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One-year change in cognitive flexibility and fine motor function in middle-aged male and female marmosets (*Callithrix jacchus*)

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Abstract

The common marmoset (*Callithrix jacchus*) is uniquely suited for longitudinal studies of cognitive aging, due to a relatively short lifespan, sophisticated cognitive abilities, and patterns of brain aging that resemble those of humans. We examined cognitive function and fine motor skills in male and female marmosets (mean age ~5 at study entry) followed longitudinally for 2 years. Each year, monkeys were tested on a reversal learning task with three pairs of stimuli (n = 18, 9 females) and a fine motor task requiring them to grasp small rewards from two staircases (Hill and Valley test, n = 12, 6 females). There was little evidence for a decline in cognitive flexibility between the two time points, in part because of practice effects. However, independent of year of testing, females took longer than males to reach criterion in the reversals, indicating impaired cognitive flexibility. Motivation was unlikely to contribute to this effect, as males refused a greater percentage of trials than females in the reversals. With regards to motor function, females were significantly faster than males in the Hill and Valley task. From Year 1 to Year 2, a slight slowing of motor function was observed in both sexes, but accuracy decreased significantly in males only. This study (1) demonstrates that marmosets exhibit sex differences in cognitive flexibility and fine motor function that resemble those described in humans; (2) that changes in fine motor function can already be detected at middle-age; and (3) that males may experience greater age-related changes in fine motor skills than females. Additional data points will determine whether these sex and age differences persist over time.

Keywords

aging; cognition; executive function; monkey; sex differences

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CONFLICT OF INTEREST

The authors have no conflict of interest.

1 | INTRODUCTION

The proportion of older people is steadily increasing in most parts of the world, including the United States, where the percentage of people over 65 years old is expected to rise from 15% in 2018 to 24% of the population by 2060 (US Census Bureau, 2017). Human aging is associated with a significant decline in cognitive function in most domains (Lindenberger, 2014; Reuter-Lorenz & Park, 2010; Salthouse, 2010), with fluid abilities, such as working memory and reasoning, being particularly affected, and experienced-based "crystallized" abilities, such as vocabulary, being more resistant to age-related decline. Aging is also characterized by a significant decline in fine motor function (Smith et al., 1999). Marked age-related changes are detected at every level of analysis in the human brain, from neuroanatomical structure, to neurochemistry and cellular and molecular levels (Raz, 2000; Raz & Rodrigue, 2006). However, it has become clear in recent years that the extent of age-related brain change and its functional consequences vary greatly between individuals. Longitudinal studies are particularly valuable to measure the rate of age-related change from an initial baseline performance and study the underlying mechanisms (Schaie, 2005).

Animal models are critically needed to answer key questions about the causes and consequences of cognitive and motor aging, and to identify and test potential treatments to alleviate age-related cognitive and motor impairment. Rodents possess many advantages as models for aging research (Bizon & Woods, 2009; Gallagher, Stocker, & Koh, 2011), but also have limitations with regards to the translation of the findings to humans. Nonhuman primate (NHPs), such as rhesus or cynomolgus macaques, are arguably better models for human neurocognitive and motor aging due to a higher degree of similarity with humans in cognitive and motor function, brain organization and patterns of age-related cognitive and motor decline (Baxter, 2001; Herndon, Moss, Rosene, & Killiany, 1997; Lacreuse & Herndon, 2009). However, the relatively long lifespan of macaques (~maximum 45 years) has hindered the design of longitudinal studies that can inform age-related cognitive and motor change and their biological concomitants. Shorter-lived nonhuman primates have long been proposed as complementary models for aging research (Austad, 1997). Among these, the marmoset, which has the shortest average lifespan of all anthropoids (~10 years) is particularly promising (Fischer & Austad, 2011; Ross, Davis, Dobek, & Tardif, 2012; Tardif et al., 2017; Tardif, Mansfield, Ratnam, Ross, & Ziegler, 2011). The marmoset possesses a number of behavioral and neuroanatomical features that make it particularly valuable as a model for human neurocognitive aging. Despite its small size, the marmoset has a relatively large brain, with a core neural architecture (Chaplin, Yu, Soares, Gattass, & Rosa, 2013; Liu et al., 2018) and resting state networks (Belcher et al., 2013, 2016; Silva, 2017) that show many similarities with humans'. Marmosets also have highly developed cognitive abilities (Huber & Voelkl, 2009; Spinelli et al., 2004; Strasser & Burkart, 2012) cooperative breeding and a rich social behavior with evidence of prosocial tendencies (Miller, 2017). They have relatively good manual control and are extensively used as models for motor degeneration such as Parkinson's disease (Eslamboli, 2005). Due to its amenability to genome editing, interest in the marmoset as a model organism for neuroscience research has dramatically increased in recent years. Yet, the development of this species as a model for aging is still in infancy (Ross et al., 2012; Tardif et al., 2011). Although there is uncertainty with regards to

the maximum lifespan of the marmoset in captivity (recorded as 21 years old, Nishijima et al., 2012), clear signs of aging are observed in the marmoset brain by the age of 8, as indicated by reduced neurogenesis in the dentate gyrus (Leuner, Kozorovitskiy, Gross, & Gould, 2007), β-amyloid deposition (Geula, Nagykery, & Wu, 2002), and increased abnormally phosphorylated Tau (Rodriguez-Callejas, Fuchs, & Perez-Cruz, 2016). However, age-related differences in cognitive and motor function have not been characterized. One of the greatest advantage provided by the marmoset relative to other NHPs is the ability to conduct longitudinal studies spanning the entire older lifespan of the animal (roughly 5–10 years old).

The first goal of this paper was to examine change in cognitive flexibility and fine motor function in middle-aged marmosets (~5 years old at study onset) studied at baseline and 1 year later. Cognitive flexibility is an ability that is markedly impaired with age in humans (Mell et al., 2005) and other animals (e.g., Lai, Moss, Killiany, Rosene, & Herndon, 1995; Rapp, 1990; Tapp et al., 2003). In this study, cognitive flexibility was assessed through performance on reversal learning, a task dependent on the orbitofrontal cortex (OFC) that requires the animal to adapt to changing stimulus/reward contingencies. Motor function was evaluated via performance on the Hill and Valley task, a motor task classically used in Parkinson's disease research. The second goal of the study was to examine sex differences in the aging process. The human literature is inconsistent with regards to the existence of sex differences in the trajectories of age-related cognitive decline. Many studies have found no evidence for sex differences in age-related cognitive decline (de Frias, Nilsson, & Herlitz, 2006; Ferreira, Ferreira Santos-Galduróz, Ferri, & Fernandes Galduróz, 2014; Finkel, Reynolds, Berg, & Pedersen, 2006; Gerstorf, Herlitz, & Smith, 2006; Karlsson, Thorvaldsson, Skoog, Gudmundsson, & Johansson, 2015). However, a recent analysis of a large longitudinal dataset from the Baltimore Study on Aging reported greater age-related cognitive decline in men than women in a number of cognitive domains, including domains for which a male advantage is present at baseline (McCarrey, An, Kitner-Triolo, Ferrucci, & Resnick, 2016). A greater decline in men than in women was also found recently in the English Longitudinal Study of Ageing (Zaninotto, Batty, Allerhand, & Deary, 2018). Only one study has examined sex differences in cognition in aging NHPs. The cross-sectional comparison of Lacreuse, Kim, et al. (2005b) in rhesus monkeys showed that in young age, males outperformed females in a spatial working memory task, but that the performance of older males was no longer different from that of older females, suggesting that males may experience a greater age-related decline than females. We also reported sex differences in fine motor function in the rhesus monkey (Lacreuse, Diehl, et al., 2005), with males showing evidence of greater age-related decline than females. Longitudinal studies are critically needed to confirm these findings, track sex differences in the rate of age-related cognitive and motor decline, and understand their biological bases. The present study examines sex differences in middle-aged male and female marmosets performing a reversal learning task and the Hill and Valley task at baseline and approximately 1 year later.

2 | METHODS

2.1 | Subjects

A total of 22 monkeys participated in this study. Eighteen marmosets (9 males, 9 females) were tested on reversal learning (Table 1) and 12 marmosets (6 males, 6 females), including 8 who performed the cognitive task, performed the Hill and Valley test (Table 2) on two occasions, approximately 1 year apart. All subjects were middle-aged, between the ages of 4 and 7 in Year 1 (mean = 4.82, SD = 0.66) and 5 and 8 years old (mean = 6.23, SD = 0.73) in Year 2. Age was not significantly different between males and females ($t(16) = 1.79$, $p = 0.9$). The monkeys were housed in opposite sex pairs in a room with a 12 h:12 h dark/light cycle. They were fed a daily diet of fresh food including fruits, vegetables, nuts and seeds, various breads, and ZuPreem marmoset food. Fruit and nuts were provided twice daily (8–9 AM and 1–3 PM) and water was available ad libitum. The monkeys were provided with daily enrichment, including foraging tubes and a variety of toys. The animals were cared for in accordance with the guidelines of the US National Research Council's Guide for the Care and Use of Laboratory Animals, the US Public Health Service's Policy on Humane Care and Use of Laboratory Animals, and the Guide for the Care and Use of Laboratory Animals (2011), 8th edition. The studies were approved by the University of Massachusetts Institutional Animal Care and Use Committee.

2.2 | Procedure

2.2.1 | Cognitive task—

Sixteen monkeys were tested on the NHP version of the CAmbridge Neuropsychological Test Automated Battery CANTAB (Monkey CANTAB Intellistation with Liquid Reward, Model 80951A), which consisted of a touch screen panel (37.78 cm) in a stainless steel frame (56 × 38 × 30 cm) using an Intel based 1.6 GHz CPU operating system. A stainless steel sipper tube in the middle of the screen delivered the reward (banana milkshake) via a peristaltic pump, at a rate of 0.2 ml per second. To encourage participation, food and water was removed from the animals' cages 2 hr prior to testing and replaced in the cage no later than 5 hr after removal. The marmoset was tested in their housing room. They voluntarily entered a transport box (34.1 × 20.65 × 30.8 cm) attached to the front of their homecage (Figure 1a). The CANTAB was positioned against the meshed front (2.5 × 2.5 cm openings) of the transport box, so animals could reach through to touch the screen and lick the reward from the sipper tube. Experimenters loaded CANTAB testing programs remotely from a desktop computer located outside of the marmoset housing rooms.

2.2.2 | Reversal learning: CANTAB

CANTAB training: We followed the procedures described by Roberts, Robbins, and Everitt (1988) and Pearce, Crofts, Muggleton, and Scott (1998) for stages of tone-reinforcement associations and touch-training. Monkeys were trained to lick the milkshake from the spout, to associate a tone (41 Hz) with reward delivery (5 s), to touch the screen, touch a large static square at the center of the screen, and touch smaller squares appearing successively at random locations on the screen, before being presented with the first pair of stimuli.

CANTAB reversal learning: In Year 1, the marmosets were presented with three pairs of stimuli shown in Figure 2. The first pair of stimuli consisted of a blue triangle and a white line. The second pair consisted either of two different white lines or two different pink shapes (the order of presentation of pairs 2 and 3 was counterbalanced between monkeys). Pair 1 was easier to discriminate than Pairs 2 and 3, because it differed both in color and shape, while Pairs 2 and 3 consisted of different shapes of the same color. Special attention was used in selecting the colors of the visual stimuli, as female marmosets can be di- or tri-chromats while male marmosets are dichromats, that is "red-green color blind" (Caine, Osorio, & Mundy, 2010; Pessoa, Tomaz, & Pessoa, 2005). Therefore, certain combinations of colors (red/green/brown/orange) were avoided. For each pair, monkeys had to perform a simple discrimination (SD), followed by a simple reversal (SR). The two stimuli appeared in any position on the touch screen. Upon touching the correct stimulus, a positive tone was played and the liquid reward was delivered. Touching an incorrect stimulus triggered a negative tone and no reward delivery. The inter-trial interval was 3 s. Animals were tested 5 days a week and were given 40 trials a day to learn the stimulus/reward contingencies (e.g., blue triangle always rewarded). Once they reached a 90% correct criterion, the stimulus/reward contingencies were reversed (e.g., the white line was rewarded). When the 90% accuracy criterion was reached on the SR, the marmoset moved on to a new stimulus pair. The number of trials to reach criterion (TTC) was computed. In addition, the number of refusals (number of trials that the monkey refused to perform) was also recorded as an index of motivation. In Year 2, the monkeys were presented with a new set of three stimulus pairs (Figure 2). Testing procedure was identical to the one described for Year 1.

2.2.3 | Reversal learning: WGTA—Two monkeys (1 male, 1 female) were unable to perform the tasks on the CANTAB and were tested on a manual version of the tests instead. These monkeys were tested in a Wisconsin General Testing Apparatus (WGTA)-like box which consisted of an opaque box (43.2 × 42.3 × 44.5 cm) containing a test tray (40.65 × 11.15 × 1.25 cm) with two food wells (each of diameter 2.5 cm; Figure 1b). The wells could be baited with mini-dried marshmallows and covered by stimulus objects. Between trials, the tray was concealed from view by an opaque screen.

The stimuli for the WGTA version were made of foamy material of the same shape and colors as the stimuli shown in Figure 2. Each stimulus ($2 \times 2 \times 0.9$ cm^3) was glued on a 3.5 cm diameter token that completely covered a food well. The procedure was similar to the CANTAB procedure, but with important differences constrained by the WGTA setting. First, trials were given by an experimenter sitting behind the WGTA across the monkey and only 20 trials per day were given to minimize satiety effects; for each trial, the experimenter followed a 20-trial test sheet indicating the location (left or right, randomized) of the rewarded stimulus. With the door closed, the experimenter baited one of the wells with a mini-dried marshmallow and covered it with the positive stimulus, while the other well was baited with the other stimulus. The experimenter lifted the door while starting a timer to let the monkey select one of the stimuli. For each trial, the experimenter recorded the performance of each monkey (coded as 0 or 1) as well as the response times (elapsed time between door opening and monkey response) on the test sheet. The monkey had a maximum

of 2 min to give a response at each trial. A lack of response was recorded as a refusal and the next trial was administered.

2.2.4 | Motor task: Hill and valley—The Hill and Valley task is a measure of fine motor ability that has previously been used in marmosets, especially in models of stroke and Parkinson's disease (Bihel et al., 2010; Eslamboli, Baker, Ridley, & Annett, 2003; Marshall & Ridley, 2003; Phillips et al., 2017). It assesses motor function in each limb as well as perceptual spatial impairment. The monkeys were tested in their housing room at times where they were not engaged in cognitive tasks. Similarly to CANTAB testing, they voluntarily entered the transport box attached to their home cage to access the Hill or Valley apparatus, securely attached to the front of the box via a Plexiglas screen. Each apparatus had two 5-steps (9 × 9 × 3 mm) staircases, either rising away from a central opening (Valley), or from two lateral openings (Hill); see Figure 1c. The monkeys had to reach through these openings, using either their right or left hand, to retrieve one of the mini dehydrated marshmallows (6 mm diameter) placed in the middle of each step. In the Valley version, the central vertical slot (7.7 × 2 cm) allowed the marmoset to use its left hand to reach the reward located on its right, or the right hand to reach the reward located on its left (contralateral hemifield to hand used). In the Hill version, entry was through two lateral slots (7.4 × 2 cm) on the side of each staircase so that the monkey had to use its right hand to retrieve the rewards on the right stairs and the left hand to retrieve the rewards on the left stairs (ipsilateral hemifield to hand used).

Marmosets were trained on the Hill and Valley apparatus until they successfully retrieved a marshmallow from each step with each hand. If the marmoset failed to perform the task after 10 attempts, it was excluded from further testing. For testing, marmosets were given a maximum of 5 min to retrieve all five marshmallows from one staircase of the apparatus. Each marmoset received four conditions (Hill Left, Hill Right, Valley Left, Valley Right) per session, one session per day, and performed a total of three testing sessions. The order of the Hill and Valley conditions was randomized (half received Hill first, half Valley first) and alternated each test day. If the marmoset failed to retrieve the five marshmallows within the 5-min time limit, the test session was rerun the following day. Marmosets received one point for retrieving the marshmallow on the 1st step, 2 points for retrieving from the 2nd step, and so on, for a maximal score of 15 points per hand. Marmosets lost one point each time a marshmallow was dropped (lost completely or fallen to another stair). All sessions were video recorded. A trained experimenter (KW) decoded the videotapes and computed the final scores (accuracy) and time to retrieval for each monkey, condition and year. The time to retrieval was the time elapsed from the first reaching through the opening until retrieval of the last marshmallow. The accuracy was the score obtained out of a maximum of 15.

Hand preference: Because hand preference had the potential to affect hand performance in the Hill and Valley test, we determined the hand preference of each marmoset using a simple hand reaching task. Monkeys performed 50 reaches through the central slot of the Valley apparatus to reach a mini marshmallow placed 7.7 × 2 cm from the slot. The number of Left and Right hand reaches was recorded. Any trials in which the marmoset used both hands were excluded. For each subject, a handedness index (HI) was determined by subtracting the

number of left-handed responses from the number of right-handed responses and dividing by the total number of responses (Hopkins, 1999). HI values ranged from −1.0 to 1.0, with the absolute value representing the strength of the preference. The positive values indicated a right-hand bias while the negative values indicated a left-hand bias. HI values were not significantly different between males (HI = 0.167, SEM = 0.18) and females (HI = 0.173, SEM = 0.25).

2.3 | Statistical analysis

2.3.1 | Cognitive task—The average TTC was not significantly different between CANTAB (M = 254.33, SEM = 23.83) and WGTA monkeys (M = 215.71, SEM = 47.29, t (16) = 0.59, ns), therefore, the data of the 18 monkeys were combined for the analysis. The percentage of refusals was much lower for the WGTA monkeys (16%, SEM = 8.6) than for the CANTAB monkeys (37.6%, SEM = 2.7), however, so the analysis for this variable was performed on the 16 monkeys with CANTAB data. The TTC and the percentage of refusals were analyzed using mixed repeated measure ANOVAs with Year (1, 2), Test Type (SD, SR), and Pair Number (Pair 1, Pair 2, Pair 3) as within-subject factors and Sex as a between-subject factor. Age at onset and Interval between Tests were initially included as covariates in the models. Because none of the covariates were significant, they were not included in the final models.

2.3.2 | Motor task—Twelve monkeys (6 males, 6 females), including 8 monkeys who also performed the cognitive test, performed the Hill and Valley at both baseline and retest (See Table 2). Because the score and time to retrieval were not significantly different between the Hill and Valley tests, the measures from both tests were averaged and analyzed with mixed measures ANOVAs with Sex, Hand, and Year as factors. As there were no indication that HI, age or interval between tests correlated with performance measures, they were not included as covariates in the models.

3 | RESULTS

3.1 | Cognitive task

3.1.1 | Trials to criterion (TTC)—The ANOVA revealed a significant effect of Year (F (1, 16) = 7.99, p = .012, partial η^2 = 0.33) on TTC, with animals taking significantly less trials to perform the discriminations in Year 2 (m = 207.037, SEM = 24.87) than in Year 1 (M = 293.04, SEM = 25.67). Additionally, test Type was also significant (F(1, 16) = 89.81, p = .0001, partial η^2 = 0.85), indicating that, independent of year of testing, monkeys took longer to learn the SRs (M = 335.06, SEM = 27.95) than the SDs (m = 165.02, SEM = 13.96). TTC varied also according to Pair Number (F (2, 32) = 14.24, p = .001, partial η^2 = 0.47) with animals taking significantly fewer trials on the 1st pair (M = 167.51, SEM = 12.45) than on the 2nd (M = 270.32, SEM = 26.34) and 3rd (M = 312.29, SEM = 33.95; Figure 3a). The main effect of Sex on TTC was not significant (F (1, 16) = 3.57, p = 0.077, partial η^2 = 0.18), however, a significant interaction between Sex and Test Type (F (1, 16) = 8.26, p = 0.011, partial η^2 = .34) revealed that females needed more trials (M = 398.96, SEM = 39.52) than males (M = 271.17, SEM = 39.52) to reach criterion on the SRs, while there was no sex difference on the SDs (M males = 152.68, SEM = 19.74; M females = 177.35,

SEM = 19.74; Figure 3b). A significant interaction between Year and test Type (F(1,16) = 4.89, p = .042, partial η^2 = 0.23) indicated that the performance improvement from Year 1 to Year 2 was significant for the SRs (F(1,16) = 7.98, p = .012) but not for the SDs (F(1,16) = 0.87, ns). Pair Number also interacted with test Type (F(2, 16) = 4.84, p = 0.15, partial η^2 = 0.23), and Year (F(2, 16) = 11.60, p = .001, partial η^2 = 0.42) reflecting differences in stimulus pairs complexity. A marginal Sex × Test Type × Pair Number (F (2,32) = 2.86, p = .072, partial η^2 = 0.15) suggested that females were especially impaired for the more complex pairs.

The speed of acquisition of the SDs varied greatly between monkeys, which also contributed to their ability to perform the reversals. In order to account for these individual differences, we computed a Reversal Index (RI) (Rajalakshmi & Jeeves, 1965) for each year of testing, as follow: RI = mean (TTC_{SR1} + TTC_{SR2} + TTC_{SR3})/mean (TTC_{SD1} + TTC_{SD2} + TTC_{SD3}). The RI evaluates how many more trials were needed to complete each of the three reversals, relative to the three simple discriminations, with higher values indicating poorer performance. A repeated measure ANOVA with Sex and Year as independent variables indicated that RI did not vary significantly with Year of testing (F(1, 16) = .035, ns). This showed that even though the TTC decreased between Y1 and Y2, reflecting improved performance, the ability to perform the reversals relative to the discriminations remained stable across years. Additionally, the RI was significantly higher in females (M = 2.31, SEM = 0.14) than in males (M = 1.84, SEM = 0.14; F (1, 16) = 5.77, p < .05), reflecting the poorer performance of females in the reversals in both years. The interaction between Year and Sex was not significant (F(1, 16) = 0.45, ns).

3.1.2 | Refusals—The two animals who performed the WGTA version of the task were excluded from this analysis. The remaining marmosets (n = 16) refused a large percentage of trials (37.6%) on the CANTAB. Interestingly, males refused significantly more trials (M = 43.7%, SEM = 3.3) than females (M = 31.5%, SEM = 3.3; F(1, 14) = 8.47, p = .011, partial η^2 = 0.38) and this sex difference depended on test Type (F(1, 14) = 4.89, p = .044, partial η^2 = 0.26). As can be seen in Figure 3c, the sex difference was specific to the reversals (F(1, 14) = 12.02, p = .004), with no significant difference detected for the SDs (F(1, 14) = 2.20, ns). The main effect of Year (F(1, 16) = 0.89, ns) and the interactions were not significant. There was no correlation between the TTC and the % of refusals (r (16) = −0.16, p = .55), even after controlling for sex (r(13) = 0.11, p = 0.70).

3.1.3 | Individual trajectories—One of the advantages of longitudinal designs is the ability to investigate individual trajectories. Figure 4 represents individual RIs for each year of testing in males and females. As can be seen from the figure, independently of sex, most individuals maintained or improved performance from Year 1 to Year 2, but a few individuals (dotted line in the figure) experienced a decline (i.e., higher RI). Our n was too small to examine this issue statistically, but we speculate that such individuals may follow a trajectory of pathological aging. Additional longitudinal points will be needed to confirm this interpretation.

3.2 | Motor task

Monkeys retrieved the marshmallows in an average of 44 s (SEM = 3.02) and obtained an average score of 12.05 (SEM = 0.16) out of the maximum of 15. No significant difference was detected between the left and right hands for either the scores or the time to retrieval. The scores dropped slightly but significantly from Year 1 to Year 2 ($F(1, 10) = 5.26$, $p < .045$, partial $\eta^2 = 0.34$) while the time to retrieval tended to increase during the same time period ($F(1, 10) = 3.65$, $p < .085$, partial $\eta^2 = 0.27$). Females were significantly faster than males in performing the tests ($F(1, 10) = 5.41$, $p = 0.042$, partial $\eta^2 = 0.35$) but there was not sex differences in accuracy ($F(1, 10) = 1.96$, $p = 0.19$, partial $\eta^2 = 0.16$). The interaction between Sex and Year was not significant either for the time to retrieval $F(1, 10) = 0.31$, $p = .59$, partial $\eta^2 = 0.03$) or for the score $F(1, 10) = 3.26$, $p = .10$, partial $\eta^2 = 0.25$). To examine this latter interaction, we conducted follow up analyses for each sex separately. As can be seen from Figure 5, females maintained a score around 12 between the 2 years (12.34 vs. 12.22, $t(5) = 0.29$, ns), while males experienced a significant drop in performance from year 1 to Year 2 (12.32 vs. 11.33, $t(5) = 3.84$, $p = .012$).

4 | DISCUSSION

We examined 1-year change in cognitive flexibility and fine motor function in middle-aged marmosets of both sexes. We found minimal age-related change in cognitive flexibility but detected significant declines in fine motor function with age. In addition, we found sex differences in both domains, underlining the importance of incorporating sex as a variable in NHP studies. We discuss these results in details below.

4.1 | Sex and age differences in cognitive flexibility

Cognitive flexibility is a dimension of executive function that is severely affected by age in a number of species including rodents (Mizoguchi, Shoji, Tanaka, & Tabira, 2010), mouse lemurs (Joly, Ammersdörfer, Schmidtke, & Zimmermann, 2014), rhesus monkeys (Lai et al., 1995; Moore, Killiany, Herndon, Rosene, & Moss, 2006), great apes (Lacreuse, Parr, Chennareddi, & Herndon, 2018; Manrique & Call, 2015), and humans (Berry et al., 2016). Age-related decline in this domain can already be observed at middle-age in chimpanzees (Lacreuse et al., 2018) and rhesus monkeys (Moore et al., 2006), but most studies have been cross-sectional, precluding an assessment of cognitive change with age. We assessed cognitive flexibility through performance on reversal learning, a task that requires the monkey to adapt to changing stimulus/reward contingencies. Decades of work in a variety of species, including marmosets, have shown reversal learning to be dependent on the OFC (Dias, Robbins, & Roberts, 1996; Hornak et al., 2004; Izquierdo, Brigman, Radke, Rudebeck, & Holmes, 2017; Marquardt, Sigdel, & Brigman, 2017; Rudebeck & Murray, 2008; Rygula, Walker, Clarke, Robbins, & Roberts, 2010), a brain region that undergoes significant changes in structure and function with age in humans (Resnick, Lamar, & Driscoll, 2007). Reversal learning has been used extensively in marmosets, but aging studies are lacking. A small study in four aged marmosets reported that aged animals were only impaired in the initial discrimination/reversal pair, catching up to the performance of historical young controls in later discriminations (Munger, Takemoto, Raghanti, & Nakamura, 2017), but larger samples are needed to confirm these findings.

Our study focused on longitudinal change in reversal learning in middle-aged marmosets tested at baseline and 1 year later. We used different stimuli between the two time points to minimize practice effects. Yet, the absolute TTC decreased significantly from Year 1 to Year 2, reflecting a test–retest effect inherent to longitudinal designs. However, as noted in early work (Rumbaugh & Jeeves, 1966), a better approach to capture reversal learning performance is to assess reversal performance relative to pre-reversal performance. This allows to circumvent differences in motivation, perceptual and/or motor skills or anxiety that contribute to individual differences in discrimination abilities. Using a Reversal Index, RI, as such a ratio, we found that reversal performance remained stable between the two time points. That is, despite overall performance improving from baseline to re-test, the proportion of trials needed to perform a reversal relative to a simple discrimination remained unchanged, with approximately twice as many trials needed to perform a reversal relative to an initial discrimination. It is possible that cognitive flexibility in the marmoset declines later in life. As we continue our longitudinal research, it will be important to investigate individual trajectories, as a few individuals showed declining performance between the two time points, a pattern that may represent a path towards pathological aging.

A robust finding from our study is the presence of sex differences in reversal learning. Relative to males, females showed slower acquisition of the reversals across the two time points. This sex difference was clearly related to task difficulty, as it was specific to reversal performance in the more complex pairs (i.e., SR2 and SR3). It is important to note that potential differences in color vision between females (di- or tri-chomats) and males (dichromats) cannot explain these results, since the same pairs of stimuli were presented for the discriminations and the reversals. In addition, the visual stimuli used in the complex pairs were of the same color. Using the refusals (% of aborted trials) as an index of motivation, we were also able to rule out lesser motivation in females as a contributing factor. Indeed, males did refuse a greater percentage of trials than females on the reversals, a finding in agreement with our previous observation that males may be more sensitive to punishment than females (LaClair & Lacreuse, 2016). The possibility that other factors, such as greater anxiety or stress reactivity in females (e.g., Johnson et al., 1996), may underlie the sex difference in reversal learning needs to be examined in future studies. However, sex differences in reversal learning have also been reported in humans, where a female impairment in reversal learning has been described in both children (Overman, Bachevalier, Schuhmann, & Ryan, 1996) and adults (Evans & Hampson, 2015). These effects are likely related to both the organizational and activational influences of sex steroids (Overman et al., 1996). Indeed, early in life, androgens facilitate the development of the OFC/better reversal performance in males and masculinized female monkeys (Clark & Goldman-Rakic, 1989). The activational effects in adulthood are less clear, but we showed previously that ovariectomized female marmosets exhibit an impairment in reversal learning following estradiol (E2) replacement (Lacreuse et al., 2014). Although we were unable to assess the relationships between endogenous E2 and performance in the present study (learning was confounded with cycle), based on these previous findings, we hypothesize that E2 has a detrimental effect on cognitive flexibility and associated brain substrates (OFC circuitry) in the female marmoset.

4.2 | Motor function

Age-related slowing in fine motor function has been well characterized in cross-sectional studies in both humans (Smith et al., 1999) and rhesus monkeys (Lacreuse, Diehl, et al., 2005; Zhang et al., 2000). Age-related slowing has been related to changes in the striatum, which undergoes significant atrophy with age in humans (Raz et al., 2003) and macaques (Lacreuse, Diehl, et al., 2005; Matochik et al., 2000). Interestingly, the age-related decline in striatal volume across a 5 years period is uniform across age (20–77 years old), indicating a steady lifespan shrinkage of this structure in humans (Raz et al., 2003). In contrast to this linear decline, there is evidence that age-related motor slowing accelerates between the ages of 47 and 62 in humans (Smith et al., 2005).

Marmosets have long been used as models for stroke and Parkinson's disease, with several studies assessing motor deficits in the Hill and Valley test (Bihel et al., 2010; Eslamboli et al., 2003; Marshall & Ridley, 2003; Phillips et al., 2017). However, a comparison of motor function based on age has not been conducted. In part because of its standard use in marmosets, we used the Hill and Valley test to assess changes in fine motor function in marmosets of both sexes. Although our sample size was small, the analysis revealed interesting findings. First, with respect to age, we found a small, but significant drop in accuracy from baseline to re-test. Interestingly, this drop in performance was significant in males only. Females were faster than males overall, but there was a marginal trend for a slowing of motor function in both sexes. Additional subjects and longitudinal data points are needed to confirm these findings. However, we note that both the speed advantage of females and the greater age-related decline in males are consistent with prior findings in humans and macaques. Indeed, a female advantage in fine motor function has been noted in several human studies (Agnew, Bolla-Wilson, Kawas, & Bleecker, 1988; Jennings, Janowsky, & Orwoll, 1998; Kennedy & Raz, 2005). In addition, we previously found evidence for greater age-related slowing in males than in females, in a cross-sectional study comparing the performance of young (7 years old) and older rhesus monkeys (22 years old) on the Lifesaver Test, a task requiring monkeys to remove a lifesaver candy from shapes of different complexities (Lacreuse, Diehl, et al., 2005).

The only other longitudinal investigation of motor function in aging NHPs examined 1-year change in motor performance in young (4–6 years old) and older (21–26 years old) female rhesus monkeys tested on the lifesaver test (Walton, Scheib, McLean, Zhang, & Grondin, 2008). In contrast to our results in marmosets, Walton et al. (2008) found improved performance at re-test in both young and older monkeys, supporting the idea that procedural memories are well preserved over time. It is likely that task differences underlie in part the discrepancies with our findings. Indeed, the lifesaver test emphasizes the speed of hand movement per se, while the Hill and Valley measures larger movements of the upper limbs, visual-hand coordination and grasping ability. An additional motor test would be useful to better characterize the nature of the observed deficits in our study. In addition, the Walton et al. (2008) study included only female subjects, leaving the question of sex differences, that is, a potential decline in males, unanswered.

5 | CONCLUSION

Having the shortest lifespan of all anthropoids, the marmoset is an NHP ideally suited for longitudinal investigations of the aging process on cognition and motor function. This report suggests that middle-aged marmosets re-tested one year after baseline assessments (1) do not show a significant age-related decline in reversal learning; (2) exhibit robust sex differences in reversal learning, with a female impairment observed across the two time points; (3) show a decrease in motor accuracy in males only, and a slight motor slowing in both sexes (4) exhibit sex differences in motor speed, with females being faster than males overall.

These data underscore the importance of sex differences in both cognitive and motor ability and suggest that motor function may be particularly sensitive to aging, as the age-related motor decline can already be observed at middle-age, as in humans. Further longitudinal data points will allow us to confirm whether males show a greater decline in motor ability with age and whether cognitive flexibility declines later in life in either one or both sexes.

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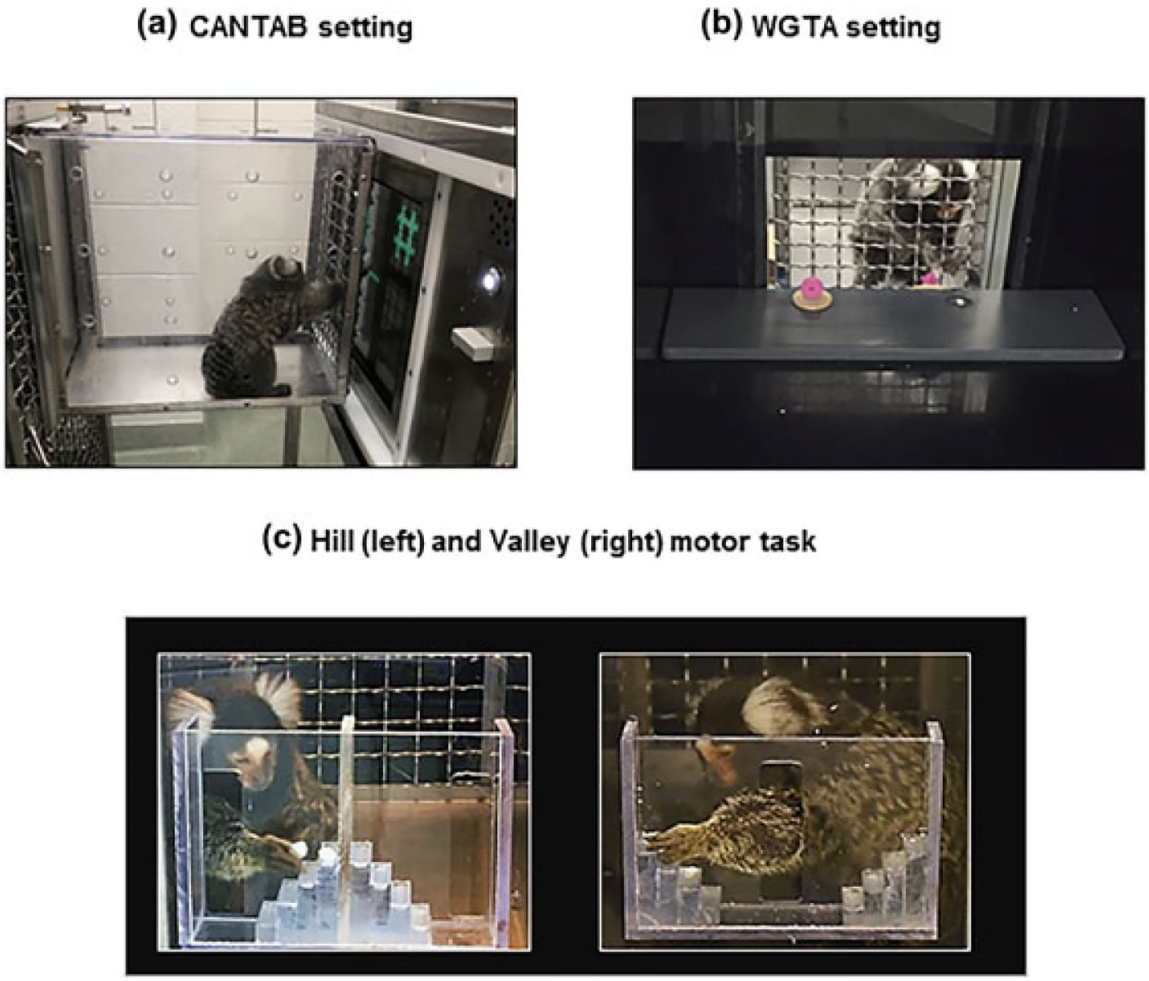

FIGURE 1.

(a) Marmoset in transport box performing a reversal learning trial on the CANTAB. (b) Marmoset performing a reversal learning trial in the WGTA. (c) Marmoset performing the Hill (left) and Valley (right) tasks

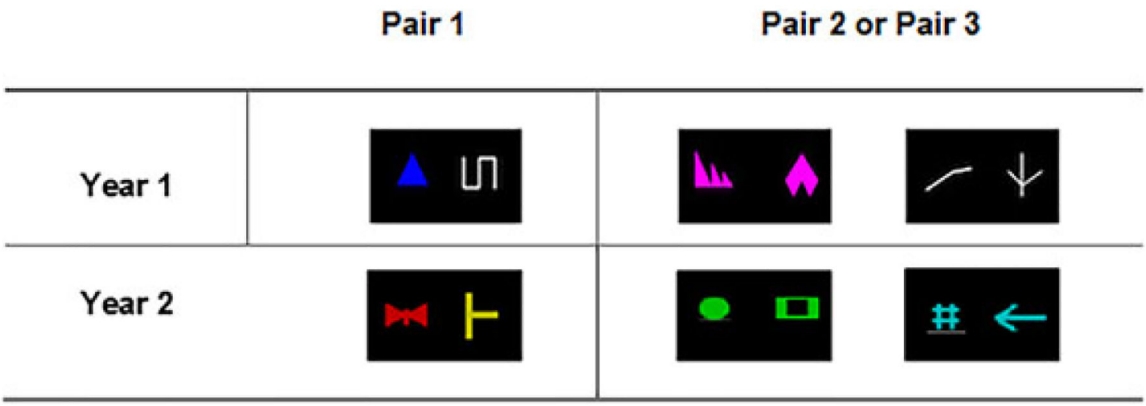

FIGURE 2.
Schematics of the stimuli used in Year 1 and Year 2

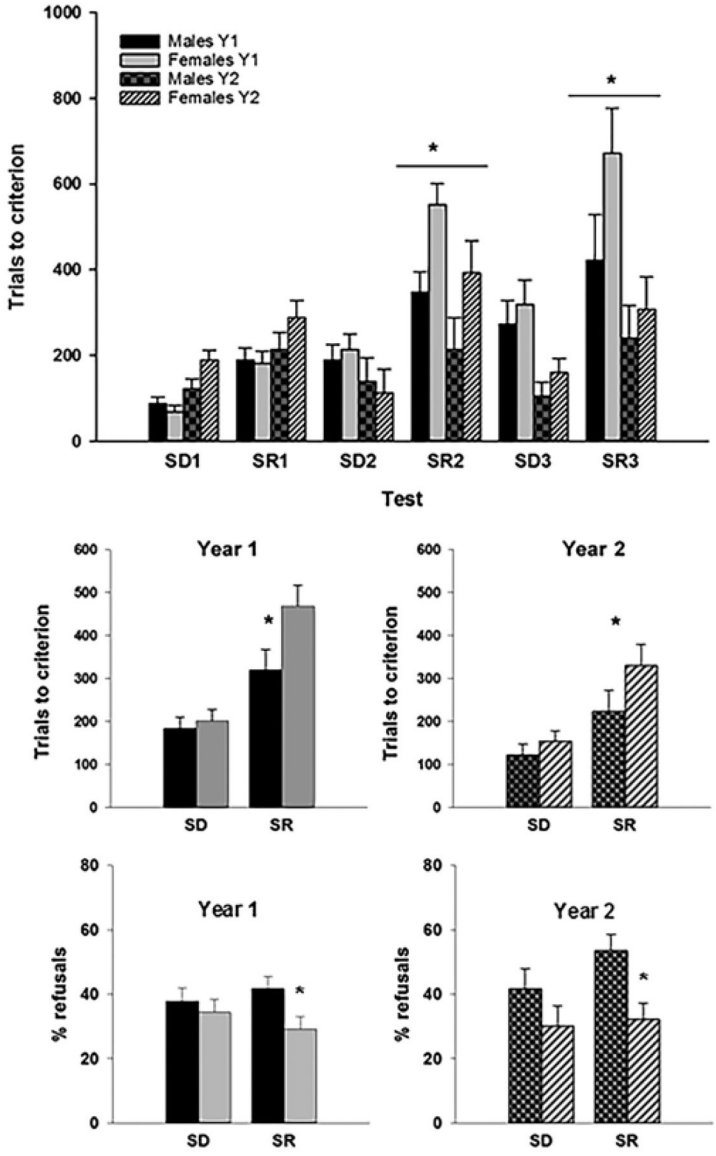

FIGURE 3.

(a) Trials to criterion of males and female marmosets as a function of stimulus pair in each year of testing. (b) Trials to criterion averaged by test Type and Sex in each Year of testing. (c) Percentage of refusals per test Type and Sex in each Year of testing. SD, simple discrimination; SR, simple Reversal. *$p < .05$

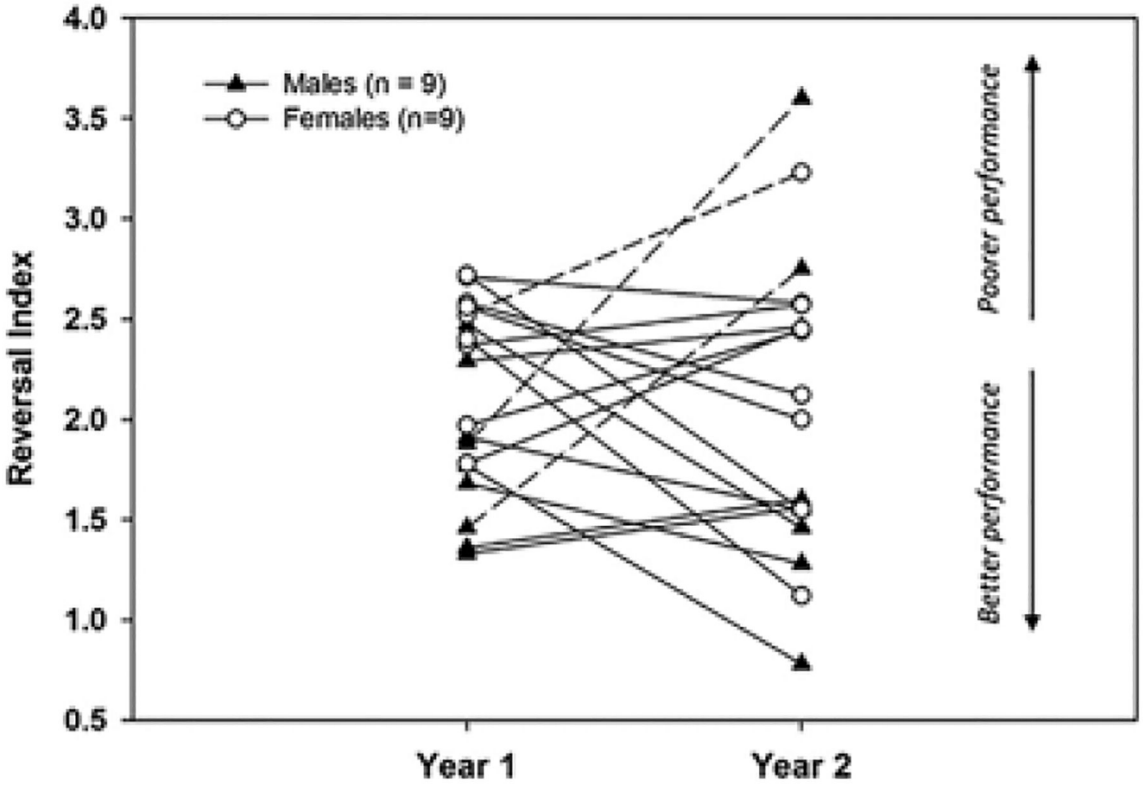

FIGURE 4.
Reversal index in Year 1 and Year 2 for each subject. The dotted line highlights individuals with RI increasing (declining performance) in Year 2

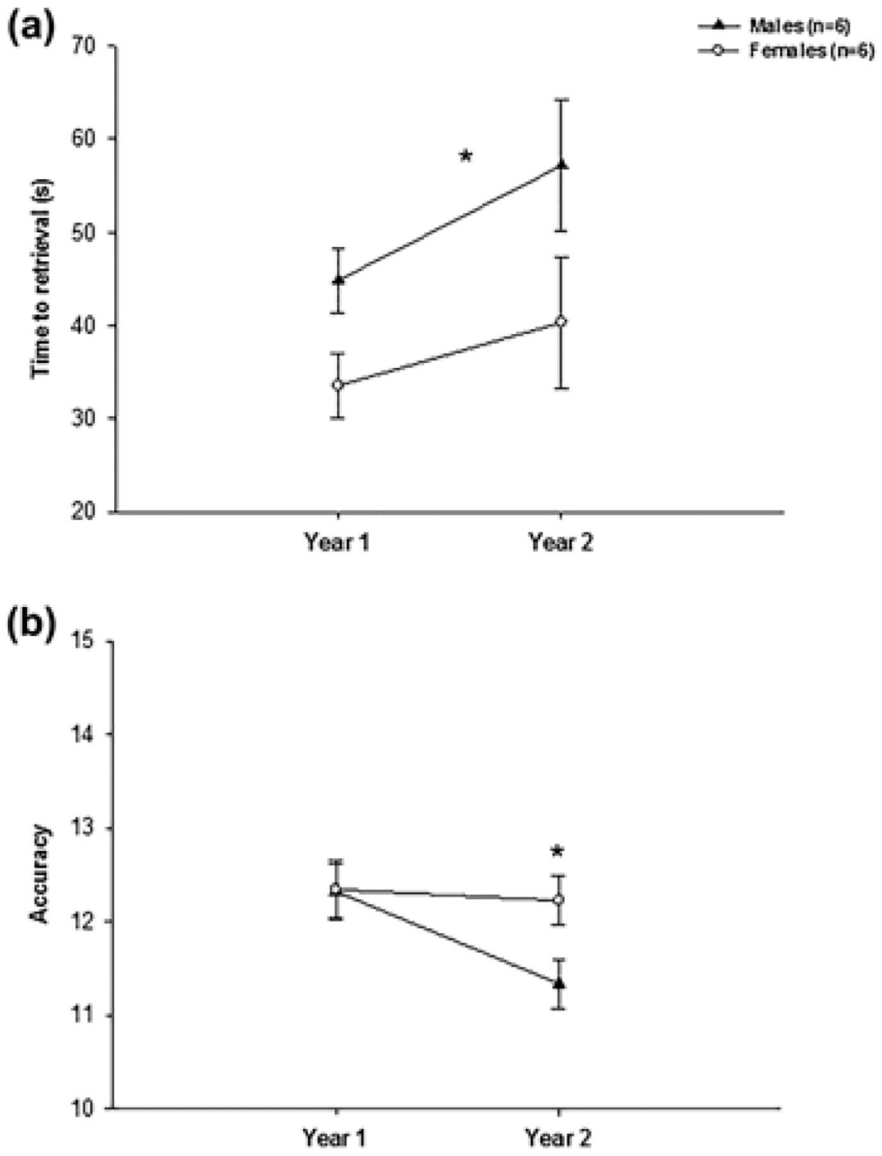

FIGURE 5.

Mean time to retrieval (s) (a) and accuracy (b) in the Hill and Valley test (combined) in males and females in each year of testing. *$p < .05$

TABLE 1

Characteristics of marmosets tested on reversal learning

Animal ID	Sex	Age BL	Age retest	Time between tests	Test method	Hill and Valley
1	M	3.96	5.33	1.38	CANTAB	No
2	M	4.65	5.79	1.14	CANTAB	No
3	M	4.69	6.37	1.68	CANTAB	No
4	M	4.77	5.84	1.07	CANTAB	Yes
5	M	5.01	6.42	1.41	CANTAB	Yes
6	M	5.21	6.43	1.23	CANTAB	Yes
7	M	5.21	6.88	1.66	CANTAB	Yes
8	M	5.56	7.40	1.84	CANTAB	No
9	M	6.86	8.12	1.26	WGTA	Yes
Mean	**Males**	**5.10**	**6.51**	**1.41**		
10	F	4.08	5.38	1.29	CANTAB	Yes
11	F	4.12	5.81	1.69	CANTAB	No
12	F	4.21	5.45	1.24	CANTAB	Yes
13	F	4.41	5.49	1.08	CANTAB	No
14	F	4.52	6.31	1.79	CANTAB	No
15	F	4.78	5.77	0.99	WGTA	No
16	F	4.82	6.48	1.66	CANTAB	No
17	F	4.93	6.19	1.27	CANTAB	No
18	F	4.99	6.71	1.72	CANTAB	Yes
Mean	**Females**	**4.54**	**5.95**	**1.41**		
Mean	**Total**	**4.82**	**6.23**	**1.41**		

TABLE 2

Characteristics of marmosets tested on the Hill and Valley test

Animal ID	Sex	Age BL	Age retest	Time between tests	Cognitive test
5	M	4.42	5.70	1.28	Yes
7	M	4.93	6.12	1.19	Yes
4	M	5.05	6.32	1.27	Yes
6	M	5.27	6.73	1.46	Yes
19	M	5.52	6.92	1.40	NA
9	M	6.48	7.67	1.19	Yes
Mean	**Males**	**5.27**	**6.58**	**1.30**	
10	F	3.96	5.20	1.25	Yes
12	F	4.07	5.33	1.27	Yes
20	F	4.47	5.73	1.26	NA
18	F	5.14	6.47	1.33	Yes
21	F	5.41	6.88	1.48	NA
22	F	6.09	7.31	1.22	NA
Mean	**Females**	**4.86**	**5.92**	**1.32**	
Mean	**Total**	**5.07**	**6.36**	**1.30**	