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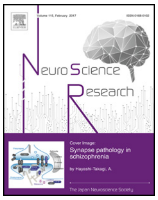

Visual discrimination and reversal learning in aged common marmosets (*Callithrix jacchus*)

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ABSTRACT

Common marmosets (*Callithrix jacchus*) have been suggested as a new model for analysis of age-related changes and neurodegenerative diseases. However, the effects of age on learning and memory processes are not well defined within this species. Therefore, we employed visual discrimination and reversal learning tasks to evaluate learning and memory in four aged common marmosets relative to a younger cohort. We found that aged marmosets commit significantly more errors in initial stages of visual discrimination and more perseverative errors in reversal learning, indicating prefrontal dysfunction. However, they showed comparable performance with younger marmosets in the later stages of both tasks.

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Learning and memory processes are believed to be similarly organized in humans and nonhuman primates (Zola-Morgan and Squire, 1993). Therefore, behavioral and cognitive studies in nonhuman primates can be used to understand human learning and, in particular, the effects of aging on cognitive processes. Previous work has demonstrated that aged macaques perform worse compared to a non-aged cohort in object discrimination and reversal learning tasks, which are designed to test functioning of the prefrontal cortex in relation to decision making and the animals ability to inhibit inappropriate responses (Clark et al., 2004; Nakamura, 2001). The findings in macaques are in line with those from human studies which have shown memory impairments such as difficulties with object retention and recognition with age (Adamowicz, 1976; Rabinowitz, 1984). Macaques have been widely used in cognitive learning research, though recently common marmosets (*Callithrix jacchus*) have been suggested as a nonhuman primate model for aging and neuroscience research (Fischer and Austad, 2011; 't Hart et al., 2012).

Common marmosets are small New World monkeys of the family Callitrichidae (Fischer and Austad, 2011). These monkeys are native to eastern Brazil and have a maximum life span of 16 years in captivity. This species reaches sexual maturity at 18 months and are said to be middle aged between ages 4–7 and are considered aged beyond 8 years (Abbott et al., 2003; Mansfield, 2003). However, the effect of aging on cognition has not been well-defined in this species (Ross et al., 2012). One study reported that common marmosets exhibit an age-related reduced neurogenesis in the hippocampus (Leuner et al., 2007). Additionally, recent studies have revealed a high incidence of β-amyloid (Aβ) deposits in common marmosets older than 7 years (Geula et al., 2002; Maclean et al., 2000; Mansfield, 2003). Alzheimer's disease (AD) is characterized by the accumulation of extra-neuronal Aβ plaques in addition to neurofibrillary tangles made up of a microtubule protein called tau within neurons (Braak and Braak, 1991; Montine et al., 2012). Therefore, marmosets may represent a new model of research that provides an opportunity to examine the effects of age and amyloid deposition separately from tau pathology.

Visual discrimination tasks, serial learning, and reversal learning have been previously tested in marmosets. In direct comparison studies with macaques, marmosets demonstrate similar learning curves to macaques but take significantly longer to reach test criteria (Miles, 1957; Miles and Meyer, 1956). In these studies, the sample age range has been very limited, with a maximum age of around four years (Koba et al., 2012; Rygula et al., 2010; Takemoto et al., 2015). Therefore, the present study examined the effects of age on the ability of common marmosets to learn and complete visual pattern discrimination tasks and reversal learning.

Four research-naïve marmosets aged ten years or older participated in this study (2 males and 2 females; Table 1). All marmosets were held at the Primate Research Institute of Kyoto University. Marmosets were transferred to individual cages located within the colony for cognitive testing. Subjects were fed 30 g of New World

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Table 1
A list of marmosets who participated in this study.

Subject	Sex	Age	Age Cohort
1	M	2 y 7 m	Young
2	M	3 y 0 m	Young
3	M	2 y 0 m	Young
4	F	2 y 0 m	Young
5	F	2 y 1 m	Young
6	M	1 y 7 m	Young
7	M	1 y 8 m	Young
8	M	2 y 1 m	Young
9	F	1 y 8 m	Young
10	F	1 y 9 m	Young
11	M	2 y 3 m	Young
12	M	2 y 5 m	Young
13	M	2 y 0 m	Young
14	F	2 y 0 m	Young
15	F	2 y 1 m	Young
16	M	3 y 2 m	Young
17	M	2 y 4 m	Young
18	F	2 y 5 m	Young
19	F	2 y 9 m	Young
20	F	2 y 10 m	Young
21	F	2 y 7 m	Young
22	F	2 y 8 m	Young
23	M	3 y 5 m	Young
24	F	3 y 5 m	Young
25	M	2 y 6 m	Young
26	M	14 y 1 m	Aged
27	M	11 y 10 m	Aged
28	F	10 y 7 m	Aged
29	F	14 y 0 m	Aged

Monkey pellets once daily as well as additional food supplements such as bananas, apples, raisins, and mealworms. Water was available *ad libitum*. This experiment was approved by the Institutional Animal Care and Use Committee at Kent State University and was conducted in accordance with the Guide for the Care and Use of Laboratory Animals of the National Research Council and the Guide for Care and Use of Laboratory Primates of the Primate Research Institute, Kyoto University.

The apparatus used in this experiment consisted of a 7-inch (17.8 cm) touch screen mini tablet computer connected to a feeder via a USB drive (Model SC, Kohjinsha, Tokyo, Japan; Takemoto et al., 2011). The apparatus would simultaneously present the visual stimuli and record responses as well as distribute food rewards. During the experiment, the apparatus was attached to the home cage of the marmoset.

Prior to visual discrimination and reversal learning, all marmosets were trained to touch a visual stimulus on the screen of the apparatus. During the first stage of training, a red square (75 mm × 75 mm) was presented in the center of the touch screen. Upon touching the screen, the red square would disappear with a tone (4 kHz, 100 ms) and a reward was presented. After a three second inter-trial interval (ITI) which consisted of a black screen, another red square was presented. A marmoset would complete up to 120 trials. Once the marmoset became proficient at touching the red square, the color of the square randomly changed between red, blue, and yellow every trial. The color would continue to randomly alter throughout the rest of training. After a few training sessions, the size of the square began to be reduced until it reached a minimum of 30 mm × 30 mm after a few days. The last stage of training involved randomly positioning the small square on the touch screen each trial.

For the visual discrimination learning, two different square graphic pattern stimuli (27 mm × 27 mm) were presented either to the left or right of center on the touch screen. One image, if touched, would provide the marmoset with a reward and a tone where the other would not. The left or right positions of the stimuli were randomly determined for each trial. An example of the events within one trial is presented in Fig. 1A. An inter-trial interval was 3 s. Incorrect responses were followed by 2-s timeout. The marmosets would complete a single session of 100 trials per day. The marmoset would continue with the same visual discrimination learning experiment until 90 correct responses out of 100 trials in one day were achieved. When the marmoset did not touch any stimulus for 15 min, the session was aborted. Once the marmoset reached the learning criterion, a new learning task was presented the following day. The marmosets in this study completed three visual discrimination learning experiments (N1, N2, N3) followed by a reversal learning (R3). Once the 90% criterion was reached in the first reversal learning, the marmosets completed a fourth visual discrimination (N4) followed by a second reversal learning (R4). In total, 8 graphic patterns were used for one marmoset. Graphic patterns were randomly selected from a stimulus pool of 20 graphic patterns (Fig. 1B).

In the reversal learning experiments, the two graphic stimuli presented were the same as the ones seen in the preceding visual discrimination learning task. However, now the stimulus that was associated with the food reward during visual discrimination is no longer. Therefore, the marmoset is required to inhibit previously learned stimulus-reward associations and form new behavioral responses.

To analyze the performance of the aged marmosets, the number of sessions and errors committed per task was compared to a younger cohort of marmosets. Marmosets within the younger cohort had already completed the same experimental design for past studies at the Primate Research Institute (11 males and 10 females; Table 1; Takemoto et al., 2015). The average number of sessions and errors committed by each cohort per task was compared using a mixed-design ANOVA. The Greenhouse-Geisser correction was used as indicated by Mauchly's test of sphericity.To further elucidate characteristics of the impairment of the aged marmosets, we separately examined the number of errors at three learning stages: "perseveration" where the percent correct was significantly below the chance, "chance", and "improvement" where the percent correct was significantly above the chance (for details see Takaji et al., 2016; Takemoto et al., 2015).

As shown in Fig. 2A, we plotted learning performance of the aged marmosets on the graphs of the learning percentiles of the younger cohort. The learning percentiles are median, 25th–75th, and 10th–90th. As clearly shown, most of the data from the aged marmosets was located below the median percentile of the younger cohort. Furthermore, three aged marmosets aborted sessions in the initial reversal learning (open symbols).

First, we compared the number of sessions to criterion between the aged and young marmosets (Fig. 2B). The main effects of age ($F_{1,27} = 7.85$ and $P = 0.009$) and task repetition ($F_{3,81} = 13.03$ and $P < 0.001$) were significant for novel learning (visual discrimination). Next, we compared the number of errors to criterion (Fig. 2C). We found that the main effects of age and task repetition were significant for novel learning ($F_{1,27} = 18.97$ and $P < 0.001$, $F_{3,81} = 13.65$ and $P < 0.001$, respectively) as was the interaction ($F_{3,81} = 3.63$ and $P = 0.016$). We also found that the main effects of age and task repetition were significant for reversal learning ($F_{1,27} = 13.47$ and $P = 0.001$, $F_{1,27} = 26.19$ and $P < 0.001$, respectively) as was the interaction ($F_{1,27} = 5.18$ and $P = 0.031$).

We separately examined the number of errors at three learning stages: perseveration, chance, and improvement (Takaji et al., 2016; Takemoto et al., 2015). As clearly shown in Fig. 3, the aged marmosets committed more errors especially in the initial learning of the improvement stage. The main effects of both age and task repetition were significant ($F_{1,27} = 10.59$ and $P = 0.003$, $F_{1,8,49.1} = 15.045$ and $P < 0.001$, respectively) as was the interaction ($F_{1,8,49.1} = 6.95$ and $P = 0.003$). In addition, aged marmosets committed more perseverative errors in the initial reversal learning. The main effects

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