



Review

Consideration of species differences in developing novel molecules as cognition enhancers

Jared W. Young^{a,*}, J. David Jentsch^b, Timothy J. Bussey^c, Tanya L. Wallace^d, Daniel M. Hutcheson^e

^a Department of Psychiatry, University of California San Diego, 9500 Gilman Drive MC 0804, La Jolla, CA 92093-0804, USA

^b Department of Psychology, University of California Los Angeles, CA 90095-1563, USA

^c Department of Experimental Psychology, University of Cambridge, Downing St., Cambridge CB2 3EB, UK

^d Center for Neuroscience, SRI International, 333 Ravenswood Avenue, M/S 100-69, Menlo Park, CA 94025, USA

^e Maccine Pte Ltd., 10 Science Park Road, The Alpha #01-05, Singapore Science Park II, Singapore 117684, Singapore

ARTICLE INFO

Article history:

Received 11 January 2012

Received in revised form

20 September 2012

Accepted 2 October 2012

Keywords:

Species

Differences

Mice

Rats

Non-human primates

Monkeys

Human primates

CNTRICS

Cognitive

Attention

Reversal learning

Impulsivity

ABSTRACT

The NIH-funded CNTRICS initiative has coordinated efforts to promote the vertical translation of novel procognitive molecules from testing in mice, rats and non-human primates, to clinical efficacy in patients with schizophrenia. CNTRICS highlighted improving construct validation of tasks across species to increase the likelihood that the translation of a candidate molecule to humans will be successful. Other aspects of cross-species behaviors remain important however. This review describes cognitive tasks utilized across species, providing examples of differences and similarities of innate behavior between species, as well as convergent construct and predictive validity. Tests of attention, olfactory discrimination, reversal learning, and paired associate learning are discussed. Moreover, information on the practical implication of species differences in drug development research is also provided. The issues covered here will aid in task development and utilization across species as well as reinforcing the positive role preclinical research can have in developing procognitive treatments for psychiatric disorders.

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Contents

1. Introduction	2182
1.1. Aspects of cross-species translational validity	2182
1.1.1. Construct validity	2182
1.1.2. Predictive validity	2182
1.1.3. Face validity	2182
1.2. Structure to assess cross-species translational validity	2183
2. Examples of tasks where differences between species' performance have been observed	2183
2.1. 5-Choice serial reaction-time task (5CSRTT)	2183
2.2. Olfactory discrimination	2184
2.3. Touchscreen testing	2184
3. Examples of tasks whereby consistency between species have been observed	2186
3.1. Reversal learning	2186
3.2. Paired associates learning	2187
3.2.1. PAL testing and training	2187
3.2.2. Pharmacology	2188

* Corresponding author. Tel.: +1 619 543 3582; fax: +1 619 735 9205.

E-mail address: jaredyoung@ucsd.edu (J.W. Young).

4. Practical implications for the drug discovery process.....	2188
5. Conclusions	2189
Acknowledgements.....	2190
References	2190

1. Introduction

CNTRICS is a NIH-funded initiative ultimately aimed at developing procognitive therapeutics for schizophrenia. In order to develop these treatments, it is understood that the drug discovery process requires testing putative treatments in animals first, prior to testing in humans. Moreover, the likelihood that an efficacious treatment in animals will be efficacious in humans is increased if the behavioral tasks used for these species examine the same cognitive construct, because it is reasoned that construct validity increases the involvement of common biological mechanisms across species. Hence, CNTRICS has identified specific cognitive constructs that require treatment in schizophrenia and have attempted to identify tasks that measure these specific constructs in animals and in man. While there exist examples of well-developed tasks with cross-species translational validity from mouse, to rat, to non-human primate (NHP), and to human primate, species differences in performance of otherwise identical cognitive tasks have been observed. The purpose of this review is to: (1) provide a structure by which the cross-species translational validity of tasks can be assessed; (2) give examples of (a) divergent behavior between species despite similarities in testing protocols and (b) convergent behavior in similar tasks – particularly from those chosen to represent specific cognitive constructs identified by CNTRICS; (3) highlight the differences in techniques that may be utilized when developing tests for mice, rats, NHPs, and human primates; and (4) comment on the practical implications of these technical differences for the drug discovery process.

1.1. Aspects of cross-species translational validity

There are numerous criteria that one can use to determine whether a task used to assess a cognitive function is similarly performed by laboratory animal species and humans. The primary interest of CNTRICS has been to develop tasks that measure a specific cognitive construct utilizing the same neurocircuitry between species. Evidence for such similarities is often referred to as construct validity. It is tempting to assume that a task is valid when tasks performed by humans activate certain structures that when lesioned in animals impair performance of a similar task. While this might indeed confer some construct validity, there are other aspects to validation that require examination because brain activations measured in humans may correlate with, but not causally mediate, performance, while lesions can sometimes exert non-specific effects on cognitive task performance. Within construct validity one can examine convergent and divergent validities (see below). Moreover, though construct validity is thought to confer predictive validity, the latter is the primary goal of the research. On the other hand, face validity, though often cited as important, can ultimately have limited impact on the cross-species translational validity of the task.

1.1.1. Construct validity

Most simply defined as the accuracy to which the test measures that which it is intended to measure (Geyer et al., 1999), construct validity is usually considered as the most important property to establish the cross-species translational validity of a test (Geyer et al., 1999; Lipska et al., 1995), but its establishment can be challenging and is – consequently – rare. Problems

arise as conceptions about what a test is supposed to measure can change as scientific theories and theoretical constructs are modified. Thus, a task's usefulness and hence its overall validity cannot be determined simply by the degree of construct validation that it has. The process of construct validation is extremely valuable in establishing the overall development, refinement and validity of the task. As new experimental and observational evidence accrues from both preclinical and clinical testing, the task can be refined and therefore enable more accurate predictions.

A test has convergent (or concurrent) and discriminant validity only in relation to other tests. Convergent validity is the degree to which a test correlates with other tests that attempt to measure the same construct (Taiminen et al., 2000). Discriminant validity is the degree to which a test measures aspects of a phenomenon that differ from other aspects that is assessed by other tests (Taiminen et al., 2000). Testing these aspects of validity of the tasks chosen by CNTRICS for each construct will be essential.

1.1.2. Predictive validity

This aspect of validity concerns the ability of a test to make correct predictions about the clinical test of interest (Geyer and Braff, 1987; Geyer and Markou, 1995). Predictive validity is often used narrowly to refer only to the test's ability to identify drugs that have therapeutic value in humans (referred to as pharmacological isomorphism (Matthyse, 1986)). This utilization is limited however, because it ignores other important aspects of a task that can be validated by making successful predictions (Ellenbroek and Cools, 2000). Predictive validation of the experimental preparation is also observed whereby variables have similar influences in the preclinical task and the clinical task and can enhance one's understanding of the phenomenon. For example, a vigilance decrement – where attention wanes over time – is observed in numerous human continuous performance tests (Parasuraman, 1998; Riccio et al., 2002), and is also observed in mice performing the 5-choice continuous performance test (5C-CPT) (Young et al., 2009a, 2011). Another example is that in the intradimensional/extradimensional (ID/ED) shifting task in humans (Owen et al., 1991), more trials are required to complete the ED vs. ID shifts, which is also the case for the animal versions of the task (Birrell and Brown, 2000; Bissonette et al., 2008; Dias et al., 1996b; Young et al., 2009b).

1.1.3. Face validity

Refers to the phenomenological similarity between the task used in preclinical testing to that used in the clinic (Lieberman et al., 1997). Although face validity is an intuitively appealing criterion with which to validate tasks, appearing desirable (Lipska and Weinberger, 2000; Weiner et al., 1996), it (a) is not actually necessary, (b) can be misleading, and (c) is difficult to defend rigorously. The latter proves most difficult as these tasks almost invariably involve subjective, arbitrary arguments that are not necessarily accepted by all investigators in the field (see Lipska and Weinberger, 1995). Thus, while face validity may provide a heuristic starting point for the development of a cross-species task with translational validity, it cannot be used to establish the validity of the task.

1.2. Structure to assess cross-species translational validity

Various aspects of validity exist and can be described both in terms of the validity that (a) animal tasks have for those used in man, and (b) models of disease states. Translating a molecule from preclinical studies to clinical efficacy is of paramount importance however. Hence, it is possible to utilize tasks that have limited validity to what is being tested in man as long as the model predicts effective treatment. An example of such targeted drug discovery is apomorphine-induced disruption of prepulse inhibition in rats, the reversal of which reliably predicts the clinical efficacy of treatments for the positive symptoms of schizophrenia (Swerdlow et al., 1994). Latterly, it was discovered that this model was effective because it revealed the ability of the compound to block dopamine D2-family of receptors at levels sufficient to treat psychosis (Kapur et al., 2000). This model was only available however, because treatments were available at the time of its development and thus novel molecules could be compared with positive controls, resulting in treatments with similar mechanisms of action (pharmacological isomorphism). Given that no procognitive treatments exist for schizophrenia however, CNTRICS has proposed a more structured task valid approach in order to assess novel molecules as procognitives for schizophrenia. As such, the validity of disease models is not discussed in this review.

Examining the validity of a task across species is vital for assessing the suitability of novel molecules to treat schizophrenia. Because divergent performance levels can be observed between species performing similar tasks (see Section 2) due to innate differences in the approach species take to such tasks, evidence for consistency of effects of the molecule across species in the same task – as opposed to evidence in one species only – would increase the confidence of a positive effect when translated to human clinical trials. Positive effects of a molecule across species would also be beneficial so that it can be tested in animal models of schizophrenia where some are more prevalent in mice (e.g., genetic models), compared with rats and NHPs (e.g., pharmacological models). Hence, convergent validation of a molecule could be generated using a range of models. Convergent validation of a molecule could also arise if the molecule improved of animals in tasks that reportedly assess the same cognitive domain (e.g., the 5C-CPT and the sustained attention task; see (Lustig et al., 2013)). Hence, in these series of meetings CNTRICS has identified at least two tasks per cognitive domain in which a molecule could be tested for convergent validation.

Before such novel molecules are tested in various models however, the cognitive tasks utilized should have cross-species translational validity. An example of a task with some reliable validity is described below (Section 3.1) with examples where validation of this task across species has been conducted. In brief, the validity of reversal learning was established by demonstrating aspects of construct, predictive, and face validities across mice, rats, NHPs, and humans. Face validity was simply established by training subjects to learn the reinforcement contingencies between two stimuli which are then swapped once pre-established criterion is attained. Construct validity in this case has been established by the necessity of an intact orbitofrontal cortex to learn reversed contingencies, while unaffected simple learning. Multiple aspects of predictive validity are observed for this task. For example, more trials are required to learn reversed contingencies as opposed to the number required to learn the initial relationship of these stimuli. Moreover, pharmacological predictive validity is supported whereby altered regulation of the dopamine D2-like receptor produces impairments in the ability to update behavior during reversed contingencies. Thus, by performing similar experimental manipulations across species, the validity of a task to assess a cognitive construct can be established.

2. Examples of tasks where differences between species' performance have been observed

Identifying possible differences between species is not only important for bringing a drug from preclinical to clinical testing, but also when comparing results between preclinical species. For example, the importance of genetic influences to psychiatric diseases is becoming increasingly apparent and the generation of transgenics that possess such mutations increasingly important. NIH first sponsored a Request For Applications and now a mainstream R21/R33 program announcement for researchers to develop and characterize novel mouse models that express human genes or human genetic elements that may be important to psychiatric disorders (PAR-08-158: Mouse Models Containing Human Alleles: Novel Tools to Study Brain Function). It is unsurprising that all awardees of these two mechanisms have utilized mice to generate these models because the vast majority of mutant rodent animals that have been created are mice and thus our knowledge on the behavioral effects of certain genes stem from our behavioral examination of these mice. In contrast, a great deal of our knowledge of pharmacological manipulation and lesion-induced alterations in behavior are performed in rats. Thus, pharmacological mouse models of cognitive disruption in schizophrenia are rare, while many mutant mouse models exist (Brigman et al., 2010; Young et al., 2012). For these reasons, inherent, qualitative differences in performance of identical tasks in rats and mice may complicate translational research that depends upon integrated study of both species.

Investigation into the ramification of drug-/gene-/lesion-induced alterations in behavior relevant to diseases cannot take such a distinct line. Indeed, efforts are being made to develop rat mutant models, while more lesion and pharmacological studies in mice are being conducted. This discrepancy between study types by species remains however, and may be important when the innate behavior of these two species is compared in identical tasks. Despite the tasks utilizing operant training techniques, it is clear that the natural behaviors of the mice can impact performance and thus perhaps the effect of a novel molecule.

2.1. 5-Choice serial reaction-time task (5CSRTT)

The 5CSRTT is a well developed test of sustained attention commonly used throughout the world. Originally devised for rats by Robbins and colleagues (Carli et al., 1983) it was not developed for mice until 16 years later (Humby et al., 1999). The large number of 5CSRTT studies performed in rats means a consistent pattern of performance that can be expected in trained rats, accuracy between 60 and 90%, omission levels below 10%, and premature responses typically above 20 in a session of 100 trials (Robbins, 2002), with some of the variability as a result of differences between strains, e.g., Long Evans vs. Wistar rats (Didriksen and Christensen, 1993), or Sprague Dawley vs. Lister Hooded rats (Mirza and Bright, 2001), which can impact drug effects on performance (Mirza and Bright, 2001; Wooters and Bardo, 2011). The consistency of these findings between studies within strain has lent great weight that the numerous 5CSRTT studies were measuring consistent aspects of performance. When studies began in mice however, it became clear that this species did not conform to this pattern of performance. Even between strains mice exhibit higher accuracy, typically 90–97%, higher omission levels, typically around 20% and above, and very few premature responses (Fletcher et al., 2007; Humby et al., 1999; Young et al., 2004), with DBA/2 mice consistently worse than C57BL/6 mice, which equaled 129/s mice (Humby et al., 1999; Loos et al., 2010; Patel et al., 2006; Pattij et al., 2007). The equality of performance between C57BL/6 and 129/s mice is of importance given that these strains are often used to

create mutant mice. The consistent performance differences observed between rats and mice however, led Spratt et al. (2000) to examine the strategy by which these two species perform the task in order to ascertain why their performance levels vary by species so consistently. Standard performance of these two species using a constant inter-trial interval (ITI) was 'blank-trial' challenged. This blank-trial challenge meant that on 1 out of 6 trials no target would appear during the period that a stimulus would ordinarily appear. Thus, if entrained to only respond to the stimuli lights, no response during this period would be recorded. During this time period, mice responded on average 15%, while rats responded 90% (Spratt et al., 2000). These data support the premise that rats use a temporally mediating strategy to perform the task during a constant ITI, while mice use the strategy to a lesser degree. These findings likely explain at least in part why rats exhibit differences in response measures compared to mice, e.g., if the rat does not see the location of the light when it is expected (timed) to appear, it will guess a location (leading to poorer accuracy and lower omissions) and an imperfect temporal ability may lead them to think stimuli appeared before the ITI was finished (increased premature responding). These studies highlight the differences in performance that can occur between species despite performing what is arguably the same task.

These species differences are important given that drug challenges may result in differing effects because of differing strategies utilized by each species as well as because of differing receptor selectivity between species. For example, amphetamine consistently increases premature responding in rats in the 5CSRTT (Robbins, 2002). In mice however, amphetamine does not always increase premature responding (Yan et al., 2011; Loos et al., 2010). This could reflect the different reliance each species puts on a temporal mediating strategy because amphetamine speeds interval timing of both species (Balci et al., 2008; Body et al., 2009; Fowler et al., 2009). An alternate hypothesis is that while amphetamine is ~4-fold more selective at inhibiting the dopamine transporter (DAT) when compared to the norepinephrine transporter in rats, it is actually ~4- to 6-fold more selective for the NET in mice and in humans compared to the DAT. Because NET inhibition might act as a global inhibitory signal in tasks requiring reduced responding (Robinson et al., 2008), the selectivity of amphetamine for NET over DAT in mice could influence its lack of effects on premature responding. The need for DAT inhibition selectivity is supported by findings that GBR 12909, a more selective DAT vs. NET inhibitor reliably increases premature responding in mice, albeit in a simpler task (Young and Geyer, 2010). As yet there appears to be no clear distinction as to whether the differences of effects of amphetamine between mice and rats on premature responding is because of the putative greater use of a temporal strategy in rats or the more selective DAT inhibition effects of amphetamine on rats. These differences exist however and should be explicable if drugs developed in mice and rats are to be efficacious in humans.

5CSRTT performance can be further examined across species because a human version exists as a part of the Cambridge Neuropsychological Test Automated Battery. Indeed, it has been reported that patients with schizophrenia exhibit poorer performance in the task, albeit only as measured by a more varied reaction-time (Barnett et al., 2010), sometimes referred to as deficits in visual motor skills (Chouinard et al., 2007; Fagerlund et al., 2007). Differences in accuracy and omissions, while forming an important description of rodent performance, do not appear to be as relevant to human testing in the 5CSRTT. Thus, although differences in rodent species' performance of the 5CSRTT may negatively impact the development of novel molecules to the clinical, the relevance of rodent 5CSRTT performance to clinical testing still needs to be established.

2.2. Olfactory discrimination

Other examples of species differences when tested in the same task have been noted. For example, rats and mice can be trained to differentiate between olfactory cues using an olfactometer developed by Slotnick and colleagues (Bodyak and Slotnick, 1999; Slotnick, 2001; Slotnick and Risser, 1990). Discriminatory accuracy of rats (Bodyak and Slotnick, 1999) and mice (Abraham et al., 2004; Rinberg et al., 2006) are near perfect even when comparing no odor vs. 0.0001% ethyl acetate.

Performance of rats and mice are affected only when odor similarities are increased by mixing (or morphing) two odors (Abraham et al., 2004; Rinberg et al., 2006; Uchida and Mainen, 2003). Interestingly, rats and mice differ in their response to these mixed odors. Rats exhibit reduced accuracy but maintain reaction-time speed when the odors are mixed (Uchida and Mainen, 2003), while the reaction-time of mice slow yet accuracy is maintained in similar circumstances (Abraham et al., 2004; Rinberg et al., 2006). Remarkably, if rats are forced to increase their sampling time when mixed stimuli are presented their reaction-time subsequently slows and accuracy increases (Slotnick and Risser, 1990). Thus, the natural strategy of rats to olfactory stimuli appear to be reacting rapidly, but when forced to slow down they will utilize the extra information gathered to improve accuracy (Slotnick and Risser, 1990). In contrast, mice appear to utilize a strategy that is primed to withhold from responding and thus they naturally make use of more information to maintain accuracy (Bodyak and Slotnick, 1999).

These baseline strategy preferences – responsivity in rats and withholding in mice – are not dissimilar to those described by rats and mice performing the 5CSRTT. In a recently developed adaptation to the 5CSRTT, termed the 5-choice continuous performance test (5C-CPT) rodents are required to not only respond to target stimuli, but also to inhibit from responding to non-target stimuli. When training rodents in the task, mice can be trained to inhibit to non-target stimuli when the ratio of target to non-target trials is 5:1 (Young et al., 2009a). Rats could not learn at this ratio however, and required initial training with increased salience of the stimulus in which they were required to withhold from responding to – utilizing a 2 target to 1 non-target ratio (Barnes et al., 2011b). These findings support the supposition of increased tendency to respond in rats compared to mice. When trained in the 5C-CPT, the bias of responding can also be measured, and interestingly, rats and mice exhibit comparable bias levels (Barnes et al., 2011a,b; Young et al., 2009a, 2011). Thus, by emphasizing discriminated responding, it may be possible that rat and mouse behaviors become comparable.

2.3. Touchscreen testing

The 5CSRTT, 5C-CPT, and olfactometers are examples of apparatus which can be used in rats and mice providing opportunities to directly compare performance using stimuli from the same modalities. Another example of where this is possible is the touchscreen testing method, which uses a computer monitor to provide a visual display for stimuli to mice and rats which can record responses in the location stimuli appear (Bussey et al., 1994, 2001). Hence, responses are made directly to stimuli via nose-pokes toward the screen (touching the screen is not required). Many tasks measuring a variety of aspects of cognition are possible using this apparatus (Bussey et al., 2011), which does not have a high motor demand allowing testing of rodents with even moderate motor impairments (Morton et al., 2006). The upper panels of Fig. 1 illustrate mice and rats performing a pair-wise visual discrimination, in which one stimulus is correct and rewarded (the S+) and the other is incorrect and not rewarded (the S-). The lower panels of Fig. 1 show the final performance levels of mice and rats following acquisition of the initial discrimination, and also their performance when the

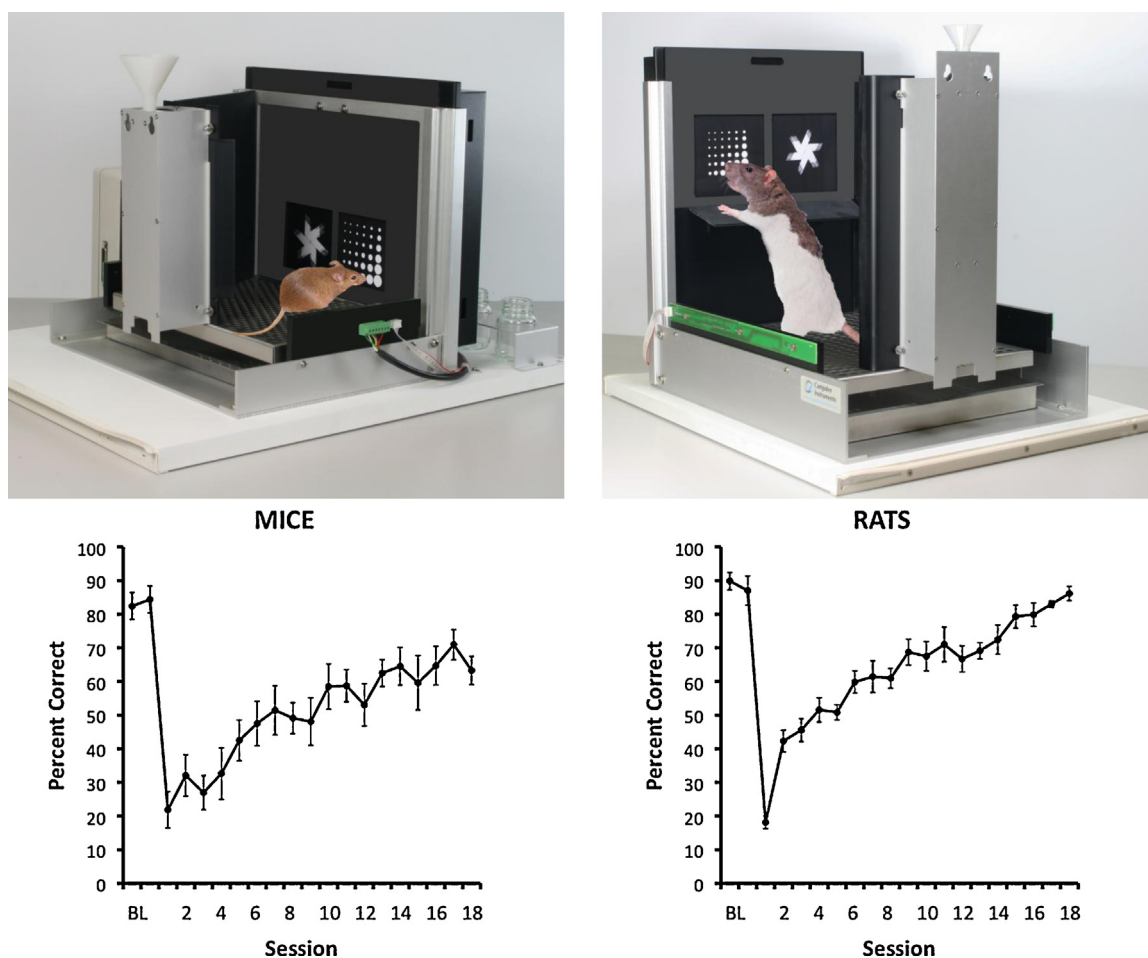


Fig. 1. The touchscreen testing apparatus and reversal learning curves for mice and rats. The upper panels show the most recent versions of the apparatus for mice (left) and rat (right). The lower panels show representative archival reversal learning curves for C57BL/6 mice ($n=7$) and Lister Hooded rats ($n=7$) obtained using this method. Data from two days of pre-reversal baseline (BL) performance are shown, followed by 18 sessions of reversal learning. The reversal curves for mouse and rat look very similar; note, however, that the number of trials per session differs for rats and mice (rat: 100 trials/session; mice: 30 trials/session). Mice are wild-type control animals from a study of M1 receptor function (Bartko et al., 2011a,b); rats are sham lesion control animals from an unpublished study of prefrontal cortical function (data courtesy of Katie McAllister). Thus the rat and mouse groups were not compared in a controlled fashion nor were the data compared statistically; the comparison is for illustrative purposes only.

Photographs of apparatus courtesy of Campden Instruments, Loughborough, UK.

reward contingency is reversed, that is, when the stimulus that is the S+ during initial acquisition becomes the S−, and vice versa (see Section 3.1 below for species comparisons on reversal learning).

Advantages of the touchscreen method over other automated methods, e.g., standard operant chambers fitted with lights and levers, include the rich possibilities for stimulus manipulation. To continue with the example of pair-wise visual discrimination, McCarthy et al. (2011) trained rats to discriminate two visual stimuli to high levels, and then ‘morphed’ (blended) the stimuli together (akin to mixing odors, described in Section 2.2) to increase the perceptual similarity of the stimuli, thus bringing baseline performance down from ceiling. On this new baseline these authors were able to see not only large improvements in performance in wild-type rats given the anticholinesterase donepezil (Aricept), but were able to observe the synergistic cognitive enhancing effects of the combination of otherwise ineffective doses of donepezil and a putative add-on therapeutic compound, FK-962 (McCarthy et al., 2011). Similar examples can be found in mice; for example Bartko et al. (2011a) found that mice with deletion of the M1 muscarinic receptor were unimpaired in the acquisition of a pair-wise shape discrimination. To challenge the animals further, mice were then tested on a more difficult pair of photographic stimuli and then, to provide an even more stringent test of the mouse’s

perceptual and learning abilities, these photographic stimuli were morphed (blended) together to create an even more difficult discrimination (the difficulties of these discriminations were reflected in their rates of acquisition). Despite the absence of M1 receptors in these animals, they were not impaired on any of these challenges (although they did show abnormal responding in the 5CSRTT in the touchscreen). In this example, the results of these challenges supported the conclusion that the ability to perform perceptually difficult visual discriminations was unaffected by global M1 receptor deletion.

2-Choice discrimination and reversal is one of simplest of several tasks currently worked up for both mice and rats in the touchscreen apparatus. So far all of the tasks that have been initially developed in rats have been successfully adapted for mice, usually with minimal changes. These include quite complex tests of, e.g., object-location paired associate learning (rat: (Talpos et al., 2009); mouse: (Bartko et al., 2011a)); CNTRICS long-term memory paper this issue and spatial working memory and pattern separation (rat: (McTighe et al., 2009; Talpos et al., 2010); mouse: (Clelland et al., 2009; Creer et al., 2010; Dudchenko et al., 2013)) as well as simple tests of conditioning (rat: (Bussey et al., 1997); mouse: CNTRICS reinforcement learning paper this issue). Indeed some touchscreen tasks, such as the 5CSRTT, have been worked up

in mice first (Romberg et al., 2011) and subsequently ported to rats. If one is pressed to comment on species differences in this method, a general observation is that variability is greater in the mouse than the rat, but such increased variability in mice is unlikely to be specific to touchscreen apparatus; indeed increased group sizes for mice, in order to combat this effect, have been suggested for behavioral testing in general (Crawley, 2007). Perhaps more interesting is a small difference in the apparatus required for mouse versus rat. In the original rat methods paper (Bussey et al., 1994), it was reported that the use of a “shelf” (fitted with springs so that the rat cannot jump up on it) was required to force rats to rear up and to make an effortful response to the screen, thus minimizing accidental and impulsive choices and increasing precise responding to the stimuli on the screen. Interestingly mice do not need the shelf. Perhaps consistent with more impulsive action of rats as observed in the 5CSRTT (see Section 2.1), mice generally behave less impulsively in touchscreen apparatus, stopping in front of the screen and sampling the stimuli on the screen before making a response. Thus, the temperament of the mouse seems to be well-suited to the touchscreen testing method – perhaps more so even than the rat.

3. Examples of tasks whereby consistency between species have been observed

A considerable amount of cross-species research has focused on aspects of executive control, which are defined as a set of processes that contribute to voluntary (top-down) modulation of behavior, affective reactions and thought processes. The rationale guiding these studies stems from the observation that a variety of forms of executive control impairment are present in most forms of major psychiatric disorders, including psychoses.

Executive control over behavior can be assessed using very simple tasks that require the flexible updating of responding when subjects are exposed to context or contingency shifts. For example, subjects can be trained to solve a discrimination problem, and once their behavior meets some pre-determined criteria for efficiency and accuracy, the associative rules that govern the discrimination can be swapped. This is referred to as reversal learning, and after the switch, subjects are usually thought of as recruiting executive control mechanisms to inhibit the initially trained responses in order to permit re-exploration of the rules and the adoption of a new, now-accurate response strategy. While the acquisition of the initial discrimination and the subsequent reversal both require the same set of motor responses, motivational states and associative learning abilities, reversal differs from acquisition in the additional need for inhibitory control mechanisms.

The simplicity of the design of most discrimination reversal learning studies has made them highly suitable for cross-species investigation, and there is remarkable consensus that common neural systems and molecular pathways determine reversal learning abilities in rodents, NHPs, and human primates.

3.1. Reversal learning

Irrespective of species, most discrimination reversal learning studies involve three dimensions: a set of discriminative stimuli that the subject uses to guide response selection, a set of operant responses and an outcome. Many variants include making an approach or foraging response towards a reward-associated cue, which is presented in the context of distractor cues that predict reward omission as opposed to reward presentation. Alternatively, variants may include pressing one operandum in the presence of one stimulus and another operandum in the presence of a different one. In both cases, the idea is that – over initial training – the discriminative cues come to efficiently, and increasingly

automatically, evoke a particular response (through associative learning mechanisms), such that updating behavior at reversal is challenging and requires effortful, top-down processes.

These procedures have been used with great success in mice, rats, NHPs, and human subjects to uncover the genetic, neural and pharmacological basis of executive control. In rodent models, the discriminative cues used are often olfactory (Birrell and Brown, 2000; Bissonette et al., 2008; Schoenbaum et al., 2002, 2003), but can also be spatial or visual (Brigman et al., 2010; Izquierdo et al., 2010; Laughlin et al., 2011a); the instrumental response is typically a foraging response or operandum manipulation and the outcome is a food reward. In NHPs, the discriminative cues are either 2-dimensional visual stimuli or objects (Arnsten et al., 1997; Butters et al., 1973; Clarke et al., 2005; Dias et al., 1996b; Ettlinger and Ridley, 1975; Groman et al., 2011; Izquierdo et al., 2007; Lee et al., 2007; Seu et al., 2009), and the response is contact with a touchscreen (see Section 2.3 for details) or a foraging response (moving the object to uncover the reward); the outcome is typically food. In humans, the stimuli are typically 2-dimensional visual stimuli on a touchscreen (Clark et al., 2004; Cools et al., 2002; Evers et al., 2005; Fellows and Farah, 2003, 2005; Ghahremani et al., 2010), the response is usually a touch to the screen and the outcome is typically social or abstract. Patients with schizophrenia take more trials to rule reverse in comparison to healthy subjects (Leeson et al., 2009). Touchscreens can also be used in rats and mice to investigate systems in these animals relevant to schizophrenia, such as the glutamatergic, dopaminergic, serotonergic, and cholinergic systems, prefrontal cortex and hippocampus (e.g., Barkus et al., 2011; Brigman et al., 2010; Chudasama and Robbins, 2003; Karlsson et al., 2009).

Additional procedural details of relevance include: the number of discriminative stimuli being learned, whether discriminanda are presented concurrently or sequentially and whether the associative rules are deterministic and probabilistic. One major difference is that human studies often use probabilistic feedback to slow down the rate of learning, while animal studies involve deterministic rules. That said, some animal studies are now including probabilistic feedback (Bari et al., 2010), while human studies are beginning to involve deterministic feedback (Ghahremani et al., 2010). Some reversal learning studies in rodents utilize signaled reversals, whereby the reversal of contingencies is clearly signaled (Abdul-Monim et al., 2003; Idris et al., 2010), unlike the seamless transition from one reward configuration to its reversal which occurs in human studies. Moreover, some studies subject animals to multiple reversals in a row (serial reversal learning), which becomes striatal-dependent as the animal ‘learns to reverse’ (Castane et al., 2010). Such differences between rodent and human reversal learning paradigms may limit the development of novel molecules for treating schizophrenia. Likewise, not all clinical studies include an assessment of reversal learning in patients, despite the evidence generated using preclinical studies. In fact, many studies do not report effects on specific cognitive domains, but instead only report composite scores. Such grouping of data limits the comparative analysis of the effects of a molecule on task performance between preclinical and clinical studies. Future clinical studies would benefit from utilizing tasks with animal equivalents where positive effects of the molecule have been observed and presenting resulting data on the primary outcome measures of that task.

Typical 2-choice discrimination reversal learning data can be evaluated for learning rate (behavioral change, post reversal, as a function of trial) and can be subjected to error analyses that indicate whether behavior is strictly perseverative (meaning that responding is rigidly following the initially trained rule) or is entropic (Clarke et al., 2004; Haluk and Floresco, 2009; Ridley et al., 1981a,b). In addition, clever behavioral experiments that include stimulus

substitutions can be used to dissect the role for response perseveration and learned irrelevance to reversal learning (Clarke et al., 2007; Tait and Brown, 2007). These sorts of manipulations can be made across species to determine whether the reversal learning deficits caused by a variety of manipulations represent the same type of cognitive impairment, allowing for a deep interrogation of construct validity. Such analyses are not typically detailed in human clinical studies however, perhaps their incorporation would be useful in future studies for cross-species comparisons.

During touchscreen reversal learning procedures, both mice and rats show a similar profile of responding: when the reward contingency is reversed, initially animals perform well below chance level, after which they first progress back up to chance levels (it is during this stage that changes in perseveration to the previously rewarded stimulus can be observed) and then finally up to asymptotic performance levels. The reversal curves for mouse and rat look very similar; note, however, that the number of trials per session differs for rats and mice; indeed on the basis of trials to criterion performance, the mice appear to learn faster than rats. Such conclusions need to be made with caution however; the spacing (as opposed to “massing”) of trials can have a substantial impact on learning rates (Barnet et al., 1995). What can be concluded that experimenter time is about equivalent when running an experiment in either mice or rats.

Another potential difference between species may be apparent in the final stages of reversal learning: it appears that whereas rats reverse to levels similar to those they attained during initial acquisition, mice never seem to get back up to those same pre-reversal levels. This species-difference has been informally observed on a number of occasions (Bartko et al., 2011a). The reason for this difference may be that mice continue to sample the previously rewarded stimulus, which might be thought of as consistent with a more impoverished prefrontal cortical function in mice. However without further head-to-head comparisons of mice and rats such ideas must remain speculative.

Irrespective of putative species differences and all the procedural details described above, there is overwhelming convergent construct validity that orbital regions of the frontal lobe contribute in a behaviorally specific manner to reversal learning (meaning it is does not mediate aspects of performance shared with the initial discrimination acquisition). Lesions of the orbitofrontal cortex impair reversal learning in mice (Bissonette et al., 2008), rats (Birrell and Brown, 2000; Boulougouris et al., 2007; Boulougouris and Robbins, 2009; McAlonan and Brown, 2003; Schoenbaum et al., 2002; Schoenbaum and Shaham, 2008; Tait and Brown, 2007), and NHPs (Butters et al., 1973; Dias et al., 1996a; Iversen and Mishkin, 1970; Izquierdo and Murray, 2004; Izquierdo et al., 2004; Rudebeck and Murray, 2008, 2011).

Even more striking is the convergent predictive evidence across species that dopamine D2-like receptor mechanisms contribute to reversal learning. In mice, knockout of the dopamine D2 receptor gene impairs reversal learning (De Steno and Schmauss, 2009; Kruzich and Grandy, 2004; Kruzich et al., 2006). In rats and non-human and human primates, pharmacological regulation of the D2 receptor produces impairments in the ability to update behavior during reversal (Boulougouris et al., 2008; Haluk and Floresco, 2009; Lee et al., 2007; Mehta et al., 2001; Ridley et al., 1981b; Smith et al., 1999). Moreover, heritable variation in dopamine D2 receptor complement in brain predicts individual differences in reversal learning in mice, monkeys and humans (Groman et al., 2011; Jocham et al., 2009; Laughlin et al., 2011b). While these data certainly do not implicate D2 receptor-dependent dopamine transmission as the only, or even most crucial, molecular regulator of executive control, it does indicate that cross-species investigations can be remarkably effective at identifying common molecular and neural mechanisms mediating a cognitive construct of interest.

What is lacking in some of the mechanistic studies described above is the use of behavioral manipulations to determine whether lesions or pharmacological substances produce identical changes in the construct of interest across species. The use of 3, as opposed to 2, discriminanda, and the employment of stimulus substitution schemes, will both permit a much more robust analysis of executive control abilities across different laboratory models and species. In addition, the use of identical sensory modalities and testing apparatus (such as visual stimuli on a touchscreen, see Section 2.3), as well as learning criterion, may be an important avenue for future comparative research. Each of these developments make it is possible to directly dissociate perseverative from random responses (e.g., in a 2-choice test, there is only one error, and its nature must be inferred, not directly assessed), and it becomes experimentally straightforward to conduct tests that identify whether a particular manipulation distinctly modulates behavioral flexibility, influences learned irrelevance or creates a disorganized pattern of choice that all affects overall reversal performance (e.g., in touchscreen tests it is possible to determine whether a manipulation only affects performance when a previously trained stimulus is present and supports perseverative responding). Thus, although there is evidence for many similarities of reversal learning performance across species, the refinement of tasks to assess this construct would aid data interpretation and the translational development of novel molecules across species.

3.2. Paired associates learning

Another example of a paradigm that has been successfully utilized across species is the visuo-spatial paired-associates learning (vsPAL) task. The vsPAL task requires subjects to associate a set of objects with particular spatial locations on a trial-by-trial basis, and involves the proper functioning of the temporal lobes, and in particular the hippocampi (Owen et al., 1995; Murray et al., 1993; Wood et al., 2002; Talpos et al., 2009). VsPAL has been successfully established and used in humans, macaques and marmosets for decades, and more recently has been translated into rats and mice (Bartko et al., 2011b; Owen et al., 1995; Spinelli et al., 2005; Taffe et al., 2002; Talpos et al., 2009). The use of the touchscreen based computerized system across species has provided consistency in the presentation of stimuli and mode of responses and enables the effective translation of this test across species.

Clinically, deficits in vsPAL performance have been demonstrated to occur with advanced age (Rabbitt and Lowe, 2000) and in specific diseases. In particular, patients with mild cognitive impairment show impaired performance in vsPAL that has been shown to accurately predict later conversion to Alzheimer's disease (Blackwell et al., 2004; Sahakian et al., 1988; Swainson et al., 2001; Barnett et al., 2005). Similarly, first episode and chronic schizophrenic patients show impaired paired-associates learning (Wood et al., 2002; Barnett et al., 2005). Possibly a deficit in PAL in these patients may be due to reduced gray matter in temporal lobe structures as shown by MRI in at-risk prodromal patients prior to first psychotic episode (Pantelis et al., 2003). Neuronal loss in key brain structures such as the hippocampus in AD patients is also a hallmark pathology of the disease progression (Selkoe, 1999) that may underlie the observed cognitive impairments in vsPAL.

3.2.1. PAL testing and training

In humans and NHPs, vsPAL requires subjects to learn to associate a specific stimulus with a particular location on a trial-by-trial basis and the cognitive demand of the task increases as the number of stimuli-locations presented increases. Varying the number of stimulus-locations within a session allows experimenters to assess task performance at different memory loads (Taffe et al., 2002). NHPs typically have up to 4 stimuli/4 locations as their

most difficult trials, whereas humans may have up to 6–8 sample stimuli locations in the most challenging trials (Fowler et al., 1997; Swainson et al., 2001; Taffe et al., 2002).

Typically in the human test, 6 white boxes appear around the periphery of the computer screen and in turn each one “opens up” to reveal a particular stimulus until all 6 stimulus-location pairings have been shown independently (sample phase). The subject is then shown one of the sample stimuli in the center of the screen and must match the stimulus to the box (location) in which it was originally presented (choice phase). Subjects go through each of the sample stimuli until they have responded to each of them. In the human version, subjects may or may not be rewarded for correct response. In addition, subjects are given task instructions either verbally or in written format prior to testing, thus minimal training is necessary.

In the NHP version of vsPAL, extensive training is necessary prior to testing. Since NHPs must acquire the rules of the task through a trial-and-error approach (i.e., without verbal instructions as for humans), modifications have been made to the task many times to facilitate training. For example, during training responding to the sample stimuli can be rewarded to help shape this behavior and modifications can be removed once the subjects are properly trained. However, in NHPs it should be noted that touch responses to the sample stimuli are required as a measure of having attended to these stimuli. A failure to touch the sample stimuli means the trial does not proceed to the test phase (and potential reward). In the CANTAB vsPAL, stimulus-locations are randomized (9 locations; 20 stimuli) so that stimulus-location pairs are not memorized. Once animals are trained to a particular criterion, the performance generally remains stable, which is imperative for chronic or cross-over study designs.

In the rodent version of vsPAL, animals learn to associate a particular stimulus with a particular location over a lengthy training period. The mouse version of the task was modeled after the rat version, so many of the same approaches were used to translate between species. Animals must learn which location is associated with each stimulus. Two stimuli are presented at once in three possible locations (i.e., 6 possible stimulus–location options), with one stimulus being in the correct location (S+) and the other stimulus in an incorrect location (S–). The animal is required to select the correct stimulus–location to receive a food reward (Bartko et al., 2011b; Talpos et al., 2009). The animals are given a fixed number of trials (mouse: 36 trials; rat: 72–trials) within each session after performing at a set criteria consistently during the training phase. Memory load remains constant throughout the test in the rodent version of vsPAL. Given the length of time and number of trials across sessions rodents are given to associate pairs in comparison to the within session changes of humans and monkeys, it may be that the former assesses long-term association formation while the latter assesses recent association formation. Comparative studies comparing rodents and primates have not been investigated as yet and so this issue remains unanswered, future studies using this paradigm may yield insight on this matter.

3.2.2. Pharmacology

A better understanding of the neurochemical receptor systems underlying the vsPAL task is emerging as more pharmacological based studies are being conducted and reported. Drugs that traditionally impair cognition such as the muscarinic antagonist scopolamine, also are reported to impair accuracy in PAL in rhesus macaques (Taffe et al., 2002) and mice (Bartko et al., 2011b), and scopolamine produced marginal impairments in healthy volunteers (Robbins et al., 1997). Intra-hippocampally injected scopolamine or mecamlamine into the rat showed no effect on vsPAL performance however, suggesting that the hippocampus may not be involved in scopolamine-induced deficits following

systemic administration (Talpos et al., 2009). Possibly broader disruptions in other cognitive functions, such as attention, following systemic injections of scopolamine in other species may explain the discrepancy in results from the rat studies. Interestingly, impairment of vsPAL performance with NMDA receptor antagonists (e.g., ketamine, MK-801) was observed in rat, as well as rhesus monkeys following intra-hippocampal or systemic injections, respectively (Taffe et al., 2002; Talpos et al., 2009). Although complementary drug studies have not been confirmed in humans to date, deficits in PAL performance have been reported in pre-psychotic individuals (Bartok et al., 2005), in first-episode schizophrenic patients (Barnett et al., 2005), and in patients with a long-standing diagnosis of schizophrenia (Wood et al., 2002), suggesting impaired NMDA receptor function could effect visuospatial learning. Interestingly, one report from (Stip et al., 2005) indicated greater sensitivity (vsPAL task performance deficit) in distinguishing patients with schizophrenia, as compared to patients diagnosed with schizoaffective disorder.

Direct and indirect cholinergic agonists have been assessed for pro-cognitive properties in vsPAL. Nicotine administered to rhesus macaques improves accuracy in the PAL model (Katner et al., 2004), whereas cholinesterase inhibitors, which are the most widely prescribed therapeutic agents for Alzheimer's disease have yielded mixed results. Tetrahydroaminoacridine was reported not to improve vsPAL performance (Riekkinen et al., 1998) in AD patients following a single administration; however, phenserine was reported to significantly enhance PAL performance in an AD patient population over a 12-week period in a placebo-controlled phase II study (Greig et al., 2005). These results are consistent with the clinical literature for the cholinesterase inhibitors in that chronic dosing is required for therapeutic benefit. More recently, donepezil has been reported to facilitate vsPAL in mice (Bartko et al., 2011b).

The catecholamine systems have also been investigated for their role in mediating the cognitive properties of visual spatial learning and memory. In particular, the dopaminergic system is involved in mediating complex cognitive processes and impairments to this neurochemical system prevalent in many CNS disorders (e.g., Parkinson's disease, attention deficit/hyperactivity disorder). Specifically, antagonism of dopamine D2-like receptors with raclopride, but not of the D1-like receptors with SCH23390, impaired vsPAL performance in rhesus macaques (Von Huben et al., 2006). Noradrenergic alpha2 receptor agonists clonidine and guanfacine improved vsPAL performance in healthy volunteers (Jakala et al., 1999), consistent with the role of this system in arousal, vigilance and attention. However, it should be noted that clonidine administration also has been reported to have no effect or to even impair vsPAL performance depending on different experimental conditions used (e.g., verbal versus non-verbal stimuli, dose; Coull et al., 1995, 1997; Frith et al., 1985). It would be useful to investigate the involvement of the noradrenergic system or dopamine-D2-like receptors to vsPAL in other species under similar conditions.

4. Practical implications for the drug discovery process

The development of novel molecules for the treatment of cognitive impairments in schizophrenia remains an important unmet medical need. The effective translation of preclinical research findings into proof of concept clinical trials remains a challenge and contributes to the high attrition rate of molecules entering into human populations (Kola and Landis, 2004). Focusing our efforts on the construct validity of particular tests and improving our understanding of the strengths and limitations of these models across species will improve the success of the discovery and development process.

Selecting the appropriate species for the key questions at hand is critical for successful translation. Rodents are particularly good for early PK-PD assessments for lead identification/lead optimization stages of drug discovery, as models can be developed to give relatively quick feedback for determining structural activity relationships. Mice in particular are ideal for the study of genetic determinations and they have been used for years to overexpress, knockout or mutate particular genes of interest; although, transgenic rat models are beginning to gain attention recently. Some challenges may arise with using mice exclusively for characterization of novel compounds due to difficulty in translating mouse pharmacology data into rat, NHP or human, for some of the reasons described in Section 2.1 (e.g., different strategies in 5CSRTT), as well as due to different pharmacokinetic properties (e.g., rapid metabolism). For example, nicotine is used commonly in animal models as a pro-cognitive agent, yet the half-life ($t_{1/2}$) of the compound varies widely depending on the species (e.g., mouse: $t_{1/2}$ 7–10 min (Petersen et al., 1984); rat: $t_{1/2}$ 60 min in rat (Miller et al., 1977); monkey: $t_{1/2}$ 100–200 min (Seaton et al., 1991); human: $t_{1/2}$ 95–227 min (Benowitz and Jacob, 1994)), a factor that can influence results from tests taking longer to complete as drug levels may not be optimal for appropriate assessment (e.g., ASST testing can take 3–6 h). Furthermore, one must take into account the preciousness of the species being tested. For example, novel molecules may be tested in well-trained rodents up to six or seven times prior to a novel cohort being trained. In contrast, NHPs will be tested with novel molecules for numerous years given the ethical considerations of constantly training a new cohort after every treatment. While many steps are taken to ensure the performance of the animals stabilize prior to testing – with positive controls included to ensure drug-induced effects can be observed – such considerations must be taken into account when evaluating the utility of each species for each stage in drug discovery.

Whereas rodents are used to assess cognitive function especially in early stages of drug discovery process, the use of NHPs provides the ability to investigate complex behavioral processes that are closely aligned with human function for both lead optimization, as well as into clinical development stages of investigation. The utility of using NHPs in the drug discovery process is of growing importance with the traditionally poor translation between preclinical and clinical studies, and costly failures in clinical development creating a “valley of death” for promising CNS-active molecules. Although within-subjects designs often are necessary in NHP studies due to lengthy training periods of some tasks (e.g., 4–6 months) and costs associated with maintaining colonies of trained animals, the translatability of the resulting data from NHPs can provide an invaluable link between data generated in rodents and human studies. An example of the utility of NHPs for drug discovery purposes can be highlighted by the successful registration of guanfacine for ADHD, which was extensively characterized in NHP cognition tasks with a focus on prefrontal cortical function in which it improved performance at orally administered doses that are identical to those used in patients (for review see Gamo and Arnsten, 2011). Proper modulation of the catecholaminergic system in the prefrontal cortex of the ADHD brain underlies the efficacy of these molecules, which were ideally investigated in a NHP species that has benefited from a more advanced cortical system. The similarities in anatomy, neuronal circuitry, neurochemistry, functional and cognitive abilities exhibited between NHPs and humans provides for an ideal approach to investigate higher cortical-mediated behaviors in particular, and allows for direct comparisons of cognitive function to be made using the same endpoints in both species (e.g., CANTAB). Overall, the ability to iterate the characterization of a novel molecule from rodent to NHP to human strengthens the understanding of the mechanism of action as well as the

identification of endpoints and patient populations most sensitive to a potential new therapy.

5. Conclusions

In order to facilitate vertical translation during the drug discovery process, it will be important for the cognitive testing that occurs in preclinical species is consistent with the cognitive testing that occurs in humans. Consistency is required in terms of the cognitive construct being assessed, the neurobiology underlying that construct, and the pharmacological effects of the treatment on that construct. In this review we have described some of the underlying differences and similarities across species in a variety of cognitive paradigms, from mice and rats to NHPs and humans.

In 5CSRTT testing it is evident that rats rely more on a temporal mediating strategy to readily perform the task than do mice. This reliance may underlie the reliability of amphetamine-induced increases of premature responses in rats not seen with mice. Alternatively, this discrepancy of amphetamine effects between rats and mice could result from the greater selectivity of amphetamine on norepinephrine transporters compared with dopamine transporters in rats while the opposite is true for mice (and humans). With the availability of the human 5CSRTT, the relevance of these data to human testing can be established. Irrespective of the underlying cause however, it is evident that there are some differences between species in terms of impulsivity measures from the 5CSRTT. Likewise, it is apparent that mice are less impulsive to stimuli they should inhibit from responding to when compared with rats, observed across numerous types of apparatus. These differences could relate to the natural behavior of the two species, where rats interact with their environment more as a predator species, while mice are predated upon by many more species, including rats. When required to inhibit prelearned responses in order to learn new reward contingencies in reversal learning, mice and rats exhibit comparable behaviors. Moreover, there is evidence of consistent neurobiological underpinnings such as orbitofrontal or dopamine D2-like receptor mediation of reversal learning across species including humans and NHPs.

The availability of translatable cognitive test batteries that are based on comparable platforms (e.g., touchscreen apparatus) allows testing in a number of behaviors to occur similarly across species, including reversal learning and vsPAL. Whereas this approach has many strengths for successful translation between species, it also highlights one of the fundamental differences between cognitive tests developed for rodents and NHPs, namely the lengthy training time, which is not needed for testing in humans given the option of verbal instructions. Extended training in some paradigms, such as the vsPAL, may result in different constructs being assessed between these species. Detailing differences between species will prove as useful in the long run as detailing consistency during experiments. Another important point regarding species differences is the numerous behavioral differences observed between strains *within* the same species. Some studies report pharmacological effects in some strains within a species (e.g., mouse) that are absent in others. While these effects may be a result of poorer performance of some strains allowing for improvements to be seen (ceiling effects) differences between strains highlight the difficulty of expecting perfect symmetry across species.

Developing novel molecules for treating cognitive dysfunction in patients with schizophrenia will require developing evidence for targeting the mechanism and testing the molecule in tasks with cross-species translational validity such as reversal learning and vsPAL. While some refinement may be needed in these tasks, more

is also required from clinical studies. Care should be taken that similar tasks should be used in clinical studies. For example, many clinical trials continue to use standardized paper and pen tests that unfortunately have little relevance to cognitive testing in preclinical species (rodents, NHPs). Designing clinical tests using tasks that can be performed in animals will also be extremely useful in future (e.g., CANTAB). Furthermore, evidence for procognitive effects of novel molecules can readily be generated in normal animals, avoiding difficulties of the need to model schizophrenia. Using early Phase I testing of the molecule in healthy volunteers offers the opportunity to confirm positive effects of the compound in 'normal' subjects prior to more expensive testing in patients in Phase II and III trials. Thus, more can be done across all levels of testing to ensure the molecule being investigated will exhibit comparable effects across species.

Despite a lack of perfect symmetry of behavior between species, even between rodents, it is clear that the construct underlying behaviors exhibit remarkable consistency across species in comparable cognitive tests. Such consistency can, and should, be used in the future to develop molecules that will treat cognitive dysfunction in neuropsychiatric disorders.

Acknowledgements

The authors would like to acknowledge the support of everyone from the CNTRICS initiative. JWY receives support from NIH R21MH091571. TJB receives support from the Innovative Medicine Initiative Joint Undertaking under grant agreement no. 115008 of which resources are composed of EFPIA in-kind contribution and financial contribution from the European Union's Seventh Framework Programme (FP7/2007–2013). TJB consults for Campden Instruments.

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