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Review

Consideration of species differences in developing novel molecules as cognition enhancers

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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.

Contents

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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 (Matthysse, 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.