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Review

A preclinical cognitive test battery to parallel the National Institute of Health Toolbox in humans: bridging the translational gap

Shikha Snigdha [a,*], Norton W. Milgram [b], Sherry L. Willis [c], Marylin Albert [d], S. Weintraub [e], Norbert J. Fortin [f,g], Carl W. Cotman [a,g]

[a] Institute for Memory Impairments and Neurological Disorders, University of California–Irvine, Irvine, California, USA
[b] CanCog Technologies Inc, Toronto, Ontario, Canada
[c] Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Washington, USA
[d] Division of Cognitive Neuroscience in the Department of Neurology at Johns Hopkins University School of Medicine, Baltimore, Maryland, USA
[e] Feinberg School of Medicine, Northwestern University, Chicago, Illinois, USA
[f] Center for the Neurobiology of Learning and Memory, University of California–Irvine, Irvine, California, USA
[g] Department of Neurobiology and Behavior, University of California–Irvine, Irvine, California, USA

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ABSTRACT

A major goal of animal research is to identify interventions that can promote successful aging and delay or reverse age-related cognitive decline in humans. Recent advances in standardizing cognitive assessment tools for humans have the potential to bring preclinical work closer to human research in aging and Alzheimer's disease. The National Institute of Health (NIH) has led an initiative to develop a comprehensive Toolbox for Neurologic Behavioral Function (NIH Toolbox) to evaluate cognitive, motor, sensory and emotional function for use in epidemiologic and clinical studies spanning 3 to 85 years of age. This paper aims to analyze the strengths and limitations of animal behavioral tests that can be used to parallel those in the NIH Toolbox. We conclude that there are several paradigms available to define a preclinical battery that parallels the NIH Toolbox. We also suggest areas in which new tests may benefit the development of a comprehensive preclinical test battery for assessment of cognitive function in animal models of aging and Alzheimer's disease.

1. Introduction

There has been little uniformity among measures used in human neuropsychological assessment to assess cognitive deficits associated with aging and Alzheimer's disease (AD). This has had a negative impact on the pace of discovery in research on aging and dementia in clinical trials, and confounds the utility of preclinical assessment. Accordingly, the National Institutes of Health supported the development of a comprehensive assessment tool, the NIH Toolbox For Assessment Of Neurological And Behavioral Function, for use in longitudinal, epidemiological, and intervention studies. The entire NIH Toolbox covers emotion, cognition, motor, and sensory function, whereas the cognition section of the NIH Toolbox provides a specific neuropsychological instrument battery (NIH Toolbox Cognitive Function Battery [CFB]), to probe several cognitive domains (working memory, episodic memory, attention, executive function, processing speed, language, and reading). To move the field of translational research forward, there is an urgent need to develop a comparable preclinical test battery using animal models.

Use of animal models for evaluation of cognitive dysfunction involves simulating specific behaviors or symptoms associated with human cognition. Three important validation criteria for evaluation of such model systems are face, construct, and predictive validity. Although construct validity relies on a match between the proposed pathophysiology of a condition and that of the model species, predictive validity focuses on a match with clinical studies in its response to interventions. The third criterion used to define validity of a model is "face validity," which relies on a match between the behavioral effects observed in a model and those exhibited by the species being modeled. Although it is used in initial design of tests, it is a less stringent criterion compared with construct and predictive validity. Two types of models that are traditionally used in brain aging and AD research are discussed here.

* Corresponding author at: University of California–Irvine, 1226 Gillespie NRF, Irvine, CA 92697-4540. Tel.: +1 (949) 824 9896; fax: +1 (949) 824 2071.
E-mail address: ssnigdha@uci.edu (S. Snigdha).

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1.1. Natural or spontaneous models

These include species that show a natural deposition of amyloid and tau proteins, both hallmarks of the disease condition in humans, together with cognitive decline. Nonhuman primates (Gearing et al., 1997; Martin et al., 1994; Price et al., 1991) and dogs (Cotman and Head, 2008; Head and Torp, 2002; Pugliese et al., 2006) are 2 of the most common species used as spontaneous models. These animals have a well-developed prefrontal cortex and a relatively long lifespan. This ensures that the animals can perform higher-order cognitive tasks and exhibit age-induced behavioral abnormalities that parallel cognitive deficits shown by aged humans.

The rhesus monkey, for instance, has a lifespan of more than 30 years. This is equivalent to about 90 human years (Price et al., 1991). These monkeys share a 92% to 95% genetic homology with humans and, similar to humans, show age-related cognitive impairments relative to their young counterparts (Herndon et al., 1997; Smith et al., 2004). Aged monkeys also show loss of cholinergic activity (as seen in human AD patients) and deposition of amyloid plaques that can be visualized by using human anti-Aβ protein antibodies (Summers et al., 1997; Voytko et al., 2001). Furthermore, pharmacological interventions that increase acetylcholine release have been successfully shown to enhance cognitive performance in aged monkeys (Terry et al., 1993).

The aged dog, which is considered to be 1 of the best and most accessible animal models of brain aging, also shows many of the key features of human brain aging, mild cognitive impairment (MCI), and early AD (Cotman and Head, 2008, Sarasa and Pesini, 2009). Like the aged human brain, the canine brain shows increased oxidative damage, mitochondrial dysfunction, selective neuron loss, decreased hippocampal neurogenesis, and accumulation of beta-amyloid (Aβ) pathology with age. The aged canine is a natural model of Aβ accumulation, as the canine and human Aβ protein is 100% homologous and the APP sequences share 98% homology. Indeed, the canine brain accumulates senile plaques with age, and the accumulation of $A\beta_{1\text{-}42}$ and $A\beta_{1\text{-}40}$ progresses in a similar fashion to that occurring in the human brain. Furthermore, pharmacological and dietary interventions, and exercise have been shown to improve health and cognitive decline in the aged dogs, lending some predictive validity to the use of the model (Cotman and Head, 2008; Fahnestock et al., 2012; Milgram et al., 2005).

However, despite the significant advantages of higher-animal models, rodents in general, and rats and mice in particular, continue to remain the most commonly used animals as experimental models of aging and AD. A high birth rate, short reproductive and life cycle, and small size make them ideal laboratory animals. Furthermore, with the increased use of transgenic and knockout mouse models, it has become more common to use induced models to evaluate the etiology of the disease and to develop pharmaceutical treatments.

1.2. Induced models

These models rely on induction of AD-like pathology using experimental manipulations such as lesions (Lescaudron and Stein, 1999 Vale-Martinez et al., 2002), drugs (Buccafusco, 2009; Decker and McGaugh, 1991; Taffe et al., 1999), amyloid-β infusion and genetic alterations (for review see (Gotz and Ittner, 2008; Zahs and Ashe, 2010)). Drug treatments that produce a disruption or loss of acetylcholine brain transmission are examples of pharmacological disruption that models Alzheimer's dementia. Such a deficit can be reproduced in animals by blocking cholinergic receptors pharmacologically with drugs such as scopolamine and mecamylamine or by using neurotoxic, electrolytic, or mechanical lesions of cholinergic brain subregions (Toledano et al., 2010). Lesion models have the advantage of producing more chronic deficits than the pharmacological models. Genetic manipulations include knockouts, knockdowns, and transgenic mice, and are extensively used to study pathological characteristics of AD, such as amyloid plaques and neurofibrillary tangles. Despite some drawbacks (reviewed in Zahs and Ashe, 2010), genetically altered species can be considered the most valid induced model based on similarities in construct (Zahs and Ashe, 2010).

Table 1
Overview of animal tasks that parallel the NIH Toolbox cognitive function battery

Domain	Task in NIH Toolbox CFB	Parallel animal task
Executive function		
Cognitive flexibility	Dimensional card sort task	Attentional set-shifting task Reversal learning task
Inhibitory control	Flanker task	Go/No-go tasks
Working memory	Single and multiple list sorting task	Discussed as a separate domain
Episodic memory	Sequential memory/learning task	What–where tasks What–when tasks What–where–when task
Working memory	Single and multiple list sorting task	DNMP/DNMS Self-order tasks n-Back task
Processing speed	Pattern comparison task	Pattern comparison task
Attention	Flanker task	5-Choice serial reaction task Visual attention task
Language	Picture vocabulary test	N/A

Key: CFB, cognitive function battery; DNMP/DNMS, delayed non-match to position/delayed non-match to sample; N/A, not available; NIH, National Institutes of Health.

Although the study of aging and AD depends on the use of animal models, the correspondence between the behavioral assays used in humans and animals to measure the key cognitive domains of the NIH Toolbox is not well established. In the following sections, we describe and evaluate tests that can be used to measure subdomains from the NIH Toolbox CFB (overview in Table 1). Such a test battery would facilitate study comparisons between different groups, make data pooling much more feasible, and improve the translational properties of preclinical research. Our goal here is to outline a battery of preclinical behavioral tests that may be used to assess 5 of the 7 cognitive domains comprising the NIH Toolbox CFB. Language and reading, which involve drawing inferences from written or printed text, are extremely difficult to reliably model in animals, and will not be addressed in this article.

2. NIH Toolbox CFB and comparable preclinical tests

2.1. Executive function

Overall, the NIH Toolbox CFB considers executive function as the top-down cognitive modulation of goal-directed activity. Executive function involves several different components or subdomains, including set shifting, inhibitory response, and updating/working memory. In the NIH Toolbox CFB, the Dimensional Change Card Sort task is used as a measure of set shifting. This task is a measure that was adapted for adults from pediatric research (Zelazo, 2006). In this task, subjects must respond to pairs of stimuli by selecting the one that is the same shape as a third target stimulus or one that is the same color. The sorting contingencies shift, requiring the ability to inhibit previous response strategies and to try new ones. In accordance, we propose that the attentional set-shifting task be used as a measure of set-shifting in animals.

The NIH Toolbox CFB describes a flanker task to evaluate the inhibitory component of visual attention and executive function. The test presents a line of arrows (or fish, for children) in the center of the computer screen (Fan et al., 2002). The central stimulus points leftward or rightward, whereas the others point either in the same