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Review

Translating cognition from animals to humans

J.F. Keeler [a,b,*], T.W. Robbins [a,b]

[a] Dept. of Expt. Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK
[b] Dept. of Behavioural and Clinical Neuroscience, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK

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ABSTRACT

Many clinical disorders, whether neurological (e.g. Alzheimer's disease) or neuropsychiatric (e.g. schizophrenia and depression), exhibit cognitive symptoms that require pharmacological treatment. Cognition is multi-faceted and includes processes of perception, attention, working memory, long-term memory, executive function, language and social cognition. This article reviews how it is feasible to model many aspects of human cognition with the use of appropriate animal models and associated techniques, including the use of computer controlled tests (e.g. touch-screens), for optimising translation of experimental research to the clinic. When investigating clinical disorders, test batteries should aim to profile cognitive function in order to determine which aspects are impaired and which are preserved. In this review we have paid particular attention to the validation of translational methods; this may be done through the application of common theoretical principles, by comparing the effects of psychological manipulations and, wherever feasible, with the demonstration of homologous neural circuitry or equivalent pharmacological actions in the animal and human paradigms. Of particular importance is the use of 'back-translation' to ensure that the animal model has validity, for example, in predicting the effects of therapeutic drugs already found in human studies. It is made clear that the choice of appropriate behavioral tests is an important element of animal models of neuropsychiatric or neurological disorder; however, of course it is also important to select appropriate manipulations, whether genetic, neurodevelopmental, neurotoxic, or pharmacological, for simulating the neural substrates relevant to the disorders that lead to predictable behavioral and cognitive impairments, for optimising the testing of candidate compounds.

Contents

* Corresponding author at: Dept. of Expt. Psychology, University of Cambridge, Downing Street, Cambridge CB2 3EB, UK. Tel.: +44 1223 333551; fax: +44 1223 333564.
E-mail addresses: jfk28@cam.ac.uk (J.F. Keeler), twr2@cam.ac.uk (T.W. Robbins).

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1. Introduction

Translational neuroscience has now become crucial to drug discovery. The vast expense of Phase 3 trials and relative lack of success of developing effective new compounds in psychiatry has necessitated a new approach to the use of animal models and preclinical strategies. Some of this lack of success is attributable to the lack of reporting of failed clinical studies which would allow more rigorous analysis and comparison across the human and animal data. Concern has also been raised relating to the shortcomings of animal models, with a failure to robustly guide the use of new compounds in the clinic, although we would suggest that there may also have been deficiencies in implementation and interpretation of the animal models themselves. Thus, for example, pragmatic requirements have often resulted in the use of less rigorous procedures or a reliance on only a single behavioral assay. Moreover, we find insufficient evidence of 'back-translation' (from humans to animals) of the fate of new drugs for us to be confident that any 'failures' are necessarily a result of inadequate animal models. Nevertheless, we believe that the new emphasis on translation has brought focus onto 'construct validity'—whether the identified cognitive processes are adequately homologous between species. This is distinct from 'predictive validity' which remains useful for predicting, for example whether a drug has an anti-depressant like action, but will too often result in another 'me-too' compound with the same basic failings as its relatives [1]. Clearly it is important to be sure that the predictive validity does not merely identify compounds that produce a particular effect if that effect is not convincingly linked to therapeutic benefit [2]. Additionally, progress in genetics and developmental biology has resulted in emphasis on the use of transgenic techniques as a new approach to understanding the aetiology of neuropsychiatric disorders and the identification of endophenotypes [3].

2. Test batteries for cognitive disorders

There are now an overwhelming number of clinical disorders requiring treatment of cognitive dysfunction, including not only obvious examples such as Alzheimer's disease, but also other neurodegenerative conditions such as Parkinson's and Huntington's disease, brain damage resulting from stroke or other injury, schizophrenia and bipolar disorder, depression, the sequelae of addiction, and developmental disorders such as autism and attention deficit hyperactivity disorder. It is important to realise that the term 'cognition' embraces a large number of distinct processes, sometimes even working in competition with one another, ranging from sensory input to motor or cognitive output (thinking). Additionally, many of the disorders mentioned above have distinct patterns of deficits—for example, the impairments of attention deficit hyperactivity disorder are very different from those of early Alzheimer's disease, although there can be some commonality in deficits (e.g. for schizophrenia and Alzheimer's disease) that probably results from overlapping pathology in particular brain regions (such as the hippocampus).

In order to design an animal model of a clinical disorder, it is necessary both to simulate some aspect of the disorder in genetic, molecular or neural system terms by a suitable intervention (e.g. genetic, environmental neurotoxin, and developmental) and also to select behavioral or cognitive variables that are relevant to the brain system or psychiatric disorder under study. Selecting a model it is important to accept that it is not possible to simulate all of the features present in a clinical disorder and for the purposes of interpreting interactions between induced deficits and the attempts to remediate them pharmacologically models should be kept simple. Clearly some animals prove much better models of human cognition than others, based on a more closely shared evolutionary ancestry. However, extensive drug profiling in non-human primates is often not possible due to a number of prohibitive factors (e.g. cost and breeding frequency) and consequently such studies often use a relatively small number of subjects. Furthermore, when investigating a new compound it is important to consider long-lasting carry-over effects and even permanent behavioral changes. Selecting the appropriate 'disease model' is a very important task that is beyond the scope of this article to review. Equally important, however, is the capacity to quantify performance appropriate to this model—and this will be our main focus.

Cognition essentially refers to the set of processes that manipulate representations in the brain in various ways to produce an appropriate output. These processes can be modular and autonomous (dedicated to producing a single type of output) or may be the result of a more complex interactive network. They include perception, various forms of attention, working memory, long-term memory, symbolic and propositional functions such as language, and executive control processes which serve to co-ordinate these functions for optimal decision-making and planning. Such mechanisms also interact with motivational and emotional processes, and also include social aspects of cognition. The cognitive processes are generally mediated by neural networks which range from relatively discrete systems to overlapping, interacting systems throughout wide regions of the neocortex, such as the temporal, parietal and frontal lobes, as well as the subcortical brain. Remarkably, with the exception of functions that may turn out to be uniquely human (language and aspects of social cognition such as the 'theory of mind'), many of these processes can be studied in experimental animals and have been used or could be used for drug discovery. The major question is always how convincing they are (and hence how predictive they are likely to be) as models of human cognition—that is, whether they exhibit a sufficient degree of functional homology. One pragmatic but not decisive test of this is to determine whether the functions are mediated by homologous brain circuitry; if they are then this strengthens the case that they may at least have arisen from common origins. The limitation of this approach of course is the controversy that often surrounds the identification of neuroanatomical homology. However, apart from many brain structures in the cortex, limbic system, basal ganglia, midbrain and brain stem, it is evident that the classical neurotransmitter systems such as acetylcholine, noradrenaline, serotonin and dopamine, have seen remarkable phylogenetic conservation. We will illustrate these themes through a survey of different aspects of cognition. An overarching consideration is that cognition has to be assessed with a battery of tests in order to determine the profile of cognitive deficits, and also whether improvements are obtained in some components of cognition at a cost to others. This 'battery' approach mirrors the recent adoption of similar batteries for testing cognition in humans, such as the MATRICS battery for schizophrenia [4], and more generally by the CANTAB battery [5,6] which utilises some tests that can be given to both humans, including clinical patients, and experimental animals. When configuring test

batteries a general consideration is the balance between tests of learning and performance. Training animals on tasks may lead to very stable performance baselines against which it is easy to detect perturbations produced by pharmacological challenge and that the return to baseline performance levels may also provide further dose-related comparisons. However, one possible outcome of such extended training is to make performance resistant to change and thus relatively insensitive to pharmacological manipulations. The alternative strategy of studying dynamic changes of performance during learning may not suffer from this disadvantage but may be impeded by greater variation and fluctuation in performance, which hinder the determination of dose related effects.

A relatively recent innovation has been the use of touch-screens to test cognitive function in humans and other animals. The requirement to actually make 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 towards the discriminative stimuli. The use of touch-screens was originally introduced for the testing of non-human primates [7], but extended to humans (e.g. via the CANTAB battery) and most recently to rodents [8]. One attraction of the use of automated measures such as the touch-screen is that the experimental protocols are objective and can therefore be easily standardised. Of course, it is important that all test procedures are standardised within laboratories, and it is also desirable to have such standardisation between labs in order to facilitate robust comparison. Whilst there are some concerns as to the ethological validity of touch-screen procedures in rodents, they do actually optimise the natural Pavlovian tendency of animals to approach and touch stimuli paired with reward.

Cognitive functions are generally componential, so that, for example, an impairment in perception, attention or motivation, caused for example by sedation or satiety, may lead secondarily to problems in memory (see Fig. 1). The ideal test therefore of memory would incorporate basic behavioral controls to show that any effects of a drug could not be ascribed to such other factors. Another important general feature for such tests, as also applied across other pharmacological assays, is the ability to test the effect of an agent over a wide manipulation range for a particular cognitive function—for example, memory tests can be conducted using a range of different delays between training and retention testing. This is analogous to the more obvious requirement for 'dose–response' functions in behavioral pharmacology. When considering the use of animal models in this context, whilst the brevity of generation turnover is useful for testing new compounds in naive subjects, it also limits the number of tasks on which an animal can be trained, often requiring time-consuming and repetitive training procedures—restricting the development of within-subject composite battery scoring systems.

Finally, one must obviously control for general sensory, motor or motivational factors which may affect cognitive function only indirectly (and thus lead to possible artefacts or mistaken reasoning). Sensori-motor functions, for example in transgenic mice, are often tested in a neurological battery assessing various sensori-motor reflexes as well as simple tests of sensory or motor function [9]. Primary motivation can be assessed, for example, in terms of ingestive behavior (eating or drinking) by varying the incentive with low or high calorie foods, as well as more esoterically in terms of threshold changes in electrical current required for intra-cranial self-stimulation behavior [10]. It is generally necessary to measure different aspects of motivation, including both appetitive (or preparatory) responding (e.g. locomotor excitement in anticipation of feeding) and consummatory behavior (whether, for example, ingestive or sexual). Thus, appetitive motivation is also often assessed in terms of instrumental (or operant) behavior directed towards 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. The best designed tests of cognition incorporate a

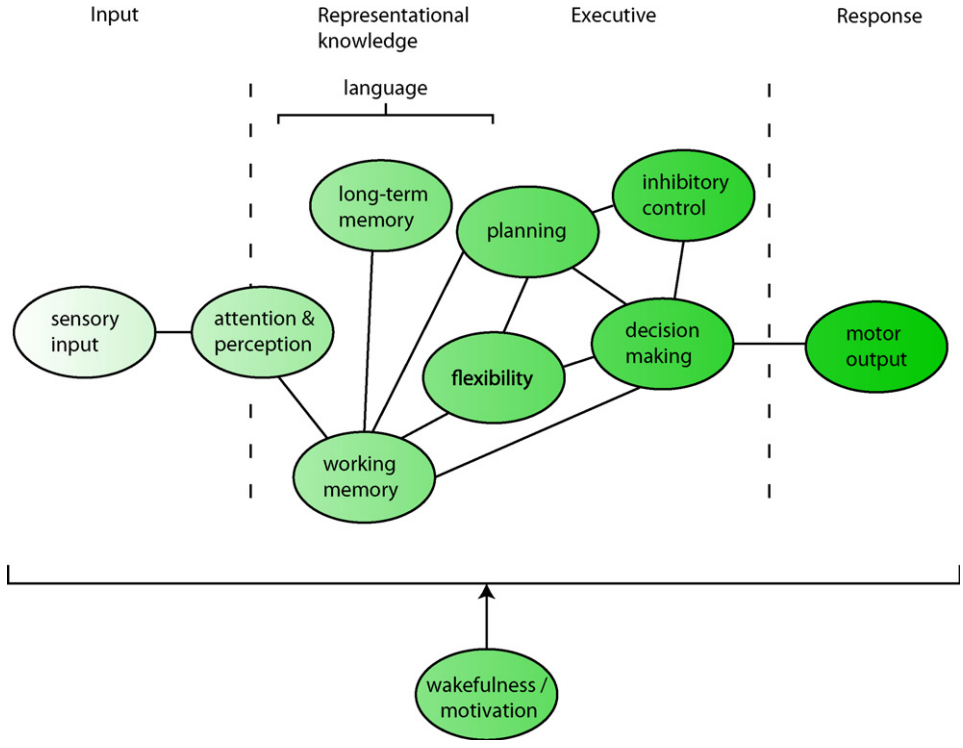

Fig. 1. A simplified diagram showing some of the core components of cognition. The emphasis here is placed on transformation from sensory information to motor output.

condition or measure that provides internal controls for motivational effects, and several examples of this will be exemplified below.

3. Testing specific aspects of cognition

3.1. Perception

Perception is the 'on-line' representation of the world by the sensory systems and must ultimately be used to make decisions. This percept of the world is the result of current sensory stimulation which is temporally bound together over transient time- and space-windows and combined with longer term memory systems. Perception is generally tested in experimental animals and humans by means of discrimination learning and recognition, whereby responding in the presence of one stimulus is reinforced (e.g. with food for food-restricted rats or feedback such as points or social praise for humans), whereas the other is not. The stimuli are presented randomly across two or more locations to avoid the use of alternative strategies (e.g. using spatial factors) to solve the task.

Test sensitivity or load is effected by varying the degree of similarity of the stimuli, and also using a titration method to determine the limits of discrimination (by which the stimuli are made more similar following a correct response and less so by an incorrect one) which may lead to a measure of sensory threshold. A comparison of different types of discrimination performance (e.g. visual, auditory, and olfactory modalities) allows the identification of core cognitive functions that are sensitive to any sensory change (modality independent). Learning factors can be excluded if the deficit occurs following training to asymptotic levels of performance. A classic quantitative technique for separating sensory/perceptual from motivational or other response biasing factors is signal detection theory, which has been applied with success to determine whether drugs or other manipulations affect primarily perceptual/sensory factors (d') or response bias (β). The main brain regions implicated in perception are in the mammalian posterior cortex, where the so-called unimodal association areas are located. The perirhinal cortex has been identified as an interface between perception and simple forms of representational memory such as recognition (deciding whether something has been perceived previously or not) [11]—and this illustrates one of the difficulties faced when drawing firm boundaries between perceptual and mnemonic processes. Furthermore, portions of the hippocampus such as the dentate gyrus, which are generally considered as mediating memory, are implicated in perceptual processes such as 'pattern separation' which becomes especially important in making fine discriminations, e.g. between different locations, which has been associated with a dependence on local neurogenesis within the hippocampus [12].

3.2. Attention

Attention can be difficult to distinguish from perception in practical terms; it is generally done so by detecting fluctuations in asymptotic test performance that cannot be ascribed to changes in motivational state. There are several types of attention that have been identified in the human work, which can also be modelled in experimental animals. These include selective attention (focusing on one input or feature, whilst 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 are well-known to occur in such disorders as attention deficit hyperactivity disorder, schizophrenia, addiction and mania, as well as after brain damage.

3.2.1. Pre-attention and covert attention

In humans attention can connote both conscious (explicit, overt) and unconscious (implicit, covert) aspects. Moreover, 'pre-attentive' filtering or gating processes have been postulated which are also assumed to be unconscious. The pre-pulse inhibition (PPI) paradigm is the most celebrated test within this domain [13], as it has been shown to have enormous translational validity and potential across species, and has also been of practical use in studies of schizophrenia, where implicit measures of cognition are particularly useful, and in screening for the effects of anti-psychotic drugs. In practical terms it is both convenient and rapid for mass testing, for example, of rats for behavioral pharmacology and transgenic mouse preparations. PPI is a modulation of the startle response to loud noises or other intense stimuli. This modulation comes from the inhibition of the startle response (frequently whole body displacement) that comes from the presentation of a brief surrogate stimulus generally of the same modality but of much reduced intensity that occurs just before the startle stimulus. PPI is impaired by dopamine D2 agonists and remediated by D2 receptor antagonists, but is also sensitive to a number of other pharmacological manipulations [13].

A form of covert attention has been described in humans that occurs when attention is cued spatially in advance to a particular location by the presentation of a "pre-stimulus" in that location; 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 instead presented elsewhere [14]. This form of attention has been attributed to mechanisms within the human parietal cortex, but similar processes can be characterised in experimental animals, including rats [15].

3.2.2. Habituation and latent inhibition

Another attentional-like process can be discerned during learning when stimuli have no consequence. This is often manifested as habituation, the waning of a response to a repeated stimulus, and this can be readily measured in several situations in animals and humans (often using psychophysiological recordings in the latter case, such as skin conductance or heart rate). However, latent inhibition is an additional consequence that can be long-lasting. Latent inhibition refers to the retardation of learning about a stimulus that can occur if that stimulus has never previously predicted reinforcement [16]. One hypothesis about latent inhibition is that it reflects an inhibitory attentional capacity—the subject simply can be thought of as 'ignoring' the stimulus. Latent inhibition (or a related process, termed learned irrelevance) has some advantages as a test of attention in that impairments in latent inhibition may be expressed subsequently as improved learning. Moreover, deficits in latent inhibition in patients with schizophrenia are thus difficult to explain as impairments in motivation, given that they may lead in certain circumstances to improved performance. Latent inhibition has translational potential; however, it is sometimes difficult for practical reasons to be sure that what is being measured in humans as latent inhibition is the same process in rodents.

3.2.3. Continuous performance tests

Continuous performance tests measure the capacity to sustain attention and generally reveal impairments in disorders such as schizophrenia or attention deficit hyperactivity disorder. A simple analogue of this in experimental animals is the 5-choice serial reaction time task, based on a paradigm of the same name once used to assess attention in human volunteers in a variety of experimental situations, including stress, distracting white noise, and following drug treatment [17]. The 5-choice task measures the

accuracy (errors of commission) and latency of detecting visual targets, as well as errors of omission (failure to respond) and impulsive responding (responding prior to target onset). A measure of the latency to collect food pellets provides a control measure of motivation. It is important to consider the overall profile of effects in the 5-choice task, for example, increased omissions can denote either an attentional impairment or altered motivational/motor deficits dependent on the pattern of effects on other measures within the task. 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, and also the occurrence of defined distractors, such as a burst of white noise interpolated into the inter-trial interval. This task has now been widely employed using rats and more recently mice to measure the effects of drugs, regional brain lesions and manipulations of the central neurotransmitters or genetic mutations. Its major uses have been to reveal beneficial effects on response accuracy of some putative 'cognitive enhancing' drugs such as dopamine D1 agonists [18], and also to characterise the neuropharmacology of impulsive behavior, which has also been shown to predict escalation of cocaine self-administration. A version of the human task has been used to demonstrate attentional improvements in patients with Alzheimer's disease given the anticholinesterase tacrine [19].

There are several variants of the standard 5-choice task, the main one of which requires the rat to initiate a trial with a centrally located response followed by detection of a peripheral target. This paradigm has been used to quantify the 'attentional neglect' that can occur after unilateral manipulations of cortico-striatal brain regions [20]. A rather different form of test requires the cross-modal integration of auditory and visual stimuli [21] and includes an important control that animals must detect not only the presence of the stimulus but also its absence.

3.2.4. Attentional set-shifting

Some tests of rodent selective attention appear to mimic strongly specific tests in humans that are sensitive to frontal lobe damage, involving the formation and shifting of attentional 'sets' and the ability to avoid a pre-potent response to one aspect of a stimulus in order to respond to another. It is this latter aspect of inhibitory control over prepotent tendencies that has resulted in these tests also being employed as tests of so-called 'executive function' (see below). Such tests have proven highly 'translational' in that they have been effected in a range of experimental animals, including mice, rats, marmoset monkeys, rhesus monkeys and humans in ways that appear to be homologous; for example, attentional set-shifting appears to implicate the prefrontal cortex (lateral PFC in primates, including humans) on the basis of both lesion [22] and neuroimaging [23] studies (refer to Fig. 2).

The attentional set-shifting task is based on the use of compound stimuli (i.e. that vary in at least two perceptual dimensions, such as color and shape for visual stimuli, or alternatively between texture and odor stimuli in different modalities). Humans, non-human 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 one, including 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 intra-dimensional shifting (where novel exemplars are introduced, but the *same* dimension, such as color, is reinforced). Finally, an extra-dimensional shift (ed shift) is arranged 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 Sort Test, which is much used to assess cognitive flexibility in human patient populations, especially those with presumed damage to the prefrontal cortex. 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 [24]. Performance across the various stages is qualitatively comparable to that seen in primates; the extra-dimensional shift is the most sensitive stage to drug effects, performance at other stages usually being employed as internal controls. There are now various versions of these tests of 'cognitive flexibility' which use similar logic for shifts between, for example, responding according to body turns or to space on a cross-maze [25], or alternatively attending to discrete (e.g. visual) cues versus changes in the gross surrounding (contextual cues) on a maze [26]. 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 extra-dimensional shifting have been found not only in patients with obsessive–compulsive disorder (OCD), but also in their first degree relatives, suggesting that the capacity to shift attention in this way is an endophenotypic biomarker for OCD [27]. By contrast, although extra-dimensional shifting is also impaired in schizophrenia, it is not apparently impaired in the unaffected siblings of patients [28]. Nevertheless, the attentional set-shifting paradigm has been shown to be sensitive to the cognitive enhancing effects of modafinil in patients with schizophrenia [29] and this has allowed a dramatic case of 'back-translation' using the rodent version of this paradigm. In this study a popular 'model' of the cognitive deficit syndrome in schizophrenia was employed—sub-chronic treatment with phencyclidine (PCP), which impairs relatively selectively the extra-dimensional shift. This deficit was rescued however by treatment of the rats with acute modafinil, mimicking the human finding [30].

3.3. Associative learning

Both Pavlovian and instrumental conditioning are considered to have cognitive aspects, given that the basis for the former is the causal prediction of events in the world leading to expectancy and, for the latter, cognitive control over environmental contingencies becomes feasible [31]. Disruptions of aspects of Pavlovian and instrumental learning almost certainly underlie all of the major forms of neuropsychiatric disorder, including drug addiction, anxiety, and probably depression and schizophrenia. For example, mismatches during Pavlovian conditioning between expected and obtained outcomes are often referred to as representing 'prediction errors'. Such processing has been linked with the phasic activity of midbrain dopamine neurons in monkeys [32], with aberrations in the generation of prediction errors being linked to the possible induction of psychosis [33].

The detection of instrumental contingencies (e.g. the arbitrary act of lever pressing leading to food delivery for a rat) can be thought of as a higher-order cognitive process which plays an important component of our ability to make voluntary actions that form part of goal-directed behavior. *Learned helplessness* is a theory about how experience of loss of control over environmental contingencies can lead to depressogenic behavior. Such loss of control can be produced by disrupting top-down connections from the rat medial prefrontal cortex to such regions as the serotonergic raphé nuclei [34]. Whilst there is some doubt now that learned helplessness is a paradigm that is specific to human depression [35], it is clear that tests such as the forced swim test in a tank of inescapable water ('behavioral despair' [36]) and the tail suspension test [37] (in mice) are somewhat crude examples of this general concept.

Learning is generally measured in simplified chambers or operant settings including touch-sensitive screens (see Fig. 3); however, maze learning is often employed when spatial cognition

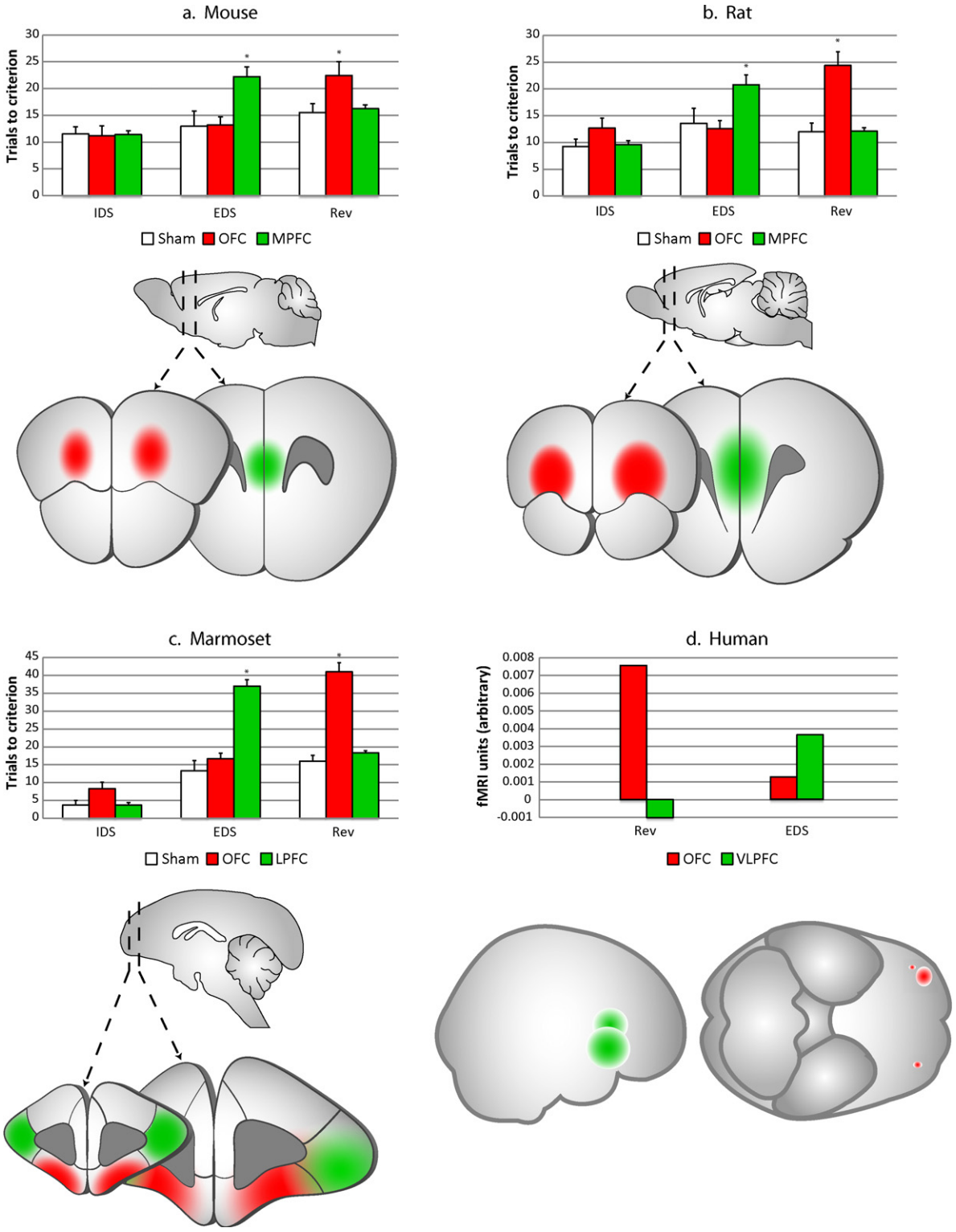

Fig. 2. Functional homology has been identified using set-shifting tasks in (a) mice [94]; (b) rats [24,95]; (c) monkeys [96]; (d) humans [23]. In figures (a)–(c) red denotes lesions to the OFC and results in a significant reversal deficit, whereas green denotes lesions to medial/lateral PFC regions and results in extradimensional-shifting deficits. Likewise, in humans (d) reversal is associated with the activation of the OFC (red) and extradimensional-shifting is associated with activation of the VLPFC (green). Figures have been adapted from the original sources. *Abbreviations*: OFC (orbitofrontal cortex); PFC (prefrontal cortex); VLPFC (ventrolateral prefrontal cortex).

is the main subject of study, being especially compatible with the well-developed foraging tendencies of rodents. Translational possibilities for learning paradigms are considerable, including even, for example, the Pavlovian phenomenon of eye-blink conditioning which can be studied readily in humans with dementia as well as rabbits [38].

3.4. Memory

Memory can be sub-divided into many processes with a basic distinction being between relatively transient short-term memory and long-term, or more permanent memory. Memory 'traces' are thus hypothesised to be 'consolidated' into long term memory.

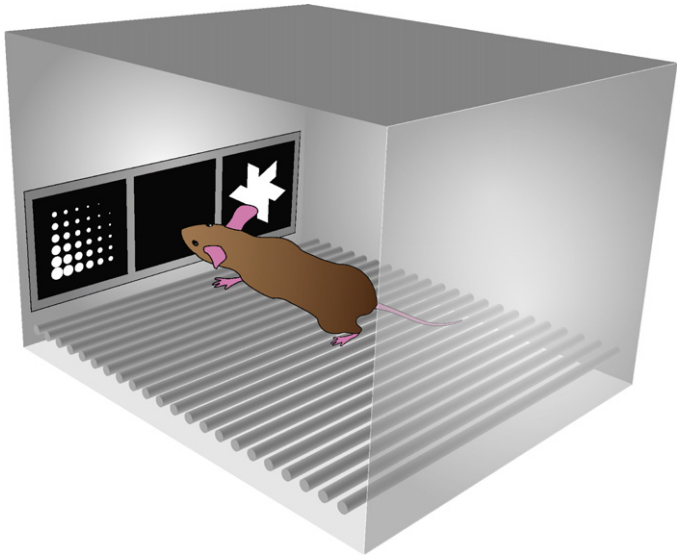

Fig. 3. A diagrammatic representation of a touch-screen task as developed and used by Bussey & Saksida.

Another distinction that has been made in human long-term memory by Tulving [39] is the categorisation of 'episodic' (generally autobiographical, the 'what, where and when' of memory) versus semantic memory (memory for meaning), which is perhaps difficult to investigate in experimental animals such as rats and monkeys, but some progress is being made.

3.4.1. Consolidation, reconsolidation and extinction

Probably the greatest contribution made to the study of memory from rodent studies has been the post-trial or post-training paradigm popularised by McGaugh [40]. 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 24h or 3d later. The post-training manipulation is thus designed to influence consolidation, either adversely or beneficially 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 great advantage of this design is that the drug cannot be said to have affected memory indirectly by its actions on perceptual, attentional or motivational mechanisms, as it is administered at a time (after training) when these mechanisms no longer impinge on learning. It is necessary however to perform controls with longer post-trial treatments to check that the drug effects are not affecting retention pro-actively (i.e. by being active at the time of retention and 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 been employed for example to demonstrate the contribution of noradrenergic, opioidergic and GABA-ergic mechanisms to emotional memories laid down in the amygdala. The paradigm has not 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 post-traumatic-stress-disorder (PTSD). However, a variation on the consolidation theme may prove therapeutically important for PTSD, anxiety and addiction. Thus, it has been shown that the presentation of a CS alone may result in reconsolidation [41], a period of memory destabilisation when the memory trace regains its vulnerable status. Thus, it may be feasible to target this phase with pharmacological agents (e.g. NMDA receptor antagonists, β-blockers [42]). The reconsolidation process is mirrored by an active process of extinction learning which occurs when the reinforcer (e.g. shock or food) is omitted. This process too is amenable to pharmacological manipulation, e.g. speeding of extinction to anxiety cues produced by NMDA receptor agonists [43] – and this has already been exploited in human anxiety trials combining behavioral therapy with D-cyclo-serine treatment [44].

3.4.2. Recognition memory, recall and declarative memory

Recognition memory refers to the ability to detect familiarity and, for humans at least, to reminisce about previous experience of objects, people or places. A commonly used task is that of object recognition (devised by Ennaceur and Delacour [45]) in which a rodent (or monkey [46]) 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). Of course, the utility of this test is limited by the degree of exploration and hence the salience of the objects to the animal. The problem can be overcome to some extent when experimental animals are used as objects in tests of "social recognition". Recognition memory is generally manifested over long delays, up to 24 h, although it can be tested at much shorter intervals also and has been shown to depend on structures such as the rodent perirhinal cortex. Recognition memory tasks generally employ stimuli only once, so that 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, and the test therefore becomes one of recency memory (how *recently* the stimulus has been experienced) rather than one of recognition memory. In that case, the test also becomes one more of frontal rather than temporal lobe function [47]. 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 [48] in both rats and monkeys. 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 [8,49,50].

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, and nor is it the earliest manifestation of Alzheimer's disease, where amnesia for *episodic* memories is more evident.

Some human and non-human primate data indicate that the hippocampus is implicated in forms of associative memory, particularly for animals involving space or other contexts; for example, remembering the location of objects [51,52]. These forms of memory are often referred to as reference memory tasks in the animal literature. Recognition and recall correspond to what Squire [53] has denoted for humans as 'declarative memory' as distinct from 'procedural memory' (memory for 'how', or for 'skill'). We have not discussed procedural memory in any detail in this article, but it may readily be tested in rodents in motor-learning situations such as the rotor-rod test, or as memory for 'habits', being part of the process of instrumental learning.

3.4.3. Reference memory

Reference memory is a form of long-term memory which refers to rodent task requirements that stay constant from trial to trial. This definition was originally applied by Olton [54] to rats remembering the constant location of food-baited arms in an 8-armed radial maze. However, it can also be applied to the Morris water-maze, a notable assay of hippocampal function [51], 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 vat of water. The rodent is allowed to swim the maze beginning from different vantage points, and so successful learning depends on the construction of a 'cognitive map' to navigate the environment. Whilst this task may seem to lack translational validity for testing, e.g. memory in patients with Alzheimer's disease or schizophrenia, in fact there are now promising 'virtual reality' tests of spatial navigation that are being validated for patient assessments—for example, by assessing effects of hippocampal damage in humans [55], as well as in patients with schizophrenia [56].

A related approach has been to 'back-translate' from human to animal studies. The CANTAB Paired Associates Learning 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 [57] (MCI; likely prodromal Alzheimer's disease) and some patients with schizophrenia [58]. It has been shown to be sensitive to impairments in MCI patients nearly 3 years before formal diagnosis [59]. Recently, it has been possible to simulate the main aspects of this test in a visuo-spatial learning task for rodents, performed on a touch-sensitive screen [60] which may thus have utility in evaluating effects of drugs designed for Alzheimer's disease. The translational utility of the human and animal versions of the test is emphasised through common effects of hippocampal dysfunction across species and also by the results of functional neuroimaging in humans with MCI.

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, but now demonstrations of 'what, where, and when' memory have appeared in the literature, beginning with food caching birds [61], but now also including rats [62] and non-human primates [63]. This is clearly an important growth area in translational neuroscience, especially in terms of modelling the earliest manifestations of Alzheimer's disease.

3.4.4. Working memory

'Working memory' is a term that refers to the active use of short-term information for the purpose of constructing representations of the world and guiding behavior [64]. Working memory is often termed as 'on-line' memory, which activates memory traces during planning and long-term memory retrieval. It stands at the interface between perceptual processes and the formation of long-term memory, and is often associated with the so-called 'executive processes'—a major component of working memory being responsible for response selection and for co-ordinating 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 a memory test procedure in which rodents are required to visit each of the 8 arms once and once only, in order to retrieve a maximum of 8 pellets (thus contrasting with reference memory, see above). So the animals 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' [54] is not quite the same as that defined by human memory theorists such as Baddeley [64], where there is a co-ordination 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 clearly related to the classical tests of spatial delayed response and delayed alternation that have been used to establish the role of the primate prefrontal cortex in working memory [65]. This involvement of the prefrontal cortex has proven important in modelling cognitive deficits associated with schizophrenia, it being evident that working memory is impaired very early in the course of schizophrenia [66], possibly even during the prodromal state [67]. 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 non-matching to position' [68]. Non-matching is an easier task for rodents than matching because of their pre-existing foraging tendency to alternate spatial choices. The operant versions of the task allow the systematic variation of delay intervals, which can extend from 0 to 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. 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 additional artefact that is difficult to surmount in the operant task is that of mediating responses, by which the rodent adopts postures or positions that minimise the memory requirement of the task [69]. One way of overcoming this problem is to use touch-screens to record responding, as there is greater freedom relating to the spatial requirements of the task when compared to a standard linear array [70], as in the CANTAB battery for humans and non-human primates.

3.5. Executive functions

These can be defined as control processes that serve to optimise performance (e.g. in terms of earned rewards or reinforcers) by co-ordinating the various components of complex cognitive functions. Executive functions are frequently (but not exclusively) associated with the prefrontal cortex and are commonly impaired in a variety of neuropsychiatric disorders, including attention deficit hyperactivity disorder (ADHD) and schizophrenia. These functions potentially include some aspects of cognition that we have already covered above, for example, cognitive flexibility in the face of changing environmental circumstances (attentional set-shifting and reversal learning) and the control of working memory, as well as the capability of resolving 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 syndromes such as obsessive–compulsive disorder and ADHD.

Perhaps surprisingly, this is 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. These include: (i) the stop signal reaction time (SSRT) test [71], which is a sophisticated form of the so-called Go/NoGo task, and is often used to measure motor impulsivity for example in ADHD [72]. This test estimates the time it takes to cancel an already initiated response (SSRT). 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 and whichever 'wins' determines the outcome of the trial. Pharmacological results with this test show a remarkable degree of translatability between human and rat studies. For example, the relatively selective noradrenaline reuptake blocker atomoxetine improves SSRT in both humans and rats [73,74] whereas the selective serotonin reuptake inhibitor citalopram has no effect in either species [74,75]. (ii) Delayed discounting of reward – also referred to as delayed gratification or delay aversion – whereby 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 by probability, and that a hyperbolic discounting function can predict 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 also be used readily in animals [76,77] as well as humans (e.g. patients with ADHD or drug abusers). Intriguingly, 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 [72]. It is of interest that structures such as the nucleus accumbens and orbitofrontal cortex are implicated in mediating delayed discounting in both rats (e.g. [78–80]) and in humans [81]. (iii) Impulsivity can also be measured in tests of visual attention such as the 5 choice serial reaction time task (5-CSRTT, see above [17]) and in tests requiring timing, such as the differential reinforcement of low rates of responding schedule (DRL). Premature (defined as impulsive) responses on the visual attentional task have been shown to predict compulsive cocaine seeking in rats [82] and may capture a similar vulnerability in human stimulant drug abusers [83]. Premature or inefficient responding on the DRL schedule (when the time intervals are relatively long) have been used as a predictor for anti-depressant drug efficacy [84], although there is no obvious counterpart in human responses to anti-depressants.

Impulsive behavior can thus be seen as a loss of inhibitory response control, which is a key feature of dysexecutive syndromes, but it is important to realise that impulsivity is not the only consequence of such a loss. Compulsive behavior is perhaps 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 modelled 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 non-rewarded stimulus now becomes correct or during extinction, when reward is omitted completely. OCD is the clinically prototypical compulsive disorder, and so the association of OCD with impairments in extra-dimensional shifting [85] and, in terms of brain activation, during the performance of reversal learning [75] 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 5-HT depletion in the marmoset orbitofrontal cortex similarly impairs reversal learning, possibly consistent with the use of SSRI pharmacotherapy in OCD [86,87]. More problematic is the impaired SSRT performance of OCD patients, given that SSRT is an obvious measure of impulsivity. However, it must be noted that an inability to stop an initiated response may well contribute to OCD symptomatology.

The concept of 'top-down' control by PFC executive mechanisms over what are probably striatal (sub-cortical) substrates can also be extended to other aspects of cognition and behavior beyond that of 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 also have roles to moderate 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 impacts their cognitive functioning [88,89]). 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 of trials, e.g. 20%), depressed patients often make inappropriate shifts in response choice following spurious negative feedback—a tendency which is accompanied by a reduced PFC-induced deactivation of the amygdala [90]. It is possible that this rather complex paradigm can actually be modelled in rats—Bari et al. [91] recently showed that manipulations reducing serotoninergic function mimic some of the effects seen in depressed patients on 'lose-shift' behavior.

3.6. Higher order cognition, including social cognition

The observations discussed so far encourage the view 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, as 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 (as distinct from apes [92]), unless it can be shown that rats are capable of anticipating future needs, and subordinating more immediate goals. In the same context, it may be too much to ask that aspects of social cognition can be modelled in rodents, although elements of the detection of others' intentions (the so-called 'theory of mind' functions) may be present again in apes (though not in rhesus monkeys [93]). The lack of social complexity in non-humans is a severe problem because of the pervasive nature of social cognitive deficits, most notably in autism and schizophrenia, which has resulted in the MATRICS battery having social cognition as one of its 7 main domains of deficit in schizophrenia. Tests of social behavior and interaction in animals may be useful, generally using ethological observation, 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, but in order for this to be considered as 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, it would be necessary to contrast them with a lack of effects, for example, in tests of visual, tactile or olfactory recognition memory.

4. Conclusions

In this survey, we have mainly discussed how it is feasible to model specific aspects of cognition in experimental animals that may bear some approximation to the greater complexity often 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, for example, even using similar types of stimulus material and response mode where feasible. Whilst testing effects of drugs on intact (i.e. 'normal') experimental

animals can often be informative, as is also the case with healthy human volunteers, the ultimate tests involve clinical trials and so 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. We have not had the opportunity to survey all of the relevant 'animal models', subsuming 'disease models' that have been employed for the different disorders, but we can comment again here that the choice of relevant 'perturbation' of normal system functioning is often crucial to the success of the model. On the other hand, of course, where a drug treatment enhances performance for a variety of preparations, this may simply indicate that certain disorders have multi-factorial aetiology, and what is important is to treat defined symptoms. It is also emphasised that the dependent variables measured should not necessarily simply be behavioral ones; the power and validity of a model will be also based on concomitant neurobiological indices 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.

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