ELSEVIER

Journal of Neuroscience Methods 146 (2005) 165–173

JOURNAL OF NEUROSCIENCE METHODS

www.elsevier.com/locate/jneumeth

A non-human primate test of abstraction and set shifting: An automated adaptation of the Wisconsin Card Sorting Test

Tara L. Moore [a, b, *], Ronald J. Killiany [a, b, 1], James G. Herndon [c, 2], Douglas L. Rosene [a, c, 3], Mark B. Moss [a, b, c, 4]

[a] *Department of Anatomy and Neurobiology, Boston University School of Medicine, 715 Albany Street, W-701 Boston, MA 02118, USA*
[b] *Department of Neurology, Boston University School of Medicine, Boston, MA 02118, USA*
[c] *Yerkes National Primate Research Center, Emory University, Atlanta, GA 30322, USA*

Received 18 November 2004; received in revised form 11 February 2005; accepted 14 February 2005

Abstract

Functional assessment of the prefrontal cortices in the non-human primate began with the seminal work of Jacobsen in the 1930s. However, despite nearly 70 years of research, the precise nature of the cognitive function of this region remains unclear. One factor that has limited progress in this endeavor has been the lack of behavioral tasks that parallel most closely those used with humans. In the present study, we describe a test for the non-human primate that was adapted from the Wisconsin Card Sorting Task (WCST), perhaps the most widely used test of prefrontal cognitive function in humans. Our adaptation of this task, the Conceptual Set-Shifting Task (CSST), uses learning criteria and stimuli nearly identical to those of the WCST. The CSST requires the animal to initially form a concept by establishing a pattern of responding to a given stimulus class, maintain responding to that stimulus class, and then shift to a different stimulus class when the reward contingency changes. The data presented here establishes baseline performance on the CSST for young adult rhesus monkeys and demonstrates that components of prefrontal cognitive function can be effectively assessed in the non-human primate in a manner that parallels the clinical assessment of humans.

Keywords: Rhesus monkey; Executive function; Prefrontal cortex; Wisconsin Card Sorting Test

1. Introduction

Assessment of the cognitive functions of the prefrontal cortex (PFC) in the non-human primate began with the seminal work of several researchers in the early 1920s and 1930s (Jacobsen, 1935, 1936; Bianchi, 1922; Breslau et al., 1994). They demonstrated that lesions in the PFC impair performance on cognitive tasks, such as delayed response and delayed alteration, tasks that are now thought to require "working memory", a short-term buffer for "working with" recently presented and remembered stimuli (Baddeley, 1986). More recent work in the field, using a variety of tests with non-human primates, has implicated the prefrontal cortices (i.e., all those regions rostral to the motor and premotor cortices) in learning, memory and executive function (Dias et al., 1996; Roberts et al., 1994; Gaffan and Harrison, 1989; Bachevalier and Mishkin, 1986; Woods and Knight, 1986; Passingham, 1985; Mishkin and Manning, 1978; Oscar-Berman, 1978; Rosen et al., 1975; Pohl, 1973; Butters and Pandya, 1969). Examples of tests include, the delayed response test, the delayed alternations test, the reversal-learning test and a test of attentional set shifting (Roberts et al., 1988; Dias et al., 1996; Diamond, 1990; Goldman et al., 1971; Pohl, 1973). Animals with damage to the prefrontal regions have been shown to be impaired on these tests (i.e., Jacobsen: delayed response test; Pohl: reversal learning). However, despite nearly 70 years of research, the precise

* Corresponding author. Tel.: +1 617 638 4054; fax: +1 617 638 4922.
E-mail address: tlmoore@bu.edu (T.L. Moore).
[1] Tel.: +1 617 638 8082.
[2] Tel.: +1 404 727 7752.
[3] Tel.: +1 617 638 4061.
[4] Tel.: +1 617 638 4200.

0165-0270/$ – see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.jneumeth.2005.02.005

nature of the cognitive function subserved by this region remains unclear. One factor that has limited more rapid progress in this endeavor has been the lack of behavioral tasks that parallel more closely those used with humans.

In humans, the Wisconsin Card Sorting Test (WCST; Grant and Berg, 1948) is the most frequently employed instrument used to assess prefrontal cortex function (Berg, 1948; Milner, 1968, 1995). The WCST assesses the ability to abstract, maintain, and shift cognitive set according to changing reward contingencies (Nagahama et al., 1996; Damasio and Anderson, 1993; Heaton et al., 1993). Essential components of the WCST paradigm have been incorporated into a task developed for non-human primates by Roberts et al. (1988). The task assesses both extra-dimensional and intra-dimensional shifting of set, but does not use the same stimuli as that of the WCST. Our adaptation of the WCST for the non-human primate, the Conceptual Set-Shifting Task (CSST), uses the same basic principles, learning criteria, as well as the identical stimuli as those of the WCST. The CSST requires the animal to initially form a concept by establishing a pattern of responding to a given stimulus class (color or shape), maintain responding to that same stimulus class, and then shift to a different stimulus class when the reward contingency is changed. The data presented below establishes a baseline performance on the CSST for young adult rhesus monkeys and demonstrates that components of prefrontal cognitive function can be effectively assessed in the non-human primate in a manner that parallels closely those used in the clinical assessment of humans.

2. Materials and methods

2.1. Subjects

The behavioral data in this study was obtained from eight young adult male rhesus monkeys (*Macaca mulatta*) that served as normal controls in our ongoing behavioral studies of normal aging (Moore et al., 2003). All of the monkeys described in this report were obtained from the Yerkes National Primate Research Center and had known birth dates and complete health records. Prerequisite to entering the study, each monkey received a complete medical examination and explicit exclusion criteria were applied for the following conditions: splenectomy, thymectomy, exposure to radiation, cancer, organ transplantation, malnutrition, chronic illness including viral or parasitic infections, neurological diseases, or chronic drug administration. All of the monkeys were individually housed and were in constant auditory and visual range of other monkeys. Monkeys were fed a diet of Purina Chow and fruit at the end of testing each day and on weekends. Water was available continuously. The monkeys were maintained under a 12-h light/dark cycle that changed gradually over the course of an hour. All animals were checked daily by animal technicians for health and well-being and were given a medical exam by staff veterinarians every 6 months. The monkeys used in the present study were behaviorally sophisticated. Each had been tested on the Delayed Non-Matching to Sample (DNMS), both acquisition of this task and delays of 2–10 min as well as the Delayed Recognition Span Test (DRST) prior to the administration of the CSST. The details of the DNMS and DRST tasks are described elsewhere (Herndon et al., 1997; Moss et al., 1997).

2.2. Apparatus

On testing days, animals were transferred from their home cage into a mobile testing cage approximately 36 in. square × 50 in. height. One side was double-walled so that the outer small mesh side could be removed exposing a larger grid with square openings 3 in. × 3 in. on a side that allowed the monkey to easily reach out of the testing cage. The mobile cage was moved into a sound-attenuating chamber that contained a 19 in. touch-sensitive and resistive computer screen controlled by a Macintosh-based computer. For stimulus presentation, the computer screen was divided into a 3 × 3 matrix (unmarked). Rewards of M&Ms or Skittles candies were delivered from an automated dispenser (Med Associates) by a tube into a tray located immediately beneath the touch screen. The interior of the testing chamber was darkened and the apparatus was located in a darkened room. White noise was presented through two speakers, one mounted on each side within the automated apparatus to mask extraneous sounds. Stimulus presentation, touch screen monitoring and reward delivery were controlled by a behavioral testing program, “Glyph”, which was developed for assessing cognitive functions in mentally challenged adults and children. A non-correctional procedure was used throughout testing.

2.3. Behavioral testing

Testing consisted of three tasks administered in the following order: a pre-training task to adapt the monkey to the touch screen, a three-choice discrimination to assess the monkeys ability to respond to stimuli of the type to be used in the CSST, and the CSST task that consists of an initial abstraction and three subsequent shifts of stimulus set.

2.4. Automated pre-training

The automated pre-training task was used simply to teach each monkey to touch the computer screen. This task required the monkey to touch a single stimulus that appeared in a pseudorandom fashion in one of the nine locations on the screen. The stimulus was an image of an apple that was left on the screen for 60 s or until the monkey touched it. The inter-trial interval was 15 s. Touching the stimulus delivered a food reward into the tray beneath the screen. The animals were initially rewarded for touching any portion of the screen, and then were subsequently shaped to touching only the apple stimulus. Pre-training was administered for 20 trials a day until the monkey correctly responded to all 20