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Research report

Attentional updating and monitoring and affective shifting are impacted independently by aging in macaque monkeys

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HIGHLIGHTS

- Macaques show age impairments on both shifting and attentional control.
- Monkeys show evidence of retroactive and proactive interference.
- Age-related deficits in attentional monitoring and shifting were independent.

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ABSTRACT

One hallmark of the normal cognitive aging process involves alterations in executive function. Executive function can be divided into at least three separable components, including set shifting, attentional updating and monitoring, and inhibition of prepotent responses. The ability to study the neural basis of cognitive aging has been enriched by the use of animal models such as the macaque monkey. In aged macaques, changes in attentional updating and monitoring systems are poorly understood compared to changes in shifting and inhibition. A partial explanation for this is the fact that the tasks designed to study executive function in aged monkeys, to date, primarily have probed shifting and inhibition processes. Here we examine how aging impacts attentional updating and monitoring processes in monkeys using an interference task designed after a paradigm used to examine multi-tasking in older humans. Young and aged macaque monkeys were tested on this interference task as well as on an object reversal learning task to study these processes in the same animals. Relative to the young monkeys, aged animals were impaired on both tasks. Proactive and retroactive interference did not differ between age groups on an array of 40 object pairs presented each day in the object reversal learning task. The levels of performance on the interference task were not correlated with levels of performance in the object reversal task. These results suggest that attentional updating and monitoring and affective shifting are separable functions in the macaque, and that normal aging affects these mental operations independently.

1. Introduction

Goal-directed behaviors allow individuals to deliberately select actions that accomplish specific objectives, differentiating them from habitual behaviors, which are executed regardless of context. The mental processes that guide the proper execution of goal-directed behaviors, collectively referred to as executive function, are thought to be supported by neural networks within the mammalian prefrontal cortex [7,15,17]. Declines in executive function can be detected in early adulthood, and are among the first cognitive impairments to emerge in normative, healthy aging [45,46,51,52,58]. Recent extensions in average lifespans worldwide have led to increases in the number of aged individuals [41], highlighting the importance of understanding the neurobiological changes that underlie age-related declines in executive function.

A number of theories have been proposed to account for the diversity of mental operations considered to be involved in executive function [44,24,12]. For example, Miyake et al. [44] suggest that executive processes can be divided into at least three sep-

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arable functions, including attentional updating and monitoring, set shifting, and inhibition of prepotent responses [23,44]. Lesion and functional imaging studies clearly show that different regions of the prefrontal cortex operate independently to give rise to each of these executive functions [18,31,60]. For example, in non-human primates, lesions to the orbitofrontal cortex result in performance deficits on an object reversal learning task but not an extra-dimensional set-shifting task, and lesions to the dorsolateral prefrontal cortex result in the exact opposite pattern of impairment [18]. In the context of normative aging, there is evidence that distinct executive processes change at different rates within and between people [22,30], suggesting that distinct prefrontal networks experience age-related neurobiological alterations independently.

Animal models of cognitive aging have enriched our understanding of the brain alterations that underlie lifespan changes in cognition (for reviews see Refs. [7,20,33,63]). The macaque monkey provides a particularly valuable model for examining the neural basis of cognitive decline during normal aging since: 1) macaques experience age-related cognitive decline similar to that of humans (e.g., [20,25,33,58,63]), 2) comparative studies of the cytoarchitectonic organization of dorsolateral and ventromedial prefrontal cortical regions in macaques and humans suggest that the two species possess numerous homologous frontal cortical fields, with discrepancies existing only in the size and delineation of these areas (e.g., [55,54]), and 3) macaques do not develop dementing neurodegenerative diseases, allowing for studies of normal aging to be carried out at molecular, anatomical and electrophysiological levels of analysis (e.g., [33,47,53]).

When cognitive tests similar to those used in humans are administered to monkeys, like humans, older macaques show clear individual differences, with some monkeys showing minimal impairment, some showing severe impairment, and most falling between the two ends of this continuum (e.g., [45,46,53,57]). Interestingly, tasks designed to assess disparate mental skills within the same group of aged monkeys suggest that distinct aspects of cognition can be impaired differently within an individual monkey [66]. For example, older animals that are impaired on an object-based task may not be impaired on spatial versions of the same task, and *vice versa* [66]. Similarly, Bizon and colleagues have shown that aged rats with impairments on a spatial working memory task can perform normally on a set-shifting task, and rats impaired on a set shifting task can perform spatial working memory tasks without impairment [4]. Together, these results suggest that normative aging alters different cognitive systems independently of one another within an individual, and the pattern in which different cognitive systems change with age varies between individuals.

Whether different components of the executive function network age independently in non-human primates is not known, and studying this question requires the same individual aged monkeys to perform multiple executive tasks. To this end, the experiments reported here examine the performance of young and aged macaques on two separate tasks that probe the executive processes of attentional updating and monitoring and affective shifting. The first task is an interference task adapted from a multitasking paradigm in humans used to probe attentional updating and monitoring [15,13]. This task is designed to deliver different forms of interference in the delay period of a delayed nonmatching-to-sample task, requiring animals to switch attention from the primary object recognition task to a secondary task and back. Basile and Hampton [2] used this paradigm with a matching rule instead of a nonmatching rule to show that interference significantly reduces performance when an active encoding strategy is used. In humans, similar tasks have been shown to engage the lateral and medial frontal cortices, but not ventromedial prefrontal areas [15,14,13]. The second task used in this study is an object reversal learning task, which tests the ability of an animal to alter behavior following changes in the emotional significance of stimuli, a process referred to as affective shifting. Lesion and imaging studies have shown that orbitofrontal cortical, striatal and amygdalar networks underlie affective shifting [18,21,38,61,67,39]. The execution of both the attentional updating and monitoring and affective shifting tasks in the same set of monkeys allow us to evaluate whether these separate executive processes are affected independently by the aging process or whether there is a common age-related pattern of decline across individual monkeys and executive processes.

2. Materials and methods

2.1. Subjects

Six young (mean: 10.5 years) and seven aged (mean: 23.4 years) female bonnet macaques (*Macaca radiata*) participated in the current study. Every monkey received a semiannual health assessment from the veterinary staff at the University of Arizona (Tucson, AZ), and no animal included in this study presented with health concerns before or during the time of testing. Animals were paired-housed in a humidity- and temperature-controlled vivarium with a 12 h light-dark cycle and ad libitum food and water. Prior to testing, all animals underwent behavioral shaping to tolerate restraint in a specialized non-human primate transport box (50.8 cm × 31.1 cm × 40 cm), which was used to transport the monkeys from their home vivarium to the behavioral testing box (below). The experiments described followed guidelines established by the National Institutes of Health and were approved by the Institutional Animal Care and Use Committee at the University of Arizona.

2.2. Testing apparatus and task stimuli

A modified Wisconsin General Testing Apparatus (WGTA; [34]) was used to acquire all behavioral data (based on Ref. [3]). The WGTA consists of a box where animals reside during the testing procedure. At one end of the box vertical bars separate the animal from a tray with three equally spaced wells where stimulus presentation and reward delivery occur. Two partitions could be manipulated by the experimenter to control the animal's access to and visibility of the stimulus objects and rewards. The first partition consisted of a wooden guillotine door, and served to block the monkeys from both visualizing and interacting with the objects/rewards. A transparent Plexiglas door was used as the second partition, which allowed the animals to visualize the objects/rewards, but not to interact with them. A one way mirror separated the experimenter from the animals, allowing their performance to be monitored without detection. Stimuli consisted of plastic toy objects of comparable size (~8 cm^3), and the rewards used were dry and fresh fruit, vegetables, and sugar free gummy bears.

2.3. Behavioral paradigms

2.3.1. Delayed nonmatching-to-sample task with differing levels of interference

The delayed nonmatching-to-sample (DNMS) task [57] begins with a single object presented over the center well of the WGTA (Fig. 1 A) – this is the "sample phase". Animals are allowed to displace the object to receive a food reward, ensuring that the sample object is encoded. Following the sample period, the wooden guillotine door is closed for a delay period of 30 s. After the delay period, the sample object is presented alongside a novel object on each of the lateral wells (this is the "test phase"). Only the novel object

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