gain control, see above.) PPI is a modulation of the startle response to loud noises or other intense stimuli. This modulation is an inhibition of the reflexive startle response (frequently whole body displacement) produced by the presentation of a brief surrogate stimulus (generally of the same modality but of much reduced intensity) that occurs immediately prior to the startle stimulus. PPI is impaired by dopamine D2 agonists and remediated by D2 receptor antagonists; it is also sensitive to a number of other pharmacological manipulations (Geyer et al. 2001). PPI is widely used in testing genetic mutants of relevance to schizophrenia because of its objective nature, reliability, and convenience (mass testing being feasible as long as there is suitable auditory insulation). However, impairments in PPI occur in other disorders besides schizophrenia and could possibly be epiphenomenal to the symptoms, although an attempt at "construct" validity suggests that failure of "sensory gating" is a fundamental cause of schizophrenia, presumably subsuming both positive and cognitive symptoms.

Covert attention. A covert form of attention has been described in humans to occur when attention is cued spatially in advance to a particular location by the brief presentation at that location of another stimulus. Attentional capture by such a stimulus occurs apparently automatically and unconsciously. The process can be demonstrated when this cueing is misleading and the subject has to disengage that process and respond to a stimulus that is presented elsewhere. This form of attention has been attributed to mechanisms within the

human parietal cortex (Posner and Petersen 1990), but similar processes can be characterized in experimental animals, including rats (Ward and Brown 1996).

Habituation and latent inhibition. Habituation, another attention-like process, can occur during learning when repeated stimuli have no consequence, leading to a waning of response. This reduction is readily measured in animals and humans (often using psychophysiological recordings in the latter case, such as skin conductance or heart rate). However, an additional consequence, that of latent inhibition, can be more persistent and long-lasting. Latent inhibition refers to the retardation of learning about a stimulus that occurs, if it has never previously predicted reinforcement (Weiner 2003). A major hypothesis of latent inhibition is that it reflects the subject simply "ignoring" the stimulus by an active process of inhibition. Latent inhibition (or a related phenomenon termed learned irrelevance) has some advantages as a test of attention in that impairments may be expressed subsequently as improved learning, thus ruling out motivational impairments. Although latent inhibition has translational potential, it is sometimes difficult, for practical reasons, to be sure that what is measured in humans as latent inhibition corresponds to the same process in rodents.

Sustained attention and vigilance. Continuous performance tests measure the ability to sustain attention, as well as vigilance, and usually reveal impairments in disorders such as schizophrenia or ADHD. A simple analogue of this task for rodents is the 5-choice serial reaction time task (5-CSRTT), based on a paradigm used to assess attention in human volunteers in a variety of experimental situations, including stress, distracting white noise, and following drug treatment (Robbins 2002). The 5-CSRTT measures the accuracy (errors of commission) and latency of detecting visual targets, as well as errors of omission and impulsive responding (i.e., responding prior to target onset). The latency to collect food pellets provides a control measure of motivation. The difficulty of the task can be enhanced in various ways, including shortening of the duration of the visual target, varying its rate of presentation and temporal predictability, as well as the occurrence of defined distractors, such as bursts of white noise interpolated into the intertrial interval. This task has been widely employed in rats, and more recently mice (as well as in nonhuman primates), to measure effects of drugs, regional brain lesions, and manipulations of the central neurotransmitters or genetic mutations. The 5-CSRTT has been used to measure beneficial effects on response accuracy of some putative "cognitive-enhancing" drugs, such as dopamine D1 agonists, as well as to characterize impulsive behavior that predicts the escalation of compulsive cocaine-seeking behavior in rats. A human "4-choice" version of the task has recently been shown to reproduce deficits in impulsive responding in patients who exhibit methamphetamine abuse (Voon et al. 2014) or humans receiving dietary tryptophan depletion, which mimics the impulsive behavior produced in rats on this task with extensive forebrain serotonin depletion (Worbe et al.

2014). The CANTAB "5-choice" version has been used to demonstrate attentional improvements in patients with Alzheimer disease treated with the anticholinesterase tacrine (Sahakian et al. 1993). This demonstration was borne partly out of data showing that cholinergic agents could improve attention in rats with lesions of the cholinergic basal forebrain, and more recently, in "triple transgenic" mutant mouse models of Alzheimer disease.

There are several variants of the standard 5-CSRTT: the primary one requires the rat to make an observing response into a central location to detect a peripheral target, and has been used to quantify the "attentional neglect" that can occur after unilateral manipulations of corticostriatal brain regions (Carli et al. 1985). Another, rather different, operant test requires the cross-modal integration of auditory and visual stimuli (McGaugh and Roozendaal 2008; Lustig et al. 2013) and includes an important control that animals must detect not only the presence of the stimulus but also its absence. Recent developments in touch-screen technology have enabled the development of a continuous performance task that is very similar to that used in humans, requiring responses to specified visual targets (see Bussey et al. 2012).

Attentional set shifting. Attentional set-shifting tests that are sensitive to frontal lobe damage in humans, such as the Wisconsin Card Sorting Test, involve the formation and shifting of attentional "sets" and the capacity to avoid a prepotent response to one aspect of a stimulus in order to respond to another (Keeler and Robbins 2011). This latter aspect of inhibitory control over prepotent tendencies has resulted in these tests being employed as tests of "executive function" (see below). Such tests have proven highly "translational" in that they have been applied to a range of experimental animals (mice, rats, marmoset monkeys, rhesus monkeys) and humans in ways that appear to reflect neural homologies. Thus, attentional set shifting appears to implicate the prefrontal cortex (lateral PFC in primates, including humans, though medial PFC in rodents) on the basis of both lesion and neuroimaging studies, whereas reversal learning appears to implicate the orbitofrontal cortex from studies of humans, marmosets, rats, and mice (see review in Keeler and Robbins 2011).

The attentional set-shifting task uses compound visual stimuli, which vary in at least two perceptual dimensions: visual shapes and superimposed lines for primates (Dias et al. 1996); texture and odor stimuli in different modalities for rodents (Birrell and Brown 2000). Humans, nonhuman primates, or rodents (rats or mice) are trained to attend to one dimension (on the basis of positive feedback or reinforcement) and to ignore the other. Training is accomplished through tests of reversal (where the two exemplars within a perceptual dimension have their reinforcement contingencies reversed so that what was previously correct is now incorrect and vice versa) and intradimensional shifting (where novel exemplars are introduced, but the same dimension, e.g., lines or shapes, is reinforced). These training stages serve to focus the animal on particular stimulus features and to ignore the others, with the result that they

have a prepotent tendency to respond to the trained dimension (e.g., shapes). Finally, an extradimensional shift (ed-shift) is programmed in which novel exemplars are again introduced, but now the previously irrelevant dimension is reinforced. This latter stage is analogous to the category shift on the Wisconsin Card Sorting Test. In the rodent version (being available for mice as well as rats), the test is implemented using olfactory cues and texture in a "digging for food" test paradigm (Birrell and Brown 2000). Performance across the various stages is qualitatively comparable to that seen in primates: the ed-shift and reversal learning are the most sensitive stages to drug effects, performance at other stages usually being employed as internal controls. There are now various versions of these tests of "cognitive flexibility" that use similar logic for shifts between, for example, responding to body turns or to space on a cross maze or alternatively, attending to discrete (e.g., visual) cues versus contextual cues on a maze. These tests do not use different stimuli at each test and so are also confounded by any response to interference.

The attentional set-shifting and reversal tasks have found many applications in neuropsychiatry. Thus, impairments in ed-shifting have been found not only in patients with obsessive-compulsive disorder (OCD) but also their first degree relatives, suggesting that the capacity to shift attention in this way is an endophenotype for OCD (Chamberlain et al. 2008). By contrast, although ed-shifting is also impaired in schizophrenia, it is apparently not impaired in the unaffected siblings of patients (Ceaser et al. 2008). Nevertheless, the attentional set-shifting paradigm has been shown to be sensitive to cognitive-enhancing effects of modafinil in patients with schizophrenia (Turner et al. 2004), and this has allowed an impressive, and rare, case of "back-translation" using the rodent version of this paradigm. In this study, a common "perturbation" to model schizophrenia was employed: subchronic treatment with the NMDA receptor antagonist phencyclidine, which impairs relatively selectively the ed-shift. This deficit was rescued by treatment of the rats with acute modafinil, thus mimicking the human finding (Goetghebeur and Dias 2008).

Associative Learning

Both Pavlovian and instrumental (operant) conditioning have cognitive aspects: the former enables the causal prediction of events in the world leading to expectancy and the latter affords control over environmental contingencies. Disruptions of different aspects of Pavlovian and instrumental learning, alone or in combination, probably underlie all of the major forms of neuropsychiatric disorder, including drug addiction, anxiety, depression, and schizophrenia. In the case of drug addiction, Everitt and Robbins (2005) have proposed that it represents a transition from instrumental action-outcome goal-directed learning (i.e., intravenous drug self-administration) to stimulus-response habit learning, performed in a compulsive fashion. Intravenous drug self-administration arguably contributes to one of the best rodent models of human behavior

that accurately predicts drug abuse liability of different compounds. Of course, it is not tantamount to addiction itself; however, a more compulsive element, specified in DSM criteria for addiction, can be discerned when rats work under a second-order schedule to earn infusions of cocaine, as well as occasional electric shocks. A small proportion of animals, rather similar to that proportion of humans who become addicted following cocaine use, continue to self-administer the drug despite these aversive consequences (Belin et al. 2008).

Habit learning can be defined operationally through tests of "outcome devaluation" (such as selective satiety for a particular food), when habitual behavior continues irrespective of the goal. These principles were worked out in studies of rats, but the general principles, as well as the underlying neural substrates, appear to generalize remarkably to normal human learning (Balleine and O'Doherty 2010).

The principles of aversive conditioning are also highly relevant to the understanding and treatment of psychiatric disorders. In the case of anxiety (see Fernando and Robbins 2011), the dominant influence has been Mowrer's two-factor theory, developed mainly in rodents, which suggests that phobic anxiety develops as a consequence of both Pavlovian and instrumental (avoidance) conditioning (Mackintosh 1983). Behavioral therapy for phobias depends on a principle of exposure (repeatedly presenting the anxiogenic stimulus in the absence of adverse consequences), which is synonymous with the procedure of extinction in experimental animals. Recently, the realization that extinction is probably a form of additional inhibitory learning has led to the successful combination of exposure therapy (extinction) with the cognitive enhancer d-cycloserine (DCS) to treat patients with vertigo. This development was motivated by extensive experiments in rodents that showed analogous effects (Davis et al. 2006)—a particularly impressive example of translation from rodent studies to human patients. In fact, DCS augmentation has now been used effectively in several other forms of anxiety disorder (Hoffman et al. 2013). However, the efficacy of this behavioral pharmacological interaction may be considerably limited by the difficulty of translating the highly controlled aspects of the laboratory to the real world.

The detection of instrumental contingencies (e.g., the arbitrary act of lever pressing that leads to food delivery for a rat) can be thought of as a higher-order cognitive process which plays an important part in our ability to make the sequence of voluntary actions that constitute goal-directed behavior. Learned helplessness is a theory of how experience of loss of control over environmental contingencies can lead to depressogenic behavior. Such loss of control can also be produced by disrupting top-down connections from the rat medial PFC to such regions as the serotoininergic raphé nuclei (Amat et al. 2005). Although there is some doubt now that learned helplessness is a paradigm specific to human depression, it is clear that tests such as the forced swim test in a tank of inescapable water ("behavioral despair") and the tail suspension test (in mice) do not simulate the main aspects of depression. These

paradigms are somewhat crude examples of the helplessness concept, and are nevertheless much used in influential neurobiological studies of the molecular basis of depression, doubtless because of their convenience and utility to predict antidepressant drug efficacy (Nestler et al. 2002). However, the lack of precise definition of stimulus-response contingencies (e.g., the exact adaptive significance of "floating" or planing without success in the forced swim test) renders these tests of dubious construct validity and thus their ultimate lack of success unsurprising.

Memory

Memory can be divided into many subprocesses. A basic, but increasingly questioned, distinction is between relatively transient short-term memory (which may include "working memory") and long-term, more permanent, memory. Memory "traces" are thus hypothesized to undergo "consolidation" into long-term memory. The distinction made in human long-term memory by Tulving (1983), between "episodic" (generally autobiographical, the "what, where and when" of memory) and "semantic" memory (memory for meaning), is perhaps more difficult to investigate in experimental animals, such as rats and monkeys, because of linguistic encoding. Nevertheless, it is apparent that animals, including rodents, have long-term memories for salient stimuli of motivational significance.

Consolidation, reconsolidation, and extinction. A major contribution of rodent studies has been the post-trial or post-training paradigm introduced and developed extensively by McGaugh (e.g., McGaugh and Roozendaal 2008). Here, what is generally a single trial or training session is followed immediately by a drug treatment that can either be amnestic (e.g., protein synthesis inhibitors) or promnestic (e.g., amphetamine). Retention is tested on a subsequent trial, perhaps 24 hours or 3 days later. The post-training manipulation is designed to influence consolidation, either beneficially or adversely, and is often most efficacious when administered directly into the amygdala, a likely site of consolidation of simple cue-related aversive and appetitive memories. The procedure most often used is of aversive memory: the rodent is punished for stepping down from a platform or through a door by presentation of electric foot shock. Memory is expressed on the retention trial by a longer response latency to step down or through the door.

The advantage of this design is that the drug cannot affect memory indirectly by its actions on perceptual, attentional, or motivational mechanisms, as it is administered when these no longer impinge on learning. Controls are necessary with longer post-trial treatments to check that the drug effects are not affecting retention proactively (e.g., by being active at the time of retention and thus affecting memory retrieval). Studies of the consolidation of appetitive memory are also feasible, but are used less often because of the

unreliability of one trial appetitive learning. The post-trial paradigm has not (yet) translated particularly well to studies on human memory, although it has been useful in highlighting possible effects on emotional memory, relevant to such syndromes as posttraumatic syndrome disorder (PTSD). The discovery of a related process of reconsolidation (Nader et al. 2000), however, may have greater applicability to the clinic. After initial conditioning, presentation of a conditioned stimulus alone in the absence of the unconditioned reinforcer may enable reconsolidation, a period of memory destabilization when the memory trace regains its vulnerable status through new protein synthesis and when it has been shown to be feasible to target this phase with pharmacological agents (e.g., NMDA receptor antagonists, β-blockers) to produce selective amnesia (or enhancement). The reconsolidation process is mirrored by the active process of extinction learning, which occurs when the reinforcer (e.g., shock or food) is omitted (see also above). It is too early to be sure that these rodent studies of reconsolidation will have therapeutic significance for disorders such as PTSD, anxiety, and addiction, but this is currently an active area of research (see Nader and Hardt 2009; Milton and Everitt 2012).

Recognition memory, recall, and declarative memory. Recognition memory refers to the ability to detect familiarity and, for humans at least, to reminisce about previous experiences involving objects, people, or places. A commonly used task is that of object recognition (devised by Ennaceur and Delacour 1988) in which a rodent (or monkey) explores a novel object during a sample trial and is then given a choice between this familiar object and a novel object, in terms of the amount of time it allocates to exploring both objects. Lesser exploration of one object indicates greater familiarity, and hence recognition of it (in a restricted sense that does not include the subjective elements). The test can also be adapted to measure "social recognition" by using experimental animals as the "object." Recognition memory is generally manifested over long delays, up to 24 h, although it can be tested at much shorter intervals and has been shown to depend on structures such as the rodent perirhinal cortex, rather than the hippocampus (Murray et al. 2007). Recognition memory tasks generally employ stimuli only once, so the test is "trial unique." If the same set of objects were to be used over many trials (as occurs in the spatial delayed alternation or spatial delayed response task, see below), this would produce considerable proactive interference. The test, therefore, becomes one of recency memory (how *recently* the stimulus has been experienced) rather than one of recognition memory (how *familiar* is the stimulus). The test also becomes one more of frontal rather than temporal lobe function (Chiba et al. 1997). As a rapid and easily implemented test, object recognition memory is perhaps the most used of all rodent assays of memory in the screening of putative cognitive-enhancing drugs, although it has been employed in several different variants (Dere et al. 2007). Its translational properties, in terms of human tests

of recognition memory, are clear, particularly when equivalent touch-screen versions of visual recognition memory are employed.

Recognition memory is, however, a less-sensitive test of memory than either cued or free recall, in which the memory has to be generated from long-term memory store. Unlike recall, recognition is not particularly sensitive to hippocampal damage, nor is it the earliest manifestation of Alzheimer disease, where amnesia for episodic memories is more evident.

Rodent (as well as primate) data indicate the hippocampus to be implicated in forms of associative memory, in animals involving space or other contexts; for example, remembering the location of objects (Murray et al. 2007). These forms of memory are often referred to as reference memory tasks in the animal literature. Recognition and recall correspond to what Squire (1992) defined as "declarative memory," which is distinct from "procedural memory" (memory for "how" or "skill"). Although procedural memory is not discussed in detail in this article, it could be tested in rodents in motor-learning situations, such as the rotor-rod test or as memory for "habits."

Reference memory. Reference memory is a form of long-term memory referring to rodent task requirements that stay constant over trials. This definition was introduced by Olton when rats were required to remember the constant location of food-baited arms in an 8-armed radial maze (Olton and Paras 1979). It can also be applied to the Morris water maze, a notable assay of hippocampal function, in which rodents are required over a number of learning trials to learn the location of a hidden platform in order to escape from a tank of water (Morris et al. 1982). The rodent is allowed to swim the maze from different starting points; thus successful learning depends on the construction of a "cognitive map" to navigate the environment. Although this task may appear to lack translational validity for testing, for example, memory in patients with Alzheimer disease or schizophrenia, promising "virtual reality" tests of spatial navigation are currently being employed to assess human memory (Hanlon et al. 2006).

A related approach has been to "back-translate" from human to animal studies. The CANTAB paired associates learning (PAL) task has some of the attributes of episodic recall ("what and where" learning), as humans are required to learn and remember the different locations of several abstract visual objects over short delays. This task is sensitive to deficits in patients with mild cognitive impairment (likely prodromal Alzheimer disease) and some patients with schizophrenia. It has been shown to be sensitive to impairments in patients with mild cognitive impairment three years before formal diagnosis (Swainson et al. 2001). Recently, the main aspects of this test for rodents have been simulated in a visuospatial learning task performed on a touch-sensitive screen (Talpos et al. 2009) and may be useful in evaluating effects of new drugs for Alzheimer disease. The translational utility of the human and animal versions of the test is emphasized through deleterious effects of hippocampal dysfunction on

performance across species as well as by the results of functional neuroimaging in humans with mild cognitive impairment.

The Morris water maze and the CANTAB PAL task effectively test the capacity of "what and where" memory, but they do not quite capture what is meant by episodic memory, which also requires the tagging of that memory to a particular time. Until recently, it has been assumed that episodic memory is uniquely human, involving the "mental time travel" of subjective reminiscence. Demonstrations of "what, where, and when" memory have appeared in the literature, beginning with food-caching birds (Clayton and Dickinson 1998), but also including rats (e.g., Eacott et al. 2005) and nonhuman primates (Martin-Ordas et al. 2010). This is clearly an important growth area in translational neuroscience, especially in terms of modeling the earliest manifestations of Alzheimer disease.

Working memory. Working memory refers to the active use of short-term information for the purpose of constructing representations of the world and guiding behavior (Baddeley 1986). Working memory is often termed "online" memory; memory traces are activated during planning and long-term memory retrieval. Working memory is at the interface between perceptual processes and the formation of long-term memory, and is often associated with so-called "executive processes." A major component of working memory is responsible for response selection and coordination of the outputs of different short-term memory buffers. In operational terms in animal studies, the use of the term "working memory" in the Olton maze refers to the requirements of that memory test procedure in which rodents are required to visit each of the eight arms once, and once only, to retrieve a maximum of eight pellets (contrasting with reference memory, see above). The rodents have to remember only where they have recently been, and this memory is irrelevant to performance on subsequent test days. It can be argued that this form of "working memory" is not quite the same as that defined by human memory theorists, such as Baddeley, where there is a coordination of different, modality-specific short-term memory buffers for use in various tasks such as planning, linguistic discourse, and logical reasoning. However, it does seem to overlap the human form of working memory in some important respects.

Olton's working memory tasks are related to the classical spatial delayed response and delayed alternation tasks that have been used to establish the role of the primate PFC in working memory (Goldman-Rakic 1996). This involvement of the PFC has been important for modeling cognitive deficits associated with schizophrenia, as working memory is impaired very early in the course of schizophrenia, possibly even the prodromal state (Wood et al. 2003). For the purpose of screening drug effects, delayed alternation in rodents is easily implemented in a maze or operant chamber, where it is often referred to as "delayed nonmatching to position." Nonmatching is an easier task for rodents than matching because of their preexisting foraging tendency to alternate spatial

choices. The operant version of the task allows the systematic variation of delay intervals, which can extend from 0–60 s. A "delay-dependent" effect in such a task is generally taken as evidence of a specific memory effect, independent, for example, of attention (Dunnett 1985).

However, for that inference to be valid, it is necessary for performance on the task at 0 s to be shown not to be similarly susceptible when the perceptual difficulty of the task is enhanced. An artifact that is difficult to surmount in the operant task is mediating responses which allow the rodent to adopt postures or positions minimizing the memory requirements of the task. One way to overcome this problem is to use sensitive touch screens to record responding, which can more precisely vary the spatial requirements of the memory tasks, as in the CANTAB battery for humans and nonhuman primates (Bussey et al. 2012).

Executive Functions

Executive functions are control processes that serve to optimize performance (e.g., in terms of earned rewards or reinforcers) by coordinating the various components of complex cognitive functions. Frequently (though not exclusively) associated with the functioning of the PFC, executive function is impaired in a variety of neuropsychiatric disorders, including ADHD and schizophrenia, and is thus a target for pharmaceutical therapy. Executive functions include some aspects of cognition already covered: cognitive flexibility in the face of changing environmental circumstances (attentional set shifting and reversal learning), the control of working memory, and the capacity to resolve conflicts between competing actions or predispositions. The latter may include what is termed "cognitive control" or "inhibitory response control," disruptions of which can lead to impulsive and compulsive behavior, relevant to such syndromes as OCD and ADHD.

Impulsive-compulsive disorders are one area in which animal models of human disorders fare surprisingly well. For example, there are several tests of impulsivity in rodents that have their equivalents in humans:

1. The stop signal reaction time (SSRT) test (Eagle and Robbins 2003) is a sophisticated form of the so-called Go/NoGo task, and is often used to measure motor impulsivity, e.g., in ADHD (Solanto et al. 2001). The SSRT test estimates the time it takes to cancel an initiated response. A stop signal is presented on about 20% of trials to indicate not to respond on that trial. This stop signal is interpolated at varying times (of the order of fractions of a second) after the onset of a Go cue; when it is presented at longer delays, it is correspondingly more difficult to cancel the response, as reflected by increased stop errors and by longer SSRTs. The SSRT task assumes that there is a "race" between a "go" process and an independent "stop" process; whichever "wins" determines the outcome of the trial. Pharmacological results with this

test show excellent translatability between human and rat studies. For example, the relatively selective noradrenaline reuptake blocker atomoxetine improves SSRT in both humans (Chamberlain et al. 2006) and rats (Robinson et al. 2008; Bari et al. 2009), whereas the selective serotonin reuptake inhibitor citalopram has no effect in either species (Chamberlain et al. 2006; Bari et al. 2009).

2. Delayed discounting of reward (also referred to as delayed gratification or delay aversion) occurs when an individual chooses between a small, immediate (or more certain) reward and a larger (or less certain) delayed one. The "impulsive choice" is to select the small, immediate or the small, certain reward. The assumption is that rewards are discounted by time or probability, and that a hyperbolic discounting function can predict an individual's choice. One of the parameters of this function (k) is essentially a measure of the "steepness" of discounting, or of impulsive responding. This task can be used readily in animals (Mazur and Herrnstein 1988; Evenden 1999) as well as humans (e.g., patients with ADHD or drug abusers). Measures of this form of impulsivity ("impulsive choice") do not always correlate in the same individual with measures of motor impulsivity (e.g., SSRT). This was the case for a large population of children with ADHD, resulting in a suggestion that ADHD reflected a spectrum disorder with different forms of impulsivity (Solanto et al. 2001). Structures such as the nucleus accumbens and orbitofrontal cortex are implicated in mediating delayed discounting in both rats (e.g., Cardinal et al. 2001; Winstanley et al. 2004; Bezzina et al. 2008) and in humans (McClure et al. 2004).
3. Impulsivity can also be measured in tests of visual attention, such as 5-CSRTT (discussed above; see also Robbins 2002), and in tests requiring timing, such as the differential reinforcement of low rates of responding schedule. Premature, defined as impulsive, responses on the visual attentional task have been shown to predict compulsive cocaine seeking in rats (Dalley et al. 2007) and may capture a similar vulnerability in human stimulant drug abusers (Ersche et al. 2012; Voon et al. 2014).

Impulsive behavior can thus be seen as a loss of inhibitory response control, which is a key feature of dysexecutive syndromes. It is, however, important to realize that impulsivity is not the only consequence of such a loss. Compulsive behavior may also be related to impulsive responding, but the difference between them is that compulsive behavior persists abnormally whereas impulsive behavior is frequently premature as a consequence of an inability to wait. Both are invariably associated with adverse consequences (e.g., more negatively valued events or a loss of positive reinforcements or rewards). Compulsive behavior may be modeled, for example, at several levels of response organization: motor stereotypy, rigidity of attention set (see above), and persistent

responding to the formerly reinforced stimulus during reversal discrimination learning when the previously nonrewarded stimulus now becomes correct or during extinction, when reward is omitted completely. OCD is the clinically prototypical compulsive disorder and is thus associated with impairments in extradimensional shifting (Chamberlain et al. 2006). In terms of brain activation, the performance of reversal learning (Chamberlain et al. 2008) helps to validate these rather general behavioral expressions of compulsive behavior as possible (neurobehavioral) endophenotypes for OCD. The parallel is heightened by the finding that serotonin depletion in the marmoset orbitofrontal cortex similarly impairs reversal learning (Clarke et al. 2004), possibly consistent with the use of SSRI (selective serotonin reuptake inhibitor) pharmacotherapy in OCD.

The Cognitive-Motivational Interface: "Hot" Cognition

The concept of "top-down" control by PFC executive mechanisms over striatal (and other subcortical) substrates can be extended to aspects of cognition and behavior other than impulsivity and compulsivity. The notion that the PFC is implicated in "emotional regulation" suggests that the PFC and associated structures (such as the anterior cingulate) have roles in moderating activity in structures which control emotional behavior and learning, such as the amygdala, with implications for clinical anxiety and depression. Observations of depressed patients suggest they have exaggerated (and indeed "catastrophic") reactions to negative feedback which impact their cognitive functioning (Elliott et al. 1996; Murphy et al. 1999). In the context of a probabilistic reversal learning task, where the correct choice is only rewarded on the majority (e.g., 80%) of occasions (with negative feedback following a minority, e.g., 20%, of trials), depressed patients often make inappropriate shifts in response choice on the next trial in response to spurious negative feedback—a tendency accompanied by a reduced PFC-induced deactivation of the amygdala (Taylor Tavares et al. 2008). It is possible that this rather complex paradigm can actually be modeled in rats; Bari et al. (2010) recently showed that manipulations which reduce serotoninergic function mimic some of the effects seen in depressed patients on "lose-shift" behavior.

Several other novel behavioral approaches to measuring affective bias in rodents have recently been introduced in both operant (Harding et al. 2004; Enkel et al. 2010; Anderson et al. 2013) and semi-naturalistic settings (Stuart et al. 2013). Enkel et al. (2010) trained rats to press a lever to receive a food reward associated with one tone, and to press another lever in response to a different tone to avoid punishment by electric foot shock. In an "ambiguous cue test," responses to tones with frequencies intermediate to the trained tones were taken to indicate expectation of a positive or negative event. In fact, a negative response bias was found in congenitally helpless rats, a genetic animal model of depression, and treatment with a pharmacological treatment mimicking stress-related changes, biased rats away from positive responding.

Anderson et al. (2013) used a similar paradigm to show that chronic citalopram induced a shift away from negative bias.

In another novel behavioral approach to measuring affective bias, rats encounter two independent positive experiences: the association between a food pellet reward and distinctive food bowls in which the pellets could be found by digging (Stuart et al. 2013). These experiences are gained on separate days under either neutral conditions or during a pharmacological or affective state manipulation (in this way it resembles the classical conditioned place preference procedure also employed for measuring reward preference). Affective bias is then quantified using a preference test where both previously rewarded substrates are presented together and the rat's choices recorded. The absolute value of the experience is kept consistent, and all other factors are counterbalanced so that any bias at recall can be attributed solely to the treatment. Similar to studies in healthy human volunteers observing emotional faces (e.g., Pringle et al. 2011), Stuart et al. (2013) observed significant positive affective biases following acute treatment with typical (fluoxetine, citalopram, reboxetine, venlafaxine, clomipramine) and atypical antidepressants (agomelatine, mirtazapine), and significant negative affective biases following treatment with drugs associated with inducing negative affective states in humans (FG7142, rimonabant, 13-cis retinoic acid). They also observed that acute psychosocial stress and environmental enrichment induced significant negative and positive affective biases, respectively, and involved memory consolidation. Thus, this is an excellent example for showing how motivational and cognitive processes may interact to generate apparent changes in affect in rodents.

Higher-Order Cognition, Including Social Cognition

I have shown that it may be feasible to decompose higher-order decision-making tasks in infra-human animals, as such components of tests—such as the Iowa gambling task (e.g., Zeeb et al. 2009), associative (trial-and-error) learning, reversal learning, delayed discounting and inhibitory control—all contribute to deficits seen in frontal and neuropsychiatric patients on this classic neuropsychological test. However, it may prove intractable to model higher-order planning tasks, at least in rodents, unless it can be shown that rats are capable of anticipating future needs and subordinating them to current ones. In the same context, it may be too much to ask that aspects of social cognition can be modeled in rodents, although elements of the detection of others' intentions (the so-called "theory of mind" functions) may be present in apes, though not in rhesus monkeys (Penn and Povinelli 2007). This altered efficiency is a severe problem because of the pervasive nature of social cognitive deficits, most notably in autism and schizophrenia; in the MATRICS battery, social cognition is one of seven main domains of deficit in schizophrenia. Tests of social behavior and interaction in animals may be useful through ethological observation (Moy et al. 2004), but they cannot hope to capture the complexity of human

social cognition. As mentioned above, social recognition has been employed as an appropriate test of certain social factors. For this to be considered a test of social (as distinct from more general information) processing, it is necessary to show that any effects are restricted to the social domain and to contrast them with a lack of effects, for example, in tests of visual, tactile or olfactory recognition memory.

Conclusions

Modeling specific aspects of motivation and cognition in rodents can bear some approximation to the greater complexity observed in human patients. As cognition is not a unitary construct, it is necessary to focus on specific aspects, for example, of memory that are highlighted by the patient's deficits. It is often important to test cognition in humans and other animals in ways that are as similar as possible, even using similar types of stimulus material and response mode where feasible. Although testing effects of drugs on intact (i.e., "normal") experimental animals can be informative, as is also the case with healthy human volunteers, the ultimate tests involve clinical trials and thus have to be paralleled by animals that have been manipulated in some way so that the potential of any cognitive-enhancing effect can be best evaluated.

It is not possible to survey here all of the relevant "animal models," subsuming "disease models" that have been employed for the different disorders, but it should be clear that the choice of relevant "perturbation" of normal system functioning is often crucial to the success of the model. In the next period, I anticipate that it will become increasingly important to compare effects of different treatments on different animal models, and to take increasing notice of "back-translation" as the critical test of validity. It is also emphasized that dependent variables measured should not necessarily simply be behavioral ones; the power and validity of a model need to be also based on concomitant neurobiological indexes, such as electrophysiological activity, neuroendocrine or neurochemical change, or genetic expression, so as to define the significance of changes in cognitive performance in the more general context of brain functioning. In addition to theoretical sophistication in the behavioral, neural, and genetic domains, there is also the increasingly important issue of methodological rigor in experimental design. Replicability and reliability, for example, across multiple laboratories or test centers are increasingly becoming important criteria that should be combined with other examples of good practice, such as random assignment of subjects to groups, unbiased blind assessments, and adequate statistical power.

First column (top to bottom): Ilka Diester, Bernd Sommer, Steve Hyman, Isabelle Mansuy, Trevor Robbins, Marius Wernig, Lennart Mucke
Second column: Franz Hefti, Akira Sawa, Trevor Robbins, Alvaro Pascual-Leone, Gül Dölen, Ilka Diester, Bernd Sommer,
Third column: Isabelle Mansuy, Marius Wernig, Lee Rubin, Karoly Nikolich, Franz Hefti, Akira Sawa, Lee Rubin