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Executive system dysfunction occurs as early as middle-age in the rhesus monkey

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Abstract

As our understanding of age-related cognitive decline advances, studies are now focusing on identification of those areas of cognitive function that undergo the first changes with age. In the present study, in order to determine whether executive function is sensitive to the aging process, we assessed the performance of 16 monkeys of middle-age (12–19 years of age) on the conceptual set-shifting task, an analogue of the Wisconsin Card Sorting Test (WCST). We compared their performance to that of seven young adult (5–9 years of age) and 18 aged monkeys (20–30). The findings showed that middle-aged monkeys, like those of advanced age, were significantly impaired on the conceptual set-shifting task (CSST). These findings parallel those of recent studies in humans demonstrating an increase in perseverative errors on the WCST by middle-aged as well as aged individuals and, in turn, support the notion that disruption of executive function is one of the earliest changes in cognition to occur in normal aging.

Keywords: Non-human primate; Middle-age; Cognition; Executive Function; Wisconsin Card Sorting Test

1. Introduction

It is well established that normal aging is characterized by a decline in multiple domains of cognitive function including short-term memory, psychomotoric speed, naming, and executive function [1,2,4,37,54]. Of these, executive function (EF) is one of earliest cognitive domains to evidence change in humans [3,25] and non-human primates alike [8,9,41,60,61,76]. Although views on the exact components of EF vary, it is generally agreed that it includes the abilities of set-shifting, planning, working memory, and response suppression (Trans-NIH Executive Function Workshop, January 2003). Among the many tasks that have been developed to assess EF in humans, perhaps the most commonly employed is the Wisconsin Card Sorting Test (WCST [10,31]). This task, which heavily emphasizes set-shifting and response suppression, has been used in studies of normal aging [26], the effects of focal cortical lesions [46,47], head injury [42], attention deficit disorder [40], depression [12], and a host of other neurologic and psychiatric disorders [38]. The popularity of the WCST for use in clinical studies and neuropsychological assessment is due in large measure to its simplicity of design, use of common stimulus classes, amenability to error analyses, and minimum dependence on language. Toward the goal of bringing behavioral studies in humans and animals into parallel, the WCST has been successfully adapted in nearly identical form [49,51,52], or in forms that are analogous to it [24] for use in non-human primates.

With regard to normal aging, the WCST was first used 15 years ago to show that subjects in their 70s and 80s were impaired in executive function [34]. Together with findings from more recent studies [11,32,36,64,65] it is clear that even in earlier stages of aging, there is a diminution in the ability

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to shift and maintain set, as well as an increased tendency to respond to previously correct stimuli (i.e., perseverative errors). We have developed the conceptual set-shifting task (CSST), a direct adaptation of the WCST, as a tool for the study of EF in a rhesus monkey model of normal cognitive aging. In studies using the CSST in aged monkeys, we demonstrated deficits in abstraction, set-shifting and set maintenance in aged rhesus monkeys that parallel those seen in the human studies [49,51]. Specifically, monkeys of advanced age (20–30 years of age, roughly equivalent to humans ages of 60–90 years) were impaired in abstraction and set-shifting on the CSST relative to young adults (5–9 years of age, equivalent to human ages of 15–27 years). Moreover, as found in aged humans, aged monkeys made significantly more perseverative errors during each shift in stimulus set of the CSST [51].

Although these data clearly demonstrate an age-related deficit in executive function, they do not pinpoint the age at which cognitive decline begins. In the present study, we have addressed this important question by using the CSST to determine whether deficits in EF are already evident in monkeys 12–19 years, a range spanning early to late middle-age.

2. Methods

2.1. Subjects

The subjects in this study were 41 rhesus monkeys (*M. mulatta*), weighing between 6.4 and 14.1 kg. Based on an extensive survival study at Yerkes National Primate Research Center [74], which suggests a ratio of 1–3 between monkey and human years of age, we have designated monkeys 5–10 years of age as young monkeys, those 12–19 as middle-aged, and those 20 and older as aged. In this study, the young group consisted of seven animals (5 males and 2 females) from 5 to 9 years of age (Table 1). The data from three of these animals (AM092, AM094, AM095) were included in previous studies as control data [51,52]. The middle-aged group consisted of 16 animals ranging from 12 to 19 years of age (13 males and 3 females). The aged group consisted of 18 animals (11 females and 7 males) ranging from 20 to 30 years of age (Table 1). The data from seven of these animals (AM024, AM048, AM063, AM068, AM090, AM091, AM098) were included in a previous study [52]. One aged male monkey (AM048) did not complete the entire CSST because of a sudden illness. Data from this monkey are only included from conditions completed prior to the onset of illness. All monkeys in this study had known birth dates, complete health records, and were obtained from the Yerkes National Primate Research Center of Emory University. Before entering the study, monkeys received medical examinations that included serum chemistry, hematology, urine analysis, and assessment of visual function. History of splenectomy, thymectomy, exposure to radiation, cancer, organ transplantation, malnutrition, chronic illness including viral or parasitic infections, neurological diseases, or chronic drug administration were explicit exclusion criteria. Once entered into the study, monkeys were individually housed in colony rooms within constant auditory and visual range of other monkeys. A diet of Purina Chow supplemented by fruit was given to the monkeys each day after testing and water was continuously available. Monkeys were maintained under a 12 h light–dark cycle. Monkeys were checked daily by trained observers for health and well-being, and were given a complete medical exam every 6 months.

Following the completion of behavioral testing, each of the monkeys underwent magnetic resonance imaging (MRI) to ensure that none of the monkeys had suffered a major cerebrovascular event, such as a stroke. All of the monkeys in this study had normal MRI findings.

2.2. Behavioral testing

The monkeys in this study were part of a larger study of normal aging and were behaviorally sophisticated, having had experience with the delayed non-matching to sample, delayed recognition span test, and a contrast sensitivity test prior to the administration of the CSST [37,54]. For the present study, an automated pre-training task, a three-choice discrimination task, and the CSST were administered sequentially. Tests were conducted in an automated general testing apparatus that contained a 19 in., touch sensitive, resistive, computer screen, driven by a Macintosh computer. White noise was played on two speakers located within the automated apparatus to mask extraneous sounds. A non-correctional procedure was used throughout testing with M&Ms™ or Skittles™ used as rewards.

An automated pre-training task was used for teaching each monkey to touch the computer screen. This task required the monkey to touch a single stimulus that appeared randomly in one of nine locations on the screen to receive a single piece of M&M™ or Skittles™ candy, the same reinforcement used for all tasks in the study. Pre-training was continued for 20 trials a day until the monkey correctly responded to 20 consecutive trials in a single day. The day after the monkey completed the pre-training task all but three began a simple three-choice discrimination task.

For the discrimination task, and for the subsequent CSST task, the computer screen was divided into a 3×3, unmarked matrix, providing nine distinct locations where a stimulus could be displayed. Monkeys responded by touching one of these locations. The discrimination task was administered to determine if there was a group difference in the ability to discriminate among three stimuli (a pink square, orange cross, and a brown 12-point star) on the basis of the reward contingency. The task presented the monkey with all three stimuli on each trial but their spatial location varied from trial to trial in a pseudo-random order. The pink square was the positive stimulus for all trials and for all monkeys and touching of this stimulus resulted in the delivery of a reinforcement. Touching