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Key periods of cognitive decline in a nonhuman primate model of cognitive aging, the common marmoset (*Callithrix jacchus*)

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ABSTRACT

It is well established that human life expectancy increases considerably with an ever-growing number of people suffering from age-related cognitive decline and degenerative brain diseases. This necessitates the development of animal models to counteract or stop the progression of the decline early enough. Presently, primate models are few, and many studies argue for the marmoset as an interesting primate model presenting a short life span and being easily available in research laboratories. In this article, we propose the marmoset as a valid model for cognitive decline. Using a computer touch screen, we trained 35 marmosets from 2 to 14 years of age to perform reversal learning and delayed-matching-to-position tasks. We found typical age-related cognitive deficits related to executive functions and spatial working memory. Applying a recursive algorithm, we detected 2 critical periods from which deficits appear. Mainly, response strategy deficits appear from age 4, whereas impairments in inhibitory control appear from age 7–8. Furthermore, the presence of outliers, sometimes at an early age, suggests pathological cognitive deficits that would require imaging exploration in parallel to behavior.

1. Introduction

Demographic studies predict there will be over 1 billion aged people (above 60 years) around the world by 2050 (Prince et al., 2013). A large proportion of aging humans suffer from various forms of dementia, the most prevalent being Alzheimer's disease (Prince et al., 2015) which is a major public health issue. Because dementia relies on slow degenerative processes, the most efficient treatments would likely act upon the earliest phases to block or even reverse the process. This is the reason why there is a critical challenge to separate out normal decline from early stages of pathological decline and to distinguish these early stages from more advanced ones (Goerlich et al 2017; Lee et al 2017). In human cohorts, a powerful approach uses multimodal combinations of various imaging methods with neuropsychological tests (Bauer et al., 2018).

In parallel to these studies on humans, animal models of neurodegenerative pathologies need to be developed using a similar multimodal approach in the hope of testing medical treatments on early pathological decline (Eaton and Wishart, 2017; Gallagher and Rapp 1997). Besides other popular animal models, nonhuman primates (NHPs) have the advantage of being phylogenetically close to humans (Heuer et al., 2012). Hence, they are particularly relevant concerning the cognitive aspect of multimodal approaches. In NHP, as in humans (Fjell et al., 2014; Moss et al., 2007), aging is clearly associated with alterations of brain functions with the known consequence of cognitive decline. However, the time course of the decline and the identification of its pathological aspects are difficult to establish because of multiple causes leading to high interindividual and across-study variability (Greenwood et al., 2014). Specifically, the first signs of cognitive decline seem to appear early around 50–60 years of age in humans (Dubois et al., 2016; Jack et al., 2013) and also in middle age in NHP (Bonté et al., 2011; Moss et al., 2007). However, this is far from being a homogeneous phenomenon.

The difficulty lies in that several processes such as working memory, processing speed, and inhibitory control may start to decline at different ages, considering the fact that some brain structures may be impacted at different time scales (hippocampus, prefrontal cortex) with large interindividual differences (Collette et al., 2014). Furthermore, although controversial, cognitive decline may not be a linear phenomenon, and some acceleration can be observed at particular critical ages. To address these issues efficiently, NHPs with short life spans could be preferable compared with species in which it is difficult to observe cognitive deficits before the age of 20 years (Bachevalier et al., 1991; Lai et al., 1995; Nagahara et al., 2010; Voytko, 1998). Besides the prosimian

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Microcebus, which is already a valuable model (Languille et al., 2012, 2015), there is an emerging plea for the marmoset monkey as a model for cognitive studies (Marx, 2016), including aging ones because of a short life span (Abbott et al., 2003; Schultz-Darken et al., 2016). Several biological markers of age-related pathologies are found in the marmoset, making it a valuable model of human neurodegenerative diseases (Mattison and Vaughan, 2017) including Alzheimer's disease (Geula et al., 2002; Philippens et al., 2017; Rodriguez-Callejas et al., 2016). However, to the best of our knowledge, only one recent study tested the impact of aging on cognitive performances (Munger et al., 2017). Nevertheless, in that study, only 4 aged (10–14 years old) marmosets were compared to a group of young ones, and there was no determination of the age at which a given deficit appears.

The present work aims at studying age-related decline in the marmoset. We tested marmosets from various ages in their home cages with computerized behavioral tasks. These tasks are diagnostic for inhibitory control/cognitive flexibility and spatial working memory deficits. Together with measurements of performances, we evaluated ages at which deficits appear. We found 2 periods from which cognitive decline begins, an earlier and a later one. Mainly, the first 1 was related to distractibility, and the second, spatial working memory and inhibitory control. This trend is comparable to what we may observe in humans (Goh et al., 2012; Salthouse, 2009). Furthermore, we observed interindividual variability, particularly regarding middle-aged and aged marmosets, similar to what is reported in humans (Greenwood et al., 2014).

2. Methods

Several aspects of the methods were already described in a previous publication (Sadoun et al., 2015).

2.1. Subjects

Thirty-five marmosets (*Callithrix jacchus*), 16 females and 19 males (2–14.3 years old), were taken from our laboratory colony. They were housed in social groups of 2–10 animals. These groups included 4 families and other groups of 2–4 animals of the same sex (Table S1). There were no blood tests for hormonal status, no castration, and no induced menopause or other types of birth control regarding these animals. Each cage was enriched with nests, perches, swings, a platform, and various toys. In the family cages, adult offsprings were kept with their parents. Testing was conducted in a social environment, in the home cage left in place in the colony. Animals were free ranging, unconstrained and without privation. Each tested animal was isolated from its mates in the upper half part of the cage only during its experimental session but stayed in visual, auditory, and tactile contact with its congeners from the neighboring cages (Fig. 1). However, those congeners could not see the stimuli during the task. During the session, if a female was carrying an infant (rare cases), it was not isolated from its mother. None of these infants were included in our behavioral testing protocol when they became adults. No animal had health problems or experimental history that could interfere with the present study.

2.2. Apparatus

We used 2 exemplars of our experimental device, which were built in our laboratory. It consisted of an LCD infrared touch screen (12.1″; Winsonic Electronics Co, Ltd). To avoid accidental body contact, transparent plexiglas plates (28 × 26 cm) with square holes (3.5 × 3.5 cm) were fixed at a distance of 1 cm in front of the screen. The animals touched the screen through these holes at the exact location where the stimuli appeared on the screen. In addition, a minicamera was placed at the side of the apparatus to monitor the behavior. These components were placed inside a black plastic box (52 × 31 × 11 cm). Behavior analysis, stimuli display and data acquisition were performed on a PC (Dell Core2duo) running MATLAB (R2011a) with Psychotoolbox.

2.3. Behavioral tasks

We used a simple visual discrimination protocol as a basic task and a simple reversal learning task mainly aiming at studying inhibitory control performances. In addition, we used a delayed matching-to-position task (DMTP) targeting spatial working memory performance.

2.3.1. Animal training

All marmosets were naive to the tasks. The order of testing for the animals was randomized every day: first the cage was randomly

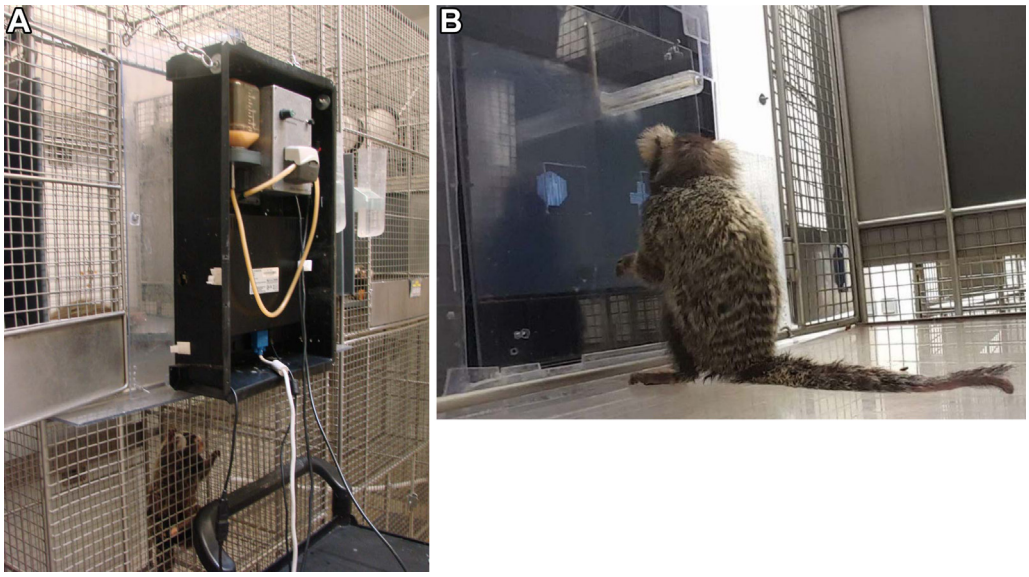

Fig. 1. (A) The experimental device on a cage of the animals during a session. (B) Example of a marmoset performing a task.

selected, and then the individuals in that cage were selected. The animals were familiarized with the setup by reaching out for a piece of gingerbread placed on the screen by the experimenter. Correct reaches were followed by a reward delivery. The size of the piece was gradually reduced until the animal touched a gray square displayed on the screen in absence of gingerbread. Each correct response was rewarded with banana compote, yogurt, or mashed chickpeas (according to the day of the week) delivered by a peristaltic pump (0.1–0.2 mL) via a centrally located licker placed above the Plexiglas plate to deliver the reward 10 cm inside the cage. This forced the animal to disengage itself from the screen at each rewarded trial to avoid position habits. After the behavioral session, each animal was fed with a piece of gingerbread and pellets and portions of fruits and vegetables. In addition, 25 mL of yogurt with vitamins and trace elements were given twice a week, and the same quantity of mashed chickpeas, once a week. Water was available ad libitum in the home cages.

2.3.2. Simple discrimination task

This task consisted of the discrimination of the positive stimulus in several pairs. Each member of the pair was pseudo-randomly displayed at 3.5 cm to the right and to the left of the center of the screen, respectively, at the same height. The stimuli remained on until the animal made a response. The learning criterion was 80% correct responses (Takemoto et al., 2011). After reaching the criterion for the first pair, animals were trained to discriminate 2 new pairs. Here, the learning criterion had to stay at least at 80% in 2 consecutive blocks of 100 trials for the first pair and be kept at this level for the next 2 consecutive blocks with the second pair. If the animal failed, up to 10 new pairs were introduced until the animal reached this criterion. The same pairs of stimuli were used for all the animals in the same order until they reached the learning criterion. There was no constraint in the number of trials in a daily session. The latter ended when the animal accumulated 25 mL of reward or when it did not perform any trial for at least 5 minutes. Correct responses were rewarded and followed by a black screen for an intertrial interval of 3 seconds. Wrong ones were punished by a blue screen for 5 seconds, followed by the intertrial interval.

2.3.3. Reversal learning task

Reversal learning consisted of 2 steps. In the first one, the pair acquisition step, animals had to learn a new pair of visual gray-level stimuli. Animals had to learn which stimulus was rewarded with a criterion of at least 90% correct responses in the last 100 trials. After reaching the learning criterion, marmosets entered the second step (reversal learning step). In this step, reward contingencies were inverted so that the positive (rewarded) stimulus in pair acquisition became negative (unrewarded), and the one that was negative in the first step became positive. The learning criterion was a performance of at least 90% of correct responses over 100 trials. All correct responses were rewarded and wrong ones were punished as described previously. Each daily session ended when the animal accumulated 25 mL of reward corresponding to its daily semiliquid diet or when it did not perform the task for at least 5 minutes for the pair acquisition or 10 minutes for the reversal learning.

2.3.4. Delayed matching-to-position task

This task consisted of 3 stages (learning, fixed delays, and randomized delays). On each trial, a single stimulus pseudorandomly appeared in 1 of 2 locations on the screen (right or left) at the same height. A 10.5-cm distance separated the 2 locations. We used the same type of stimuli as in the simple discrimination (SD) and reversals with different exemplars (varied polygonal shapes filled with various textures). To reduce proactive interference, the stimuli were different across trials adding up to 271 exemplars. The first stage was divided into 2 steps. The first 1 was a training 1, where a stimulus appeared pseudorandomly on one of the 2 locations. As soon as the animal touched the stimulus, a white screen was displayed for a delay (0.5–1s) after which it reappeared again in the same location. In the second step, we used a delay of 1.5 seconds. It consisted of displaying pseudorandomly a stimulus (sample phase) on each trial. As soon as the animal touched it, a white screen was displayed during the delay period, and then, the same stimulus reappeared (choice phase) in the 2 locations (right and left) at the same time. The marmoset had to touch the stimulus that appeared in the same location as in the sample phase of the current trial to get a reward.

We defined the learning criterion as follows. First, the animal reached 80% of correct responses in 2 consecutive sessions of 100 trials. If these sessions were distributed over more than 2 daily sessions, the animal had to have also 80% of correct responses in at least 2 consecutive daily sessions. Second, after having reached this performance, the animal had to maintain it stably during 500 trials. After that, the animal entered the fixed-delays stage in which we increased the delay every 2 sessions of 100 trials until reaching 12 seconds (delays were 3, 4.5, 6, 9, and 12 seconds). In the last stage, the delays were randomized during 1200 trials.

All correct responses were rewarded and followed by a black screen for an intertrial interval of 2 seconds. Wrong responses were punished by a blue screen for 6 seconds, followed by the intertrial interval. In addition, in case of a significant side bias (20 consecutive responses to 1 side), a correction procedure was applied: the correct stimulus was displayed on the nonpreferred side until the animal performed 5 consecutive correct responses.

2.3.5. Stimuli

We used visual stimuli (3 × 3 cm, 17° of visual angle at a marmoset arm reach) of different geometric shapes filled with different gray-level textures. These stimuli were displayed on a touch screen fixed in front of the home cage as described in a previous work (Sadoun et al., 2015). We used visual gray-level stimuli rather than colored ones to avoid a possible discrimination bias related to different phenotypes of color vision in this species (Pessoa, 2005).

2.4. Assessing performances and learning quantification

We used the method proposed by Gallistel et al. (Gallistel et al., 2004) and used by Takemoto et al. (Takemoto et al., 2015) in the marmoset to quantify the individual evolution of learning performances. This method allows the detection of individual progression steps in learning curves by a recursive algorithm. Because the data were binary, a χ^2 test was used ($n \geq 5$) or Fisher's exact test ($n < 5$) to measure the changes in the frequency of correct responses. We set the decision criterion at logit = 1.7 ($p < 0.02$) (Takemoto et al., 2015). Behavioral changes for each individual step-like learning curve were featured by 2 change points: (1) the Onset Trial (OT) and (2) the Achieving Trial (AT). The OT was the trial in which the performance was higher than the chance level using a 1-tailed binomial test ($p < 0.02$). OT is thus a learning parameter that reflects the number of trials needed to exceed the chance level. The AT was the trial from which an asymptotic level of performance was reached (Takemoto et al., 2015). The dynamic interval (DI) was considered as the number of trials between OT and AT, corresponding to a measure of a transition from a chance level with unconditioned state to a conditioned learning. These parameters, summarized in Fig. 2, allowed us to quantify behavioral learning. For the reversal learning, we divided each learning curve into 3 phases: (1) perseverative, (2) chance, and (3) learning. In the perseverative phase, performances were significantly below the chance level (binomial 1-tailed test, $p < 0.02$). In the chance phase, they were not significantly different from the chance level (2-tailed binomial test, $p < 0.02$). In the last phase,

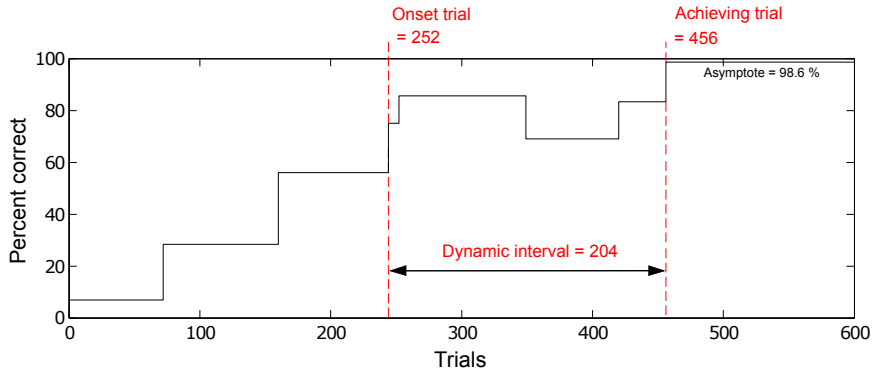

Fig. 2. Example of a learning curve of an 8-year-old animal in the reversal step as obtained with the recursive algorithm. We added the precisions regarding the onset trial, dynamic interval, achieving trial, and the asymptote.

performances were significantly above the chance level (1-tailed binomial test, $p < 0.02$).

In addition, cognitive decline and brain aging may appear and, in some conditions, accelerate from a given period of age (Charles and Carstensen, 2010; Raz and Rodrigue, 2006; Staffaroni et al., 2018). When we found a significant effect of age on a given parameter, we also applied the change-point algorithm to determine at what age an abrupt change occurs. A change point appears as a significant modification in the slope of the cumulative curve of that parameter as a function of age. When the parameter was a real or integer-valued data, we applied a Kolmogorov-Smirnov test (Gallistel et al., 2004). When there were outliers (see the following sections) in the data, we varied the decision criterion from logit 1.7 to 2.7 to reduce their influence.

2.5. Behavioral measures

We considered the number of trials needed to reach the criterion, the OT, AT, DI, the median response latencies (RL; the latency to respond to the stimulus from the moment it appeared on the screen in the sample phase), and the median response time (the latency to respond to a stimulus from the moment it appeared on the screen in the choice phase, after the delay period). Before calculating the median RL and response time, we discarded trials with latencies faster than 100 milliseconds considering them as anticipatory responses. For the reversal step, we calculated the number of errors (discarding the criterion session), the number of trials needed to reach the criterion, and the RL for each phase. In addition, we considered the Win-Stay/Lose-Shift (WSt/LSh) response strategies. Using these strategies, each subject should reproduce the same response if it was rewarded in the preceding trial (WSt) and should shift to another 1 if it has resulted in an error (LSh). They reflect the capacity of an individual to analyze a feedback (positive or negative) of a recent response and may depend on working memory (Bizon et al., 2012; Frank and Kong, 2008).

2.6. Statistical analysis

All statistical analyses were performed in R version 3.3.2 (https://www.r-project.org/). (See supporting information)

3. Results

3.1. SD task

As a basic task, marmosets performed the SD task.

3.1.1. Learning latency, OT, DI, and AT

For this and subsequent tasks, data are expressed in mean ± standard error of the mean. All animals (n = 35) finished the task in 806.2 ± 49.1 trials corresponding to 10.3 ± 1 daily sessions, with a median performance level of 97.3 % (Table S2). Mean OT = 9.4 ± 3.2; DI = 541.6 ± 52.7; and AT = 551 ± 54.5. There was no significant correlation and no significant age effect on the number of trials to criterion, OT, DI, and AT (Table S3).

3.1.2. WSt/LSh strategies

As the DI corresponds to a phase where performances were significantly higher than the chance level, we examined learning strategies during this phase. A weak correlation was found between age and the proportion of WSt. Logistic regression analysis showed a mild-tendency age effect on WSt strategy but no effect on the proportion of LSh (Table S3).

3.1.3. Response latencies

We found no significant effect of age on the RL and no sex or age × sex interaction effects for all parameters measured in this task (Table S3).

3.2. Reversal learning task

Among the 35 animals that participated in the SD task, 32 performed the reversal learning task (see supporting information 3.2).

3.2.1. Pair acquisition step

The animals performed this step in 254.1 ± 27 trials corresponding to 3.1 ± 0.2 daily sessions. They reached a median performance of 98.9 % (Table S2). We did not find any significant effect of age on any of the measured parameters (Table S4).

3.2.2. Reversal learning step

Animals reached a median performance of 98.07% (Table S2). Spearman correlation test and robust linear regression analysis showed a significant age effect on the number of trials to criterion (Table S4). The number of trials increased from 283.9 (back-transformed least squares mean (LS-mean), 95% confidence interval [CI] = [223,352.4]) for the youngest animals to 1087.9 trials (95% CI = [776.4 1452.8]) for the oldest ones corresponding to a significant increase of 11.8% for every year of age (Fig. S1A). Fig 3A shows an example of a learning curve for an 8-year-old animal who needed 600 trials to reach the criterion. In addition, 2 outliers (Table S9) were found (females aged 8 and 11 years). Using the change-point algorithm, we found 2 change points in the

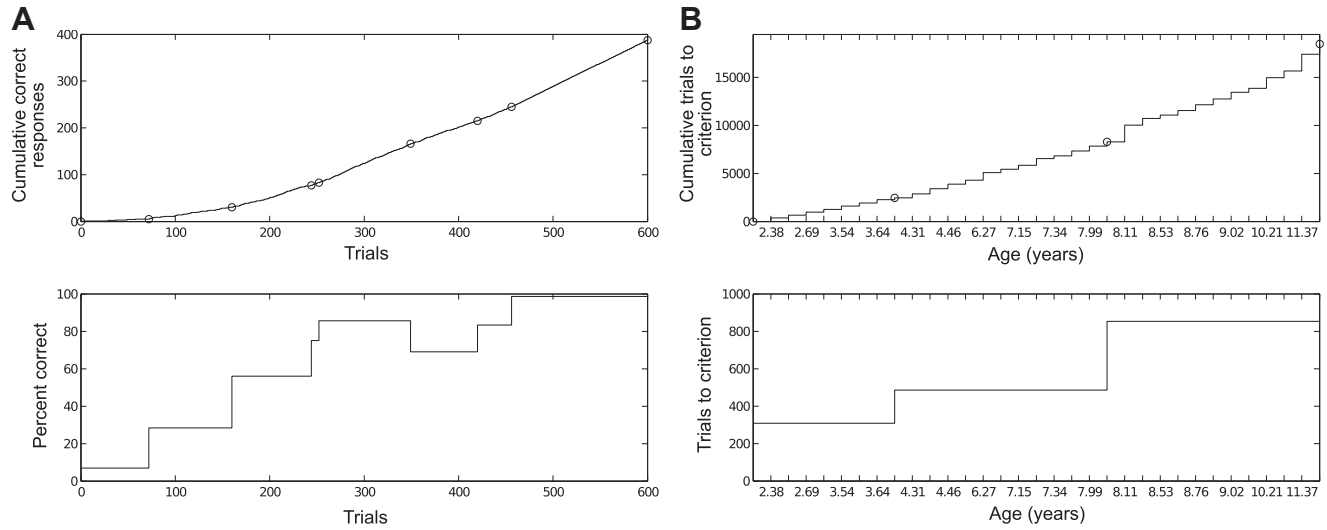

Fig. 3. (A) Example of a learning curve of an 8-year-old animal in the reversal. (B) Change-points in the cumulative curve of trials to criterion as a function of age in the reversal task for all the 32 animals. In every figure, the upper part represents the cumulative curve of a given parameter (correct responses, trials to criterion). The lower part features a staircase curve with step changes corresponding to abrupt increases in these parameters (proportion of correct responses, trials to criterion). Circles represent the change points.

cumulative curve of the number of trials to criterion as a function of age; the first 1 was at 3.9 years and the second was at 8.07 years, corresponding to an abrupt increase of the number of trials to reach the learning criterion from those ages (Fig 3B).

In addition, Spearman correlation test and robust linear regression showed a significant age effect (Table S4) on the number of errors to criterion (Fig. S1B), with 15.45% increase for every year of age. Errors to criterion significantly increased from 113.4 (back-transformed LS-mean, 95% CI = 76.9–156.9]) for the youngest marmosets to 641 (back-transformed LS-mean, 95% CI = 370.4–985.8) errors for the oldest ones. The change-point algorithm showed that the number of errors abruptly increased from 7.3 years (Fig. S2).

3.2.2.1. Onset trial, dynamic interval, and achieving trial. Spearman correlation test and robust linear regression revealed a significant age effect (Table S4) on OT with an increase of 12.3% of OT every year of age (Fig. S3A). OT increased from 147.5 (LS-mean, 95% CI = 103.2–199.7) for the youngest animals to 599.5 trials (LS-mean, 95% CI = 362.1–896.8) regarding the oldest ones. In addition, we found 2 outliers that are the same animals as in the analysis of learning latency (Table S9). The change-point algorithm showed that OT abruptly increased from 7.1 years.

Spearman correlation test and robust linear regression revealed a significant age effect on DI (Table S4) with an increase of 27.1% for every year of age (Fig. S3B). DIs increased significantly from 30.4 (back-transformed LS-mean, 95% CI = 14.2–52.2) for the youngest subjects to 561.2 trials (95% CI = 187–1127.8) for the oldest ones. Moreover, 1 outlier was found (the same female aged 11.3 years) (Table S9). The change-point algorithm showed that DI increased abruptly at 3.9 and 8.8 years.

AT was positively correlated with age (Table S4). Robust linear regression revealed a significant age effect on AT (Table S4) with a 14.9% of increase of AT for every year increase of age (Fig. S3C). Likewise, the LS-mean value of AT increased significantly from 190.9 (95% CI = 138.4–252) for the youngest subjects to 1021.8 (95% CI = [649.4–1479]) for the oldest ones. In addition, we found 2 change-points in the cumulative curve of the AT as a function of age. DI increased abruptly at 3.97 and 8.07 years.

3.2.2.2. Response latency. We found a weak correlation between age and RL (Table S4). Robust linear regression showed a significant age effect (Table S4) on RL with a slight increase of RL by 4.9% for every year increase of age (see supporting information).

3.2.2.3. The number of trials in each phase. In the perseverative phase, we noticed a significant correlation between age and the number of trials in this phase (Table S5) indicating that older animals required more trials to reach the chance phase than younger ones. Robust regression analysis revealed a significant age effect (Fig. S5) on the number of trials (Table S5) with an increase of 16.2% with every 1-year unit of age. The number of trials in this phase significantly increased from 88.2 (LS-mean, 95% CI = 53.6–131.4) for the youngest animals to 540.1 (95% CI = 264.1–913.2) for the oldest ones indicating that the perseverative phase was longer in the aged animals than the young ones. Moreover, 1 change-point was found in the cumulative curve of the number of trials as a function of age corresponding to an increase of the number of trials from the age of 8.07 years in this phase. In the chance phase, no significant correlation was found between age and the number of trials with no significant age effect (Table S5). However, in the learning phase, both Spearman correlation test and robust linear regression revealed a significant age effect on the number of trials (Table S5) with a 12.8% increase by 1-year unit of age (Fig. S6). The number of trials significantly increased from 122.5 for the youngest marmosets (LS-mean, 95% CI = 88.5–162) to a value of 526.2 for the oldest ones (95% CI = 333.5–763.1). In addition, we found a change-point in the cumulative curve of the number of trials as a function of age corresponding to an increase of the number of trials from the age of 4.3 years, hence appearing earlier in this phase than in the perseverative one.

3.2.2.4. WSt/LSh strategies. Likewise, we analyzed the proportions of WSt and LSh strategies in the 3 phases. We did not notice a significant effect of age, sex, and their 2-way interaction on the proportion of WSt, neither in the perseverative phase nor in the chance phases (Table S5). Similarly, no significant effect of age was observed on the proportion of LSh in these 2 phases (Table S5). However, analyzing those strategies in the learning phase, we found a significant negative correlation between age and the proportion of WSt strategy (Table S5). Logistic regression analysis revealed a significant effect of age (Fig. 4A) on the proportion of WSt (Table S5). WSt significantly decreased from 93% for the youngest animals (LS-mean, 95% CI = 89.9–95.5) to 75% for the oldest ones

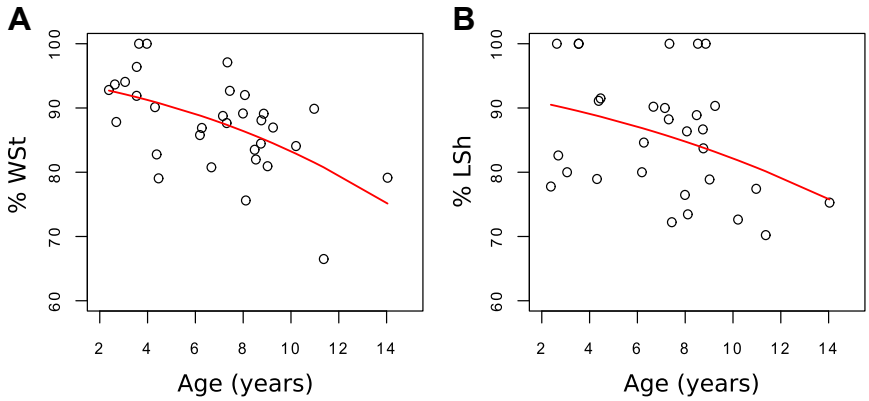

Fig. 4. (A) and (B) Age effect on the Win-Stay (WSt) and Lose-Shift (LSh) strategies, respectively, in the learning phase of the reversal learning step. Red curves represent the logistic regression fit. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(95% CI = 65.7–83.5). We noticed a negative weak correlation between age and LSh strategy (Table S5). Logistic regression analysis revealed a significant effect of age (Fig. 4B) on the proportion of LSh (Table S5). LSh decreased from a value of 90.8% for the youngest subjects (LS-mean, 95% CI = 85.1–95.2) to 75% for the oldest ones (95% CI = 62.6–86.9). However, because there was a slight overlap of the confidence intervals, the age effect may also be considered as a slight tendency effect.

In addition, we found a change-point at 3.97 years in the cumulative curve of the proportion of WSt strategy as a function of age but none in the LSh curve.

3.3. DMTP task

This task probes our main hypothesis that aged animals may be impaired with regard to spatial working memory. Data analysis will concern 34 animals. No sex or age × sex interaction effects were found unless indicated in the text (Table S6).

3.3.1. Learning stage

We found a weak but not significant correlation between age and the number of trials to learning criterion (Table S6). Robust linear regression analysis showed a weak age tendency effect (Table S6) of 3.7% increase for every 1-year unit of age (Fig. S7). In addition, 2 outliers were found: (1) a female of 7.7 years of age and (2) a male of 8.2 years of age (Table S10). We did not find any significant statistical effect of age on all the parameters, except for aborted trials (AbTs) (Table S6). AbTs are those where an animal did not respond to a stimulus for 20 seconds in the choice phase. Both Spearman correlation test and logistic regression analysis revealed a significant effect of age on the proportion of AbT (Table S6). The proportion of AbT significantly increased from 0.83% (LS-mean, 95% CI = 0.44–1.36) for the youngest animals to 4.01% (95% CI = 2.03–6.62) for the oldest ones (Fig. S8).The change-point algorithm showed that the percentage of AbT increased from 4.4 years of age (Fig. S9).

3.3.2. Fixed-delays stage

3.3.2.1. Percentage of correct responses. Data analysis showed a significant decrease of the performances by increasing the delays, which is strengthened by an age × delay interaction effect (Table S7). Delays significantly reduced the performances between 3-second and 12-second phases from 75.1% (95% CI = 73.4–76.7) to 52.6% correct responses (95% CI = 50.4–54.8). This effect was significantly reinforced in the intermediate delays (4.5 seconds and 6 seconds) by the effect of age × delay interactions leading to a further significant decrease of the performances in the older subjects (Fig. 5A) by 41.7% and 33.9%, respectively, compared with the younger ones (odds ratio (OR) = 0.58, $p < 0.01$; OR = 0.66, $p < 0.05$). However, this effect was not observed in the longer delays (OR = 0.81, $p > 0.05$; OR = 1.02, $p > 0.05$, respectively, for 9 and 12 seconds).

3.3.2.2. Onset trial. In this stage, given that the number of trials was fixed, we focused our analysis on the OT to evaluate whether the individual performances were maintained above the chance level in each delay phase.

Thus, 2 types of analysis were performed for OT. In the first 1, we looked directly for the effect of age, sex, delays, and their interactions on OT, excluding data points corresponding to the absence of OT for a given delay and subjects. Only a significant delay effect on OT was found in the first type of analysis (Table S7). OT increased significantly between 3 seconds and 12 seconds (LS-mean = 5.4; 95% CI = 2.6–11.3; 45.8, 95% CI = 13.3–157.3). Because the OT reflects the number of trials needed to reach a performance above a chance level, this result indicates that all the subjects maintained a learning set related to the previous learning stage (1.5 seconds) during the short delays (3 and 4.5 seconds). Nevertheless, by increasing the delays, animals needed more trials to reach an OT. The second type of analysis considered in each phase all data points whether an OT occurred or not as the delays increased. Here, we focused on the delays 4.5, 6, 9, and 12 seconds given that OT always occurred in the first 3-second phase. A mixed-effect logistic regression analysis showed a significant effect of the delay and age × sex interaction (Table S7). Post hoc analysis revealed that OT's occurrence significantly decreased (Fig. S10) between 4.5 seconds and 12 seconds by 96.7% (OR = 0.03, $p < 0.001$). This decline was also observed between 6 seconds and 12 seconds (−82.1%, OR = 0.17, $p < 0.05$) and between 9 seconds and 12 seconds (−78.7%, OR = 0.21, $p < 0.05$). In addition, as revealed by the significant age × sex interaction, this effect was more pronounced in older male subjects. Indeed, OT's occurrence significantly decreased by 36.3% (OR = 0.63, $p < 0.01$) for older males compared with their age-matched females.

3.3.2.3. Response latency and response time. There was no effect of age but a significant effect of the delay on RL and response time (Table S7) (See supporting information).

3.3.2.4. WSt/LSh strategies. There was no effect of age but a significant effect of the delay and age × delay interaction on the WSt strategy (Table S7). The proportion of WSt significantly decreased from 75.2% (95% CI = 73.2–77.1) to 51.3% (95% CI = 48.6–54.0). In

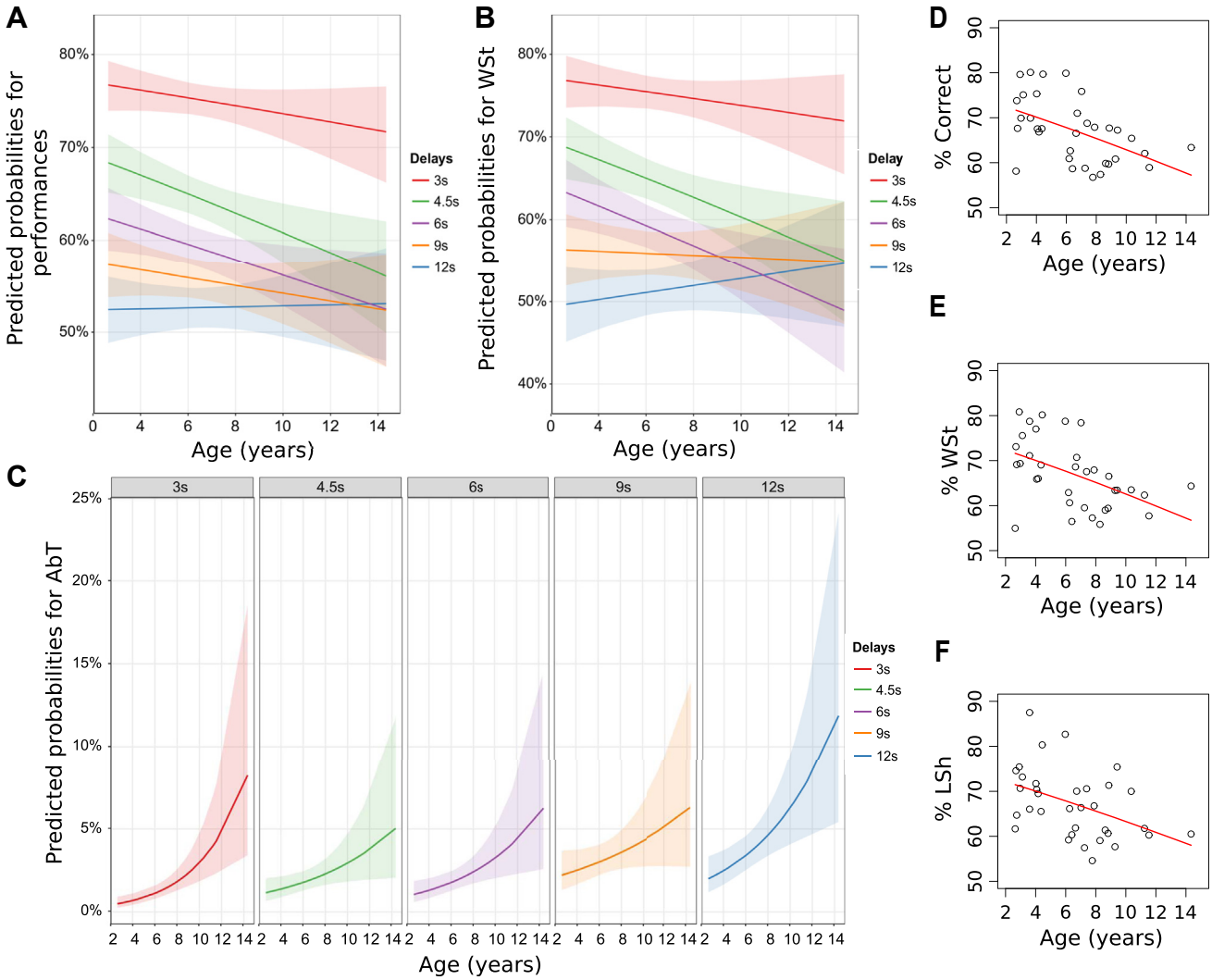

Fig. 5. (A) Interaction effects of delay and age on performances (% correct). (B) Interaction effects of delay and age on Win-Stay (WSt) strategy. (C) Interaction effects of delay and age on aborted trials (AbT). A, B, and C figures are related to performances in the fixed-delay step. Colored curves indicate the predicted probabilities, and colored band, the 95% confidence intervals. (D) Age effect on the proportion of correct responses. (E) Age effect on the WSt strategy. (F) Age effect on the Lose-Shift (LSh). D, E, and F figures are related to performances in the randomized-delays stage. Red curves correspond to the logistic regression fit. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

addition, in the delays 4.5 seconds and 6 seconds, the proportion of WSt was lower in the older subjects than that in the younger ones (OR = 0.547, $p < 0.01$; OR = 0.548, $p < 0.01$, respectively for 4.5 and 6 seconds) (Fig. 5B). Regarding LSh, we found no effect of age or age × delay interaction (Table S7). However, we observed a significant effect of the delay (Fig. S13) on LSh strategy (Table S7). LSh decreased significantly from 73.8% (95% CI = 71.2–76.2) to 55.7% (95% CI = 51.8–56.7). In addition, we observed a sex tendency effect (Table S7) where the proportion of LSh appeared 13.1% lower in females.

3.3.2.5. Aborted trials. We observed a significant effect of age, delay, sex × delay, age × delay, and a tendency effect of their 3-way interactions but no effect of sex or age × sex interaction (Table S7). As revealed by the significant age × delay interaction, aged animals more often aborted trials from the 3-second delay phase than the younger animals which were more resistant to the delay increase. Between 3 and 12 seconds, AbT increased from 0.4 ± 0.1% to 1.7 ± 0.5% for the youngest animals, whereas it increased from 7.5 ± 3.1% to 11.2 ± 4.1% for the older animals (Fig. 5C). Regarding the sex × delay interaction, we noticed that at 9 seconds delay phase females significantly increased the proportion of AbTs by 67.2% (OR = 1.67, $p < 0.05$). From the cumulative curve of AbT as a function of age for each delay phase, we observed a change point corresponding to 5.97 years in 3-, 4.5-, 6-, and 9-second delay phases and 4.36 years in the longest delay phase.

3.3.3. Randomized-delays stage

3.3.3.1. Percentage of correct responses. We found a significant negative correlation between age and the percentage of correct responses with a significant age effect (Table S8). The proportion of correct responses significantly decreased from 71.6% (LS-mean, 95% CI = 68.2–74.9) for the youngest animals to 57.2% (95% CI = 50–63.8) for the oldest ones (Fig. 5D). However, no significant sex or age × sex interaction effects were observed (Table S8). In addition, the change-point algorithm showed that the proportion of correct responses as a function of age decreased from 5.9 years (Fig. S14).

3.3.3.2. Onset trial. Similar to the fixed-delays stage, we focused our analysis on the OT to evaluate if the individual performances

stayed above the chance level. Given that all the subjects had a change-point in this stage, indicating performances above the chance level, we looked directly for the effect of age, sex, and their interactions on OT. Spearman correlation test did not show a significant correlation between age and OT (Table S8). No effect of age or age × sex interaction was observed (Table S8). However, we found a sex tendency effect on OT, with males displaying higher OTs than females (53.1 ± 17.1 and 15.8 ± 7.1, respectively). In addition, 1 outlier, a 6-year-old male, was found (Table S10).

3.3.3.3. Response latency and response time. We found no significant correlation between age and the RLs and no significant effect of age, sex, or age × sex interaction on RL (Table S8) (See supporting information).

3.3.3.4. Win-Stay/Lose-Shift strategies. Older subjects used WSt/LSh strategies less than the younger ones. Spearman rank correlation test revealed a significant negative correlation between age and the proportion of both WSt and LSh (Table S8). Logistic regression analysis showed a significant age effect (Table S8). Indeed, WSt significantly decreased from 71.6% (LS-mean, 95% CI = 67.9–75.1) for the youngest animals to 56.8% (95% CI = 49.6–63.7) for the oldest ones (Fig. 5E). In addition, LSh significantly decreased from 71.5% (LS-mean, 95% CI = [67.6–75.1]) for the youngest animals to 58% (95% CI = [50.6–65.1]) for the oldest ones (Fig. 5F). The change-point algorithm showed an abrupt decrease of the proportion of both WSt and LSh at 5.9 years.

3.3.3.5. Aborted trials. No significant age effect on AbT was found. However, a weak statistical tendency was observed concerning the age × sex interaction (Table S8).

4. Discussion

In this study, we evaluated the common marmoset as a model of age-related cognitive decline in NHPs using behavioral tasks on a touch screen. Our results showed clear age-related impairments in tasks, such as reversal learning and delayed matching-to-position. In addition, we determined for the first time, in the marmoset monkey, the key periods at which the deficits appear (between 4 and 8 years of age). It is important to stress the early and late periods in which cognitive functions decline (mainly inhibitory processes and spatial working memory).

4.1. Cognitive decline in aging and task performances

We first need to rule out that the cognitive impairments that we found were due to visuomotor deficits. Indeed, all animals learned to discriminate all pairs of stimuli with more than 97% median performance level. This result is in line with several studies showing that aging does not affect simple visual shape discrimination (Bartus et al., 1979; Brushfield et al., 2008; Languille et al., 2012; Moore et al., 2003). Hence, all the impairments seen in subsequent tasks are unlikely to be linked to sensory or visuomotor deficits. In addition, the absence of a significant age or sex effect on the RLs in the simple visual discrimination indicates that all animals were highly motivated and free from peripheral motor pathologies.

In the reversal learning, we observed several features in favor of the age-related cognitive decline. To perform this task efficiently, when the reward contingencies are inverted, the initial response should be inhibited, and the other alternative should be chosen and maintained. This implies the extinction of the previous association and learning the novel 1 in the same perceptual dimension (Bari and Robbins, 2013; Dias et al., 1996). Our study showed a clear deficit in aged marmosets. Thus, learning latencies were longer in the older animals with a significant increase in the number of errors to criterion. These results are in line with previous reports of age-related impairments in reversal tasks in other species (Bartus et al., 1979; Brushfield et al., 2008; Picq, 2007; Zhuo et al., 2007). Bartus and collaborators, using colors and symbols as stimuli, observed that aged rhesus macaque monkeys performed the initial discrimination part as efficiently as younger ones but presented greater perseveration in the reversal task (Bartus et al., 1979). Interestingly, older monkeys required more trials to reach the learning criterion. Likewise, longer DI observed in our aged animals may indicate, in accordance with the longer learning phase, a stimulus-reward association deficit or a proactive interference of the previous association. Subdividing the reversal into 3 phases allowed us to find that the longer learning latencies are explained by a longer perseverative phase in addition to a longer learning phase. Each phase contains different types of errors. First, the longer perseverative one is characterized by more perseverative errors. According to several studies (Bari and Robbins, 2013; Bonté et al., 2014), the increase of perseverative errors in the older individuals is related to a deficit of inhibitory control, indicating an inefficiency to inhibit nonrelevant information and adapt behavioral responses to a changing environment. Second, the longer learning phase may be a consequence of regressive errors. Therefore, in this phase, the emergence of the ancient association due to a proactive interference may explain the poor performance of aged animals (Marx, 2016). In addition, the cognitive flexibility decline may also explain these results. Indeed, in the context of changing reward contingencies, 1 needs to focus attention on the current rewarded stimulus and, at the same time, disengage from the previous nonrelevant association (Abbott et al., 2003; Colman, 2018). Both the increase of perseverative responses and the presence of stimulus-reward–association deficits suggest impaired executive functions in old marmosets as previously reported in marmosets and other species (Lai et al., 1995; Moore et al., 2003; Munger et al., 2017).

Given that the average of OT is 9 trials in the SD task, marmosets rapidly learn the visual discrimination (Takemoto et al., 2015) independent of their age. According to the report of Gallistel (Gallistel et al., 2004), using a decision threshold, learning may begin from the first trial, a phenomenon called abrupt learning. It may emerge from an accumulation of evidence, probably leading to a sudden insight (Epstein et al., 1984) as a consequence of reaching a given threshold triggering a behavioral response (Gallistel et al., 2004). Abrupt changes in the reversal learning as measured by OT appear later in the aged animals that required more trials than the younger ones. This suggests that the sudden insight, known to be represented in frontal cortex (Durstewitz et al., 2010), is deficient in aging, in the case of contingency change.

The DMTP task tests if aging impairs spatial working memory (Dunnett et al., 1988; Spinelli et al., 2004). To solve the DMTP, subjects need to remember the relevant location in the choice phase according to that of the sample one, after a retention period (delay). This information should be updated on every trial, implying the use of spatial working memory. Animals reached a high accuracy with stable performances in the first stage (1.5-second delay) with no effect of age on the learning latencies. This is in line with previous reports showing an absence of age effect in the short delay stages given a weak memory load. For example, Dunnett et al (Dunnett et al., 1988), who tested groups of rats of 3 different ages on delayed-response tasks, observed a deficit in performances of the aged groups only for long delays. Similarly, in our study, increasing the delay led to significant deficits. The performances of our oldest subjects significantly fell to the chance level from the medium delay (4.5 seconds), but younger ones were more resistant to the delay increase. This indicates that the retention of spatial

information is less efficient in older individuals as classically observed (Darusman et al., 2014; Dunnett et al., 1988; Rapp and Amaral, 1989).

We may assume that the main behavioral deficits we observed are typical of alterations of various brain structures in aging, as found by other groups. We should first make the cautious statement that it is difficult to distinguish the causal direct link between the structural damage and behavioral deficits from a correlation (Fjell et al., 2014). Furthermore, at this stage, we can only infer the contribution of brain structures to our marmosets' deficits. Normal aging is associated in primates with white matter changes that correlate with cognitive deficits (Liu et al., 2017; Madden et al., 2012; Shobin et al., 2017). The alteration of myelin is expected to contribute to perceptual speed and RL deficits (Gazes et al., 2016), in agreement with the RL deficits of our aged marmosets. In addition, myelin hyperintensities in the prefrontal cortex has also been correlated to a perseverative behavior (Gunning-Dixon and Raz, 2003), similar to the perseveration shown by old marmosets in the reversal task. Aging is also associated with a reduction in the number of synapses and thin spines in prefrontal cortex, which have been shown to correlate with a decrease in cognitive performance in macaques and an increase in the number of trials needed to learn a task for aged macaques with respect to young ones (Dumitriu et al., 2010; Peters et al., 2008). Furthermore, it has been shown that the turnover of spines is necessary for learning processes (Chen et al., 2014; Frank et al., 2018; Roberts et al., 2010) and appears to be perturbed in aging (Mostany et al., 2013). Hence, it is likely that this neuronal mechanism contributes to the longer period required to learn the tasks by the old marmosets. Alterations in spines turnover are likely to be an important consequence of alterations of the neuronal activity (van der Zee, 2015). For instance, the weaker firing rate in the dorsolateral prefrontal cortex (DLPFC) during the delay phase of a working memory task in aged animals (Wang et al., 2011) may lead to weaker performances in DMTP for our aged animals and for macaques tested in a similar task (O'Donnell et al., 1999). Furthermore, this delay-dependent effect may also be linked to the reduction in dopaminergic neurotransmission in aged individuals (Mizoguchi et al., 2009; Williams and Goldman-Rakic, 1995).

Beyond DLPFC, many cerebral structures, such as the hippocampus (Morrison and Baxter, 2012), in various animal species including primates, are subject to age-related synaptic transmission alterations and neuronal or white matter morphological changes (Dickstein et al., 2013; Li et al., 2009; Morrison and Baxter, 2012; Raz et al., 2005; Resnick et al., 2003; Xie et al., 2014). In Microcebus, for instance, the atrophy of mediotemporal structures causes a deficit in a reversal learning task (Picq et al., 2012). As the relative importance of DLPFC, precentral sulcus, and temporal cortex in aging is debated (Mackey et al., 2016; Picq et al., 2012), it would be interesting to explore the brain correlates of behavioral deficits in old marmosets. Because a marmoset colony allows both longitudinal and cross-sectional studies, we think that it offers a valuable opportunity for this approach.

4.2. Aging effects on distractibility and motivation

RLs increased in aged subjects in the perseverative phase of the reversal. The latter finding is often related to low motivation or high distractibility (Mar et al., 2013). Cognitive activity cost increasing with age is indeed related to a decrease of motivation (Ennis et al., 2013). In addition, aged subjects require more cognitive effort as they recruit more brain regions than younger ones to perform a difficult task (Cappell et al., 2010). Indeed, Cappell and his collaborators reported that prefrontal regions show different patterns of activation between young and aged subjects, particularly regarding areas 9 and 46. These regions are known to be involved in executive functioning. Given that animals reached a high and stable performance in the first stage of the DMTP, irrespective of their age, we consider that testing in social context does not affect their learning abilities (Fagot and Paleressompoulle, 2009; Gazes et al., 2013; Picq et al., 2015). However, old subjects made more AbTs in this stage. Although this may indicate that they were less motivated, possibly because of frustrations by errors (Darusman et al., 2014), they also could be more distracted during the task in the presence of congeners. For instance, pronounced distractibility can be observed in aged individuals as a result of a difficulty of focusing attention on a given task, and this is more easily brought out in natural conditions (Bock, 2008; Connelly et al., 1991). This is also supported by anatomical and imaging studies that found structural and functional changes in areas known to belong to the default mode network, as the possible origin of distractibility in the aged population. Mainly, alterations in the medial prefrontal cortex and in the neural connectivity between this region and the visual cortex underlie the distractibility and the difficulties of aged subjects to suppress irrelevant information (Chadick et al., 2014; Guerreiro et al., 2015; Staffaroni et al., 2018; Vidal-Piñeiro et al., 2014). Indeed, Chadick and his collaborators found an absence of deactivation of this region, in aged subjects only, during an attention-demanding task. Interestingly, they also found a significant link between volumetric reductions of gray matter in the medial prefrontal cortex and the distractibility pattern observed in old subjects. Structural changes were also related to the white matter in the same region and in the posterior cingulate cortex. Furthermore, distractor-resistance decrease or attentional set maintenance alteration (Cools and D'Esposito, 2011) have also been linked to the dopaminergic levels in the prefrontal cortex (Bloemendaal et al., 2014; Cools and D'Esposito, 2011).

Increasing the delay length, we found a significant age × delay interaction effect with an increase of the AbT in older subjects. Interestingly, we did not find an effect of age on RLs in all stages of the DMTP task. Aged subjects are less inclined to expend cognitive effort on a difficult task (Neupert et al., 2006). This may explain why aged subjects aborted more trials during the difficult-choice phase while no significant effect of age was found on RLs given that the sample phase is easier to perform. In the randomized-delay stage, we did not find an aging effect on the rate of AbTs or on RLs. In this stage, all animals had a performance higher than chance level, meaning that they acquired a learning set when learning the task rule in the first stage. Consequently, they made fewer errors and were less prone to distractions or frustrations.

Moreover, as in the reversal task, we noticed a significant age × sex effect in the fixed-delays stage, and a weak age tendency and a weak sex effect with slightly longer response times for males than females for the randomized delays. A previous report (LaClair and Lacreuse, 2016) showed that male marmosets are more prone to distraction and demotivation than females with a greater sensitivity to punishment. These sex differences seem to be related to the fact that males of this species are more interested and attentive to the environment whereas females show more interest in working for food (LaClair and Lacreuse, 2016; Schubiger et al., 2015). Our results suggest that this tendency may be exacerbated with aging.

4.3. Cognitive decline of the learning strategies

Win-stay and Lose-shift strategies allow behavioral adaptation to the outcome of a previous recent action (Frank and Kong, 2008). They allow, in natural conditions, repetition of actions leading to reward and avoidance of those leading to punishment or a lack of reward (Riceberg and Shapiro, 2012). Failing to adopt the appropriate strategy may be a disadvantage for older subjects in learning.

We observed a decrease in the rate of the learning strategies in the older subjects only in the learning and the last phase of the reversal and the last stage of the DMTP. An alteration of behavioral strategies may be a consequence of an alteration of monoaminergic systems with age, although the respective contributions of dopamine and serotonin are a complex issue (Daw et al., 2002). The decrease of WSt is in line with the dopaminergic hypothesis of neurocognitive aging (Li and Rieckmann, 2014). Indeed, a lower rate of WSt is considered to be caused by a reduction of dopaminergic levels in aged individuals in several brain regions given that an increase of dopamine favors a positive reinforcement learning (Daw et al., 2002). Therefore, during learning, older subjects are expected to show deficits in the evaluation of the outcome of their own action. Furthermore, a deficit in LSh in our aged subjects is also relevant considering that a difficulty to learn from negative outcomes may be linked to a decrease in serotoninergic levels in aging (Versijpt et al., 2003).

4.4. The key periods of cognitive deficit

By using the recursive algorithm on learning and strategy parameters and on latencies as a function of age, we found 2 key periods where signs of cognitive decline are present in each task (Fig. 6). These 2 key periods do not start at the same age for both the tasks (4 and 7–8 years old for the reversal and 4.5 and 6 years old for the DMTP, respectively). This is expected considering each task as a different problem space with a different cognitive load. Interestingly, the earliest period of deficits, around 4–4.5 years of age, concerns regressive errors and longer RLs for the reversal and an increased number of AbTs for the DMTP. This indicates an early susceptibility to distractibility that interferes with the need for a sustained ability to update working memory information across trials (Morrison and Baxter, 2012). We think that testing marmosets in their social environment is an advantage as it may favor the occurrence of distracting events and therefore the observation of these early deficits. As observed by others in animal and humans, less apparent cognitive deficits (Germain and Hess, 2007; Goh et al., 2012; Hedden and Gabrieli, 2004; Salthouse, 2009; Singh-Manoux et al., 2012; Tapp and Siwak, 2006), such as motivational and attentional deficits with distractibility, may appear earlier than inhibitory control and working memory impairments. Furthermore, in agreement with the literature on other species (Colman, 2018), the inhibitory control deficit or cognitive rigidity appeared later compared with the stimulus-reward association one (7 and 4 years old, respectively, in our study). Likewise, it is interesting to note that response strategies are affected at different ages in each task. This result stresses the point that a cognitive capacity may be affected at different ages according to the problem space in which it operates.

Finally, we observed 2 change-points in the cumulative curve of DI as a function of age (at 4 and 8 years of age). The change-point observed at 8 years of age may correspond to a worsening of the stimulus-reward association deficit (Fig. 6). This may underline the fact that several cortical structures contributing to the same process (Collette et al., 2005) may be affected at different ages (Glisky, 2007; Hedden and Gabrieli, 2004; Kennedy et al., 2015). This suggests the need to pursue this study by coupling the behavioral results with analyses of magnetic resonance imaging (MRI) scans.

4.5. The interindividual variability issue

Another feature of our results is the interindividual variability with the presence of outliers (Tables S9 and S10), particularly for aged subjects, leading us to use robust statistical methods. Some aged animals were outliers for at least 2 parameters. These cases are critical for the marmoset model because it means that individuals with pathological aging are detectable in our experimental conditions.

It is known that aging leads to high interindividual variability in cognitive tasks in animal models (Joly et al., 2014; Picq, 2007; Picq et al., 2012), as in humans (Belsky et al., 2015; Greenwood et al., 2014; Ylikoski et al., 1999). Interindividual variability is a complex issue because of the number of factors that are possibly involved. On a given cognitive task, one expects both aged humans and animal subjects to achieve different levels of performance according to their (history of) health status, diet, fitness, stress, and breeding, for instance, (Barnard et al., 2014; Baumgart et al., 2015; Gow et al., 2012; Rivera et al., 2016) together with their own genetic factors (Greenwood et al., 2014). All these factors may contribute to the presence of various alterations of brain tissues (Raz and Rodrigue, 2006) that may lead or be correlated to the variability of performances (Djelti et al., 2017; Dong et al., 2015). For instance, age-related small-vessel disease, associated with white matter hyperintensities and brain atrophy, follow a very heterogeneous progression across individuals (van Leijsen et al., 2017; Wardlaw et al., 2015). Because these variable alterations are known to be linked to age-related cognitive deficits (Rizvi et al., 2018), the presence of some outlier performances may be a direct consequence of them and need an anatomical examination of these subjects. A similar heterogeneous profile is observed for regional brain atrophy in middle-aged humans (Bajaj et al., 2017; Ferreira et al., 2017). Indeed, some of our outliers can be considered as middle-aged animals (Table S10). These and older outliers may be considered as candidates for unsuccessful aging or may correspond

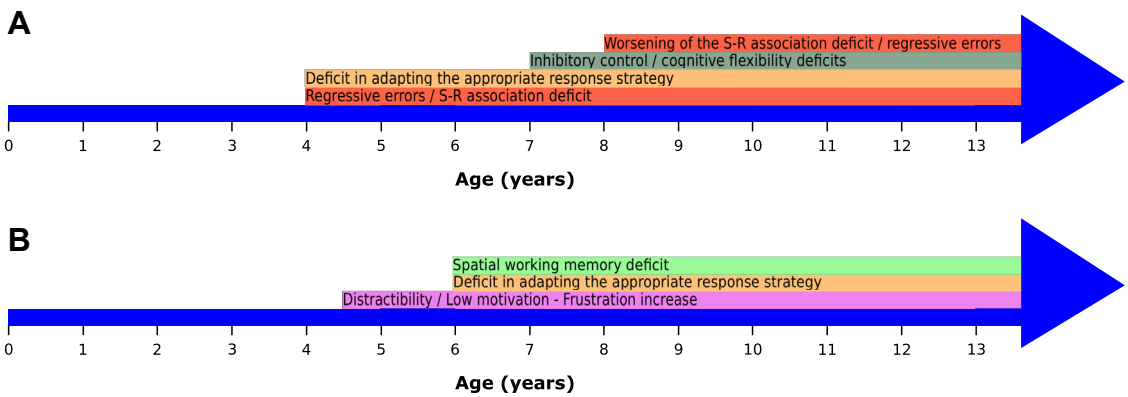

Fig. 6. The key periods of cognitive deficit occurrence. (A) Reversal learning. (B) DMTP. S-R, stimulus-reward; DMTP, delayed matching-to-position task.

to preclinical subjects (with the limitation that monkeys do not spontaneously develop the full spectrum of human neurodegenerative diseases) (Walker and Jucker, 2017). Some compensatory mechanisms may explain that other marmosets of our cohort have a more successful aging. For instance, the age-related loss of synapses in the prefrontal area, 9 and 46, in humans (Cappell et al., 2010) and macaques (Peters et al., 2008) could theoretically be compensated by a regulation of neuronal excitability caused by phenomena such as morphological changes in the axon initial segment (Atapour and Rosa, 2017).

Neuroinflammation is probably the starting point of white matter age-related alterations (Shobin et al., 2017). It is a complex cascade of events that may be triggered or amplified by several deleterious life events such as fat diet and stress (Abate et al., 2017; Niraula et al., 2017). In our experimental conditions, we think we can exclude part of the variability factors. First, all animals are submitted to the same diet, with no special hypercaloric or hypocaloric content. Second, testing the animals in the cage alleviates isolation stress, which might be deleterious over repetitive testing sessions. Third, all animals were maintained in enriched breeding conditions with the same variety of toys, perching stands, and so forth and in direct social contact. This is an important point because it is well known from rodent studies that poor environment is deleterious to spine density (Moser et al., 1994) and would, in a sense, mimic or exacerbate unsuccessful aging (Bloss et al., 2010). On the contrary, an enriched environment promotes neuronal plasticity necessary to build a solid cognitive reserve in humans and animals (Bezzina and Rampon, 2013; Birch and Kelly, 2018; Fischer, 2016; Mandolesi et al., 2017). Consequently, a cognitive reserve counteracts aging effects, and the direct link between the anatomical alterations and performance may be difficult to establish (Rusmaully et al., 2017).

Despite the fact that our breeding conditions tend to be optimal and equivalent for each subject, other factors remain that could bring some variability to the cognitive performances, especially genetic ones (Greenwood et al., 2014; Harris and Deary, 2011). For instance, some authors (Greenwood et al., 2014) found that the performances in spatial working memory for older subjects are related to different alleles for the catechol-O-methyltransferase and dopamine betahydroxylase genes.

Finally, even in the wild conditions, animals may perform differently to the same test, possibly in relation to the social status (Gunhold et al., 2014). Although it is known that social hierarchy can have a deleterious impact on health in NHPs (Shively and Day, 2015), the consequences on aging remain to be determined to the best of our knowledge.

5. Conclusion

The present report supports that common marmoset is a new powerful NHP model of cognitive aging. Several highlighted characteristics of cognitive deficits were present in this species. First, executive deficits were present in both the tasks. Second, signs of cognitive decline appear early, which is reminiscent of findings in other primate species (Bonté et al., 2011), including humans (Lo, 2017). Finally, we observed interindividual variability such as aged poor performers which may be linked to pathological cognitive aging. Those outliers may be considered as reflecting pathological aging because a first check of an underway MRI did not show anomalies unrelated to aging (Sadoun et al., 2015). Likewise, our ongoing MRI will help us to explore in detail morphometric anomalies related to cognitive aging. Our findings, in addition to amyloid and the recent report of a tauopathy in this species (Rodriguez-Callejas et al., 2016) and to the existence of potential models of human diseases with transgenic marmosets (Okano et al., 2012; Sasaki et al., 2009), make it a reliable model of normal and even abnormal aging cognitive decline. Such a model would help to gain a better understanding of mild cognitive impairments and neurodegenerative diseases such as Alzheimer's and other types of dementia.

Disclosure statement

The authors declare no conflicts of interest.

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Research involving animals/ethical approval: All procedures performed in this study were in accordance with the National Committee for Ethical Reflection on Animal Testing (regional MP/03/76/11/12) and national agreements (Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche [MENESR n° 05,215.03]).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.neurobiolaging.2018.10.003.

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