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RESEARCH ARTICLE

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Age-related changes in myelin of axons of the corpus callosum and cognitive decline in common marmosets

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Executive control is a higher-level cognitive function that involves a range of different processes that are involved in the planning, coordination, execution, and inhibition of responses. Many of the processes associated with executive control, such as response inhibition and mental flexibility, decline with age. Degeneration of white matter architecture is considered to be the one of the key factors underlying cognitive decline associated with aging. Here we investigated how white matter changes of the corpus callosum were related to cognitive aging in common marmosets (*Callithrix jacchus*). We hypothesized that reduction in myelin thickness, myelin density, and myelin fraction of axonal fibers in the corpus callosum would be associated with performance on a task of executive function in a small sample of geriatric marmosets ($n = 4$) and young adult marmosets ($n = 2$). Our results indicated declines in myelin thickness, density, and myelin fraction with age. Considerable variability was detected on these characteristics of myelin and cognitive performance assessed via the detoured reach task. Age-related changes in myelin in Region II of the corpus callosum were predictive of cognitive performance on the detoured reach task. Thus the detoured reach task appears to also measure aspects of corticostriatal function in addition to prefrontal cortical function.

KEYWORDS
brain aging, cognitive aging, primate models

1 | INTRODUCTION

Executive control is a higher-level cognitive function that involves a range of processes that are involved in planning, coordination, execution, and inhibition of responses to stimuli (Glisky, 2007). As such, executive control is believed to play a major role in almost all aspects of cognition. Many of the processes associated with executive control, such as response inhibition and mental flexibility, decline with age (Lezak, Howieson, Bigler, & Tranel, 2012). Executive function depends particularly on the prefrontal cortex, and in humans, the prefrontal cortex volume and functionality decline with age (Raz, 2000). Critically, it is the degeneration of white matter architecture or "structural disconnection" (Raz & Rodrigue, 2006) that is considered to be one of the key factors that underlie cognitive decline associated with aging (Gunning-Dixon & Raz, 2000; Madden et al., 2012).

The genu of the corpus callosum (CC) contains axonal fibers that mediate interhemispheric transfer of information across the prefrontal cortex. Overall, the CC does not appear to show significant age-related volumetric decline (Driesen & Raz, 1995; Sullivan, Pfefferbaum, Adalsteinsson, Gwan, & Carmelli, 2002; Sullivan, Rosenbloom, Serventi, & Pfefferbaum, 2004) as measured via in vivo MRI. However, microstructural changes could be occurring in the CC with age. Doraiswamy et al. (1991), in a MRI study of healthy volunteers ranging from 26 to 79 years, reported older individuals to have a smaller

callosal area and greater callosal T1 relaxation times than younger individuals. T1 spin-lattice relaxation time is sensitive to water content of tissue and changes in T1 relaxation times reflect significant changes in water composition of the neural tissue. While this measure does not indicate the nature of these biophysical tissue changes, the change can be used to quantify age-related biophysical tissue changes including alterations in myelin composition, such as demyelination or dysmyelination (Doraiswamy et al., 1991). Recent innovations including diffusion tensor imaging (DTI) are currently used to quantify characteristics of biophysical tissue changes such as white matter integrity, including axon density, diameter, and thickness via measure of fractional anisotropy (FA) and mean diffusivity (MD). Numerous studies have shown decreases in FA and increases in MD with aging (Bennett & Madden, 2014; Salami, Eriksson, Nilsson, & Nyberg, 2012; Sexton et al., 2014), though there is considerable individual variability. Sullivan, Rohlfing, and Pfefferbaum (2010), in a longitudinal study, reported a greater decrease in FA in distal regions of the CC compared to medial regions with age in human subjects. However, it remains unclear how these microstructural changes found with imaging techniques are linked with functional cognitive change in humans, and how these changes are associated with variability in human healthy aging and variable decline.

One way to evaluate these microstructural changes and their association with cognitive decline is to focus on non-human primate models that can combine cognitive assessment and histological assessment. However, to our knowledge only one such study has been conducted. Peters and Sethares (2002) reported age-related changes in myelin of area 46 of the prefrontal cortex and splenium of the CC in rhesus monkeys (*Macaca mulatta*). Myelin in aged macaques was described as splitting or showing a disconnection of the layers, which were filled with cytoplasm. These myelin changes were associated with reduction in performance on a delayed nonmatch to sample task (a test of executive function).

Common marmosets (*Callithrix jacchus*) are small New World monkeys increasingly used as models of aging and age-related disease due to their similarity to humans in physiology, neuroanatomy, reproduction, cognition, and social complexity (Mansfield, 2003; Phillips et al., 2014; Tardif, Mansfield, Ratnam, Ross, & Ziegler, 2011). While the breadth of assays to evaluate phenotypic change associated with aging is developing in marmosets, as of yet there are few reports of cognitive changes associated with aging. As a growing model for aging studies, it is crucial to understand normal cognitive and brain structure changes in aging in order to distinguish changes associated with disease. A few studies have investigated cognitive aging in marmosets. Cognition in middle aged marmosets has been found to be significantly altered in the presence of oestrogen. Oestrogen interferes with prefrontal-mediated tasks, but improved performance on hippocampal-dependent studies (Lacreuse et al., 2014). In a study with a few aged marmosets ($n = 4$), older animals were found to make significantly more errors in the initial stages of a discrimination task and more perseverative errors on a visual reversal learning task (Munger, Takemoto, Raghanti, & Nakamura, 2017).

To further develop the marmoset as a model for studies of cognitive aging, our laboratory is investigating normal cognitive aging profiles in marmosets and associated changes in brain structure and function. In particular, we are interested in how white matter changes of the corpus callosum (especially myelin thickness) are related to cognitive aging. We hypothesized that reduction in myelin thickness of axonal fibers in the corpus callosum would be associated with cognitive aging in geriatric marmosets. Specifically, we predicted that reduced myelin thickness in the genu of the corpus callosum would be correlated with diminished performance on an executive function task.

2 | METHOD

2.1 | Subjects

All subjects were part of a broader cross-sectional assessment of phenotypic change and health parameters associated with aging (Ross et al., 2018). As part of this study six common marmosets (*Callithrix jacchus*; young adult: one female, one male; 4 years old; geriatric: two female, two male; 15–20 years old) were randomly selected from the subject pool for euthanasia and investigation in this study. Marmosets were housed at the Southwest National Primate Research Center (SNPRC), Texas Biomedical Research Institute, San Antonio, TX. Animals were socially housed with room temperatures ranging between 76 and 84 °F (set point of 80 °F). The facility was on a 12h light-dark cycle with lights off at 19:00; natural light was also present due to windows with husbandry following Layne and Power (2003). Fresh food was available *ad libitum*; the base diet consisted of Teklad 8794 pellets, ZuPreem Marmoset Diet, and fresh fruit or vegetables. Geriatric individuals also received hardboiled egg, Ensure pudding, and raspberry or banana diet gel. All procedures were approved by the Institutional Animal Care and Use Committee at SNPRC, and followed the ethical guidelines outlined by the American Society of Primatologists.

2.2 | Procedure

Prior to euthanasia individuals were tested on the detoured reach cognitive assessment as described (Ross et al., 2018). Briefly, this task assesses prefrontal dysfunction and evaluates executive function via an animal's ability to inhibit a latent response to retrieve a reward using line of sight reaching via a detoured reach task (Dias, Robbins, & Roberts, 1996). Individuals were tested in their home rooms, and voluntarily transferred into a separate testing enclosure via tunnel for trials. A curtain surrounded the testing enclosure to provide visual separation from other marmosets during testing.

Marmosets were presented with a clear 5-sided box containing a preferred treat reward either in the center or edge of the box. During habituation trials the open side of the box faced the subject, and they could simply reach straight into the box to retrieve the reward. During testing trials, the box was rotated such that the opening of the box was either on the left side, right side, or facing the marmoset. Individuals

were presented with 20 trials in each daily session, with a maximum of 30 s to retrieve the reward. Trials were scored as successful or unsuccessful, and overall % correct was summed for each session. All trials were videotaped and scored by an individual who was blind to subject age. After habituation to the task, animals were tested once weekly until they either reached criterion (80% correct across two consecutive testing sessions) or eight testing sessions had been completed.

Brains were collected at the time of necropsy following euthanasia, none of the brains included in this study showed gross abnormalities or pathology on veterinary inspection. All brains were immersion-fixed in 10% buffered formalin immediately at necropsy. After a 5-day period of fixation, brains were transferred into a 0.1 M phosphate buffered saline (PBS, pH 7.4) solution containing 0.1% sodium azide and stored at 4 °C. The corpus callosum from each subject was sectioned from the left hemisphere of the brain bisected at the midsagittal plane. After removal, the corpus callosum was subdivided into five regions based off DTI tractography to determine functional subdivisions of the corpus callosum in nonhuman primates (Hofer & Frahm, 2006; Phillips & Hopkins, 2012). These Regions are as follows: I = prefrontal lobe, II = premotor and supplementary motor cortices, III = motor cortex, IV = sensory cortex, V = parietal, temporal, and occipital lobes. A 1 × 2 mm section was cut from the center of each Region and placed into a microcentrifuge tube containing 1% glutaraldehyde and 4% paraformaldehyde, for a period of at least 1 week. Samples were then prepared for transmission electron microscopy using a modified technique for processing nerve biopsies. Samples were postfixed in 1% Zetterqvist's buffered osmium tetroxide, dehydrated, infiltrated with resin, and embedded before sectioning. Semithin sections were first cut and stained with toluidine blue and examined under a light microscope to verify correct orientation. Subsequent ultrathin silver sections were cut mounted on EM grids and stained with uranyl acetate before viewing under the electron microscope.

Myelin thickness was determined from electron micrographs from 5000× digital images taken by a digital camera coupled to a JOEL JEM 1200EX electron microscope. Counts and measurements of axon diameter were made over a 26.3 × 26.3 μm^2 region in each micrograph in a systematic-random fashion using fractionator sampling implemented in NIH Image software (ImageJ version 1.48). We only analyzed myelinated axons because they could be identified unambiguously in these samples. Axon diameter was defined as the average of the fitted major and minor axis lengths for major-minor ratios, and otherwise as the minor axis (Zhang et al., 2009). Measurements were conducted by CMW who was blind to age and sex of individuals; validation checks were conducted by KAP.

3 | RESULTS

Due to the small sample size in this study (two young adult and four geriatric marmosets), we were unable to perform statistical tests comparing young adult and geriatric marmosets sorted into two age groups and instead report average axon density for each age group and the degree of variance. A regression analysis was used to assess whether cognitive performance on the detoured reach task was associated with axon density or mean myelin area.

3.1 | Myelin thickness

Electron micrographs of callosal tissue from young adult and geriatric marmosets are shown in Figure 1. Myelin showed considerable degradation of appearance in geriatric individuals, with the layers splitting (Figure 1). Similar degradation of myelin was reported in aged rhesus monkeys (Peters & Sethares, 2002). Across all Regions, the most frequently occurring myelin thickness was approximately 0.10 µm; myelin thickness was infrequently greater than 0.25 µm (Figure 2). While there was a wide range of myelin thickness present in

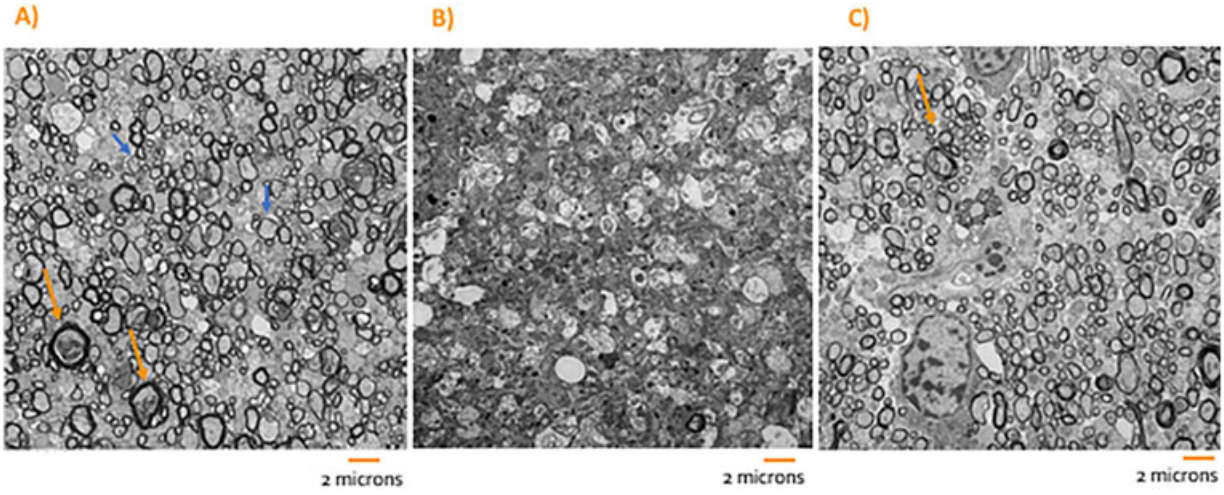

FIGURE 1 Electron micrographs of axons in Region I of young adult (a) and geriatric (b, c) marmosets. Note the thick myelin in (a), indicated by orange arrows, contrasted with thin myelin (indicated by blue arrows). Very few myelinated axons are present in (b). Orange arrow indicates splitting of myelin in (c). Magnification 5000×

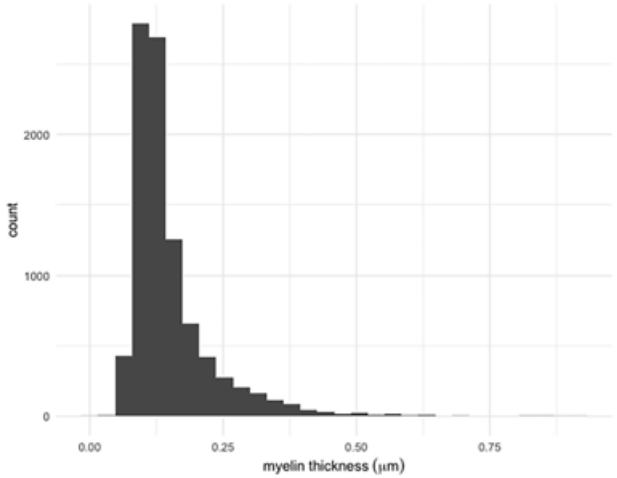

FIGURE 2 Frequency histogram of myelin thickness across the entire sample of young adult and geriatric marmosets. The most frequently occurring myelin thickness was approximately 0.10 μ; myelin thickness was infrequently greater than 0.25 μ

marmosets of all ages, the distribution displayed positive skew (Figure 3).

The overall number of myelinated axons by callosal Region across young adult and geriatric marmosets revealed interesting patterns. Young adult marmosets (YAM) had more myelinated axons in Regions I and II than geriatric marmosets (GM) (Region I: $\bar{X}_{YAM} = 435.5$, $\bar{X}_{GM} = 170.5$, $SE_{GM} = 46$; Region II: $\bar{X}_{YAM} = 341.5$, $\bar{X}_{GM} = 165$, $SE_{GM} = 43.25$); young adult marmosets had less myelinated axons in Region III than geriatric marmosets ($\bar{X}_{YAM} = 198.5$, $\bar{X}_{GM} = 265$, $SE_{GM} = 46$); and young adult and geriatric marmosets had similar numbers of myelinated axons in Regions IV and V (Region IV: $\bar{X}_{YAM} = 398$, $\bar{X}_{GM} = 417.75$, $SE_{GM} = 2$; Region V: $\bar{X}_{YAM} = 340$, $\bar{X}_{GM} = 348.75$, $SE_{GM} = 27$).

3.2 | Myelin fraction

Myelin fraction (MF) was quantified from the callosal Region sampling frames for each subject using a method similar to what has been used to quantify neuropil fraction (Sherwood, Wahl, Erwin, Hof, & Hopkins, 2007; Spocter et al., 2012). This allowed us to quantify the proportion of area consisting of myelin. MF was then calculated using the formula for calculating area of an ellipse, and subtracting the area of inner ellipse (representing axon) from the area of the outer ellipse (representing axon + myelin):

$$MF = \frac{\sum \frac{\pi}{4} (O_1 O_2 - I_1 I_2)}{area\ of\ image}$$

where O_1 = semi-major axis of outer ellipse, O_2 = semi-minor axis of outer ellipse, I_1 = semi-major axis of inner ellipse, and I_2 = semi-minor axis of inner ellipse.

To determine whether there was a correlation between age and MF, we first converted each subject's MF values into a standardized MF score. Each individual's MF for each callosal Region was calculated

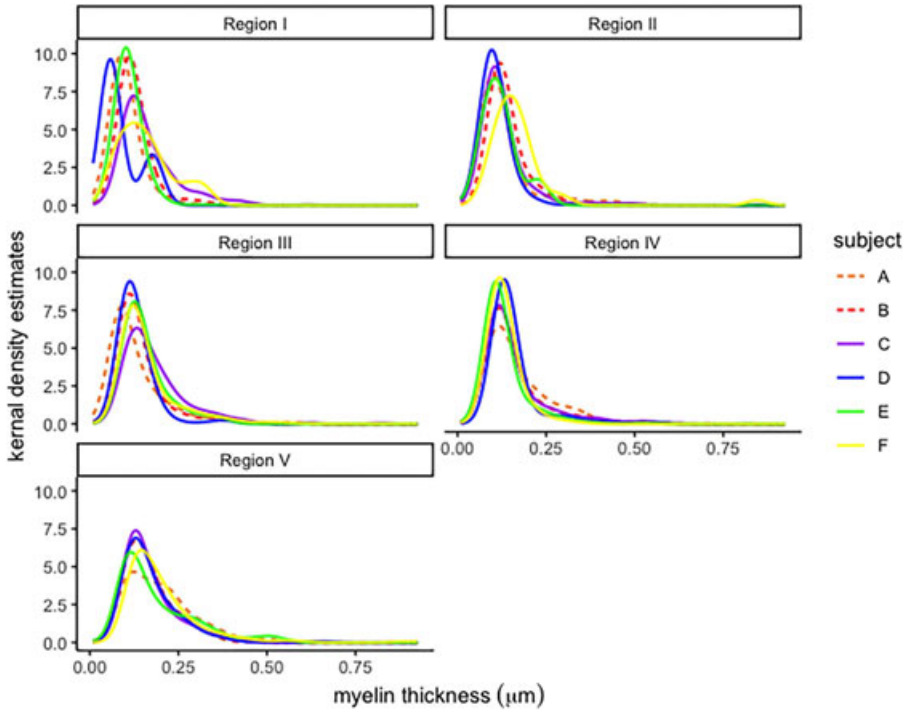

FIGURE 3 Kernel density estimation plot of myelin thickness in callosal Regions I–V. Dotted lines represent young adult marmosets, solid lines represent geriatric marmosets. Plots are truncated at 1 μ as extremely small numbers of myelin thickness were greater than this in all subjects examined

and subtracted from the sample mean for that Region. The proportion of MF for each callosal Region for young adult and geriatric marmosets is illustrated in Figure 4. As expected, MF significantly decreased with age across all Regions of the CC, $r < -0.765$, $p = 0.039$.

3.3 | Density of myelinated axons

The density of myelinated axons (DoMA) was calculated by dividing the total number of myelinated axons counted per image by the area of image ($26.3 \times 26.3\ \mu m^2$); DoMA is reported as mean number of myelinated axons per μm^2. DoMA for each callosal Region for young adult and geriatric marmosets is illustrated in Figure 5. As expected, DoMA significantly decreased with age across all Regions of the CC, $r < -0.857$, $p = 0.015$.

3.4 | Cognitive task

Subjects were tested on the detoured reach task until they either reached criterion (80% correct across two consecutive testing sessions) or eight testing sessions had been completed. The number of test sessions on the task varied between three and eight. Overall, geriatric marmosets performed more poorly on this task of executive function ($\bar{X}_{GM} = 0.54$) than did young adult marmosets ($\bar{X}_{YAM} = 0.81$), having a lower proportion of successful trials than young adult marmosets (Figure 6). However, one geriatric marmoset (subject C) performed quite well on the task, completing proportion of successful trials similar to the young adult marmosets.

3.5 | Myelin characteristics of Region I and executive function performance

As we were particularly interested in the associations between myelin characteristics in the genu (Region I) and performance on the detoured reach task, we ran regression analysis relating success rate on the task with age, myelin thickness of the genu, MF of the genu, and DoMA of the genu. Results indicated that age was the only predictor variable that was associated with performance on the task, explaining 50% of the variance in performance ($F[1, 5] = 4.94$, $p = 0.09$). Myelin thickness and DoMA explained 5% of the variance in success rate (myelin thickness: $F(1, 5) = 0.27$, $p = 0.63$; DoMA: ($F[1, 5] = 0.28$, $p = 0.62$). MF explained 10% of the variance in performance but this was not significant ($F[1, 5] = 0.56$, $p = 0.50$).

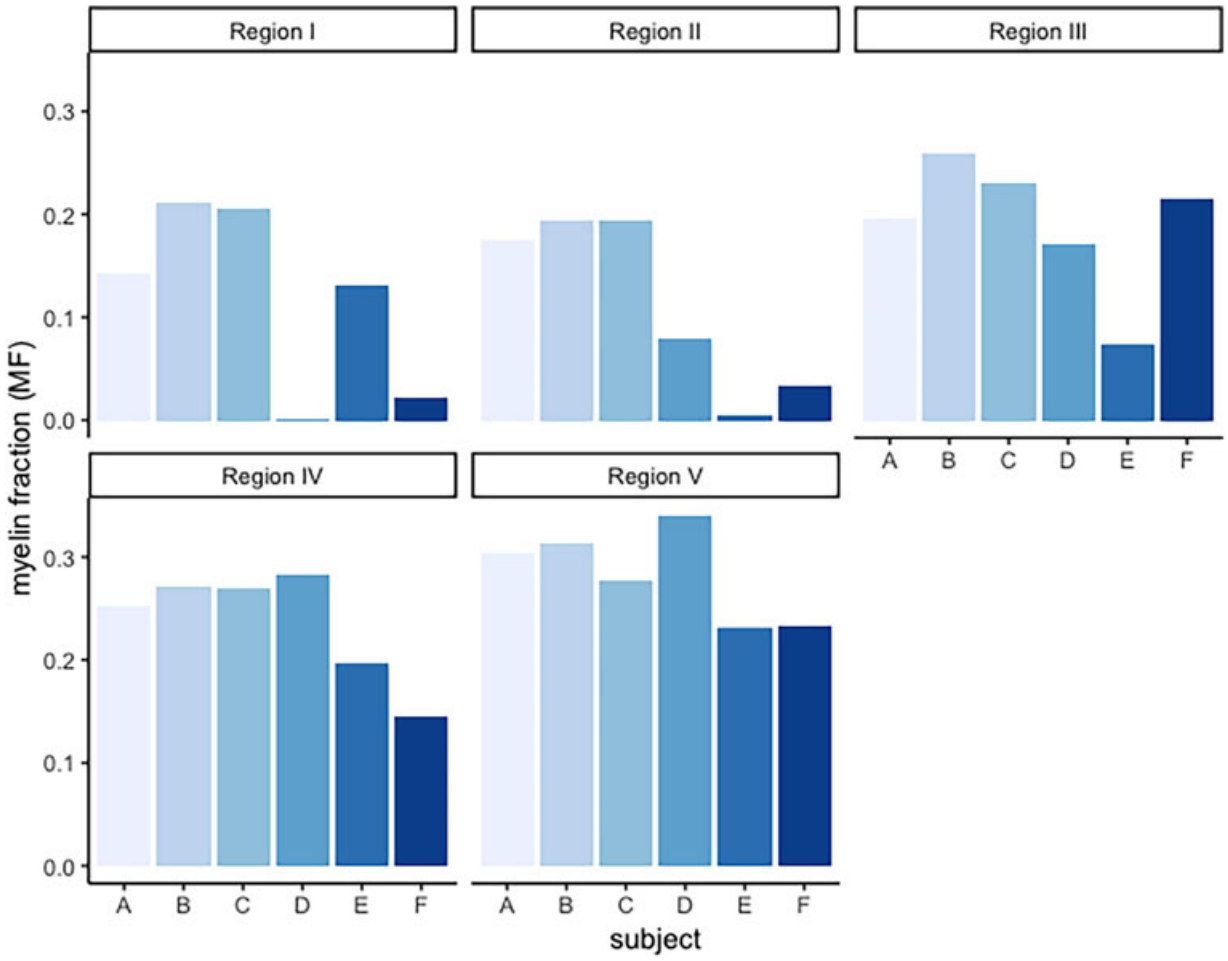

FIGURE 4 Proportion of MF in callosal Regions I–V for young adult (a and b) and geriatric (c–f) marmosets

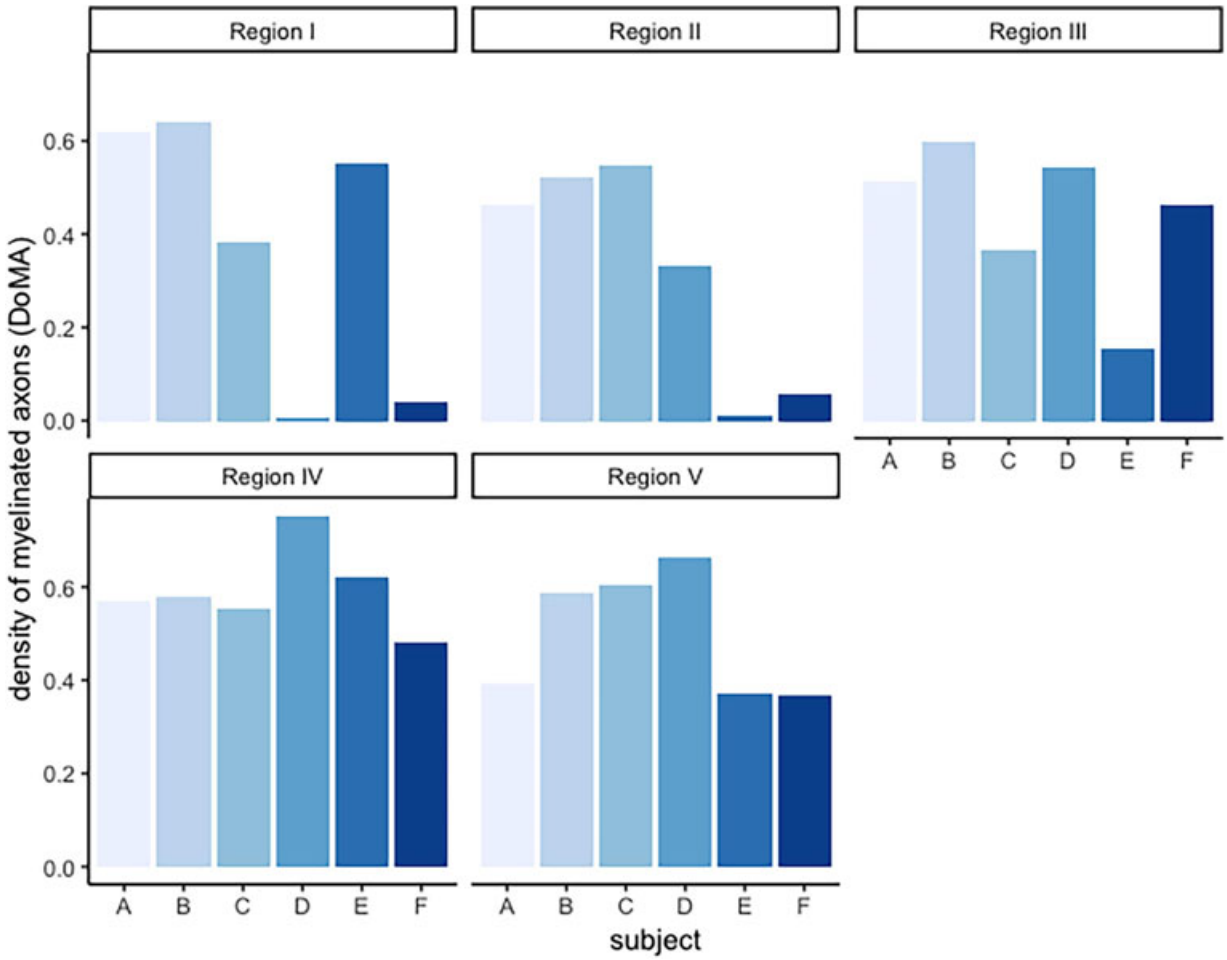

FIGURE 5 Density of myelinated axons (DoMA) in callosal Regions I–V for young adult (a and b) and geriatric (c–f) marmosets

3.6 | Myelin characteristics of Region II and executive function performance

Visual examination of the data on myelin characteristics indicated that Region II of the corpus callosum presented changes in a similar degree as Region I. We therefore conducted analyses to determine if cognitive performance was associated with characteristics of myelin (myelin thickness, DoMA, and MF) in Region II. Results indicated that MF explained 74% of the variance in performance and was significant ($F[1, 5]= 11.68$, $p = 0.03$). DoMA explained 56% of the variance in success rate and trended toward significance (DoMA: ($F[1, 5] = 5.06$, $p = 0.09$). Myelin thickness was not significantly associated with performance on the detoured reach task ($F[1, 5] = 0.07$, $p = 0.80$).

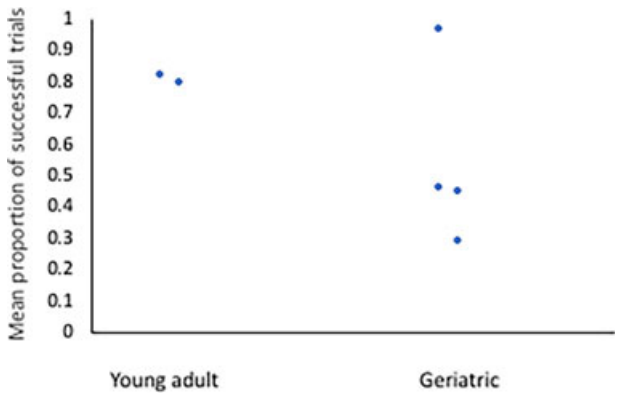

FIGURE 6 Performance on a task of executive function for young adult and geriatric marmosets

4 | DISCUSSION

In this study we examined age-related changes in myelin of callosal axons (especially in the genu), and whether these changes were related to performance on a task of executive function. Our results indicated declines in myelin thickness, density, and MF with age; performance on the task also declined with age. Considerable variability was detected on these characteristics of myelin and cognitive performance. Cognitive performance on the task was associated with white matter characteristics in Region II of the CC but not Region I.

Age-related changes in myelin of the genu of the CC were detected. Myelination of callosal axons in Regions I and II in geriatric marmosets showed reduction in overall number, appearance, and thickness. Characteristics of myelin showed variability across age groups and different regions of the CC. Higher values of MF and DoMA were found in posterior regions. These results are similar to those

found via imaging (Berman, West, Does, Yeatman, & Mexer, 2018; Mohammadi et al., 2015) and histology in the macaque (Stikov et al., 2015). Frontal regions of the brain are believed to be especially vulnerable to age-related white matter changes (Madden et al., 2012). The g-ratio, the ratio of the inner to outer radius of the myelin sheath wrapped around the axon, significantly declined in the motor and anterior sub-regions of the genu (equivalent to Regions I and III in this study) with age in humans (Berman et al., 2018). Whether changes in white matter are associated with cognitive performance, however, is unclear. While some have reported such associations generally (Burzynska et al., 2010; Davis et al., 2009), changes in white matter microstructure of specific brain regions have not been strongly linked to cognition (Salthouse, 2011).

Our *a priori* hypotheses focused on Region I, the region of the CC that provides interhemispheric connectivity of fibers of the prefrontal cortex. Other studies have shown an object retrieval task not only involves the prefrontal cortex but additional frontal lobe areas whose fibers cross via Region II. Large frontal legions (in areas including dorsolateral prefrontal, medial prefrontal, and premotor cortices) impaired performance on an object retrieval task (Moll & Kuypers, 1977). Jentsch, Roth and Taylor (2000) demonstrated that vervet monkeys treated with phencyclidine (PCP, a psychotomimetic drug of abuse which impairs corticostriatal function) exhibited impaired acquisition of an object-retrieval detour task. We found two characteristics of age-related changes in myelin in Region II were predictive of cognitive performance on the detoured reach task: MF and DoMA. Thus the detoured reach task appears to also measure aspects of corticostriatal function in addition to prefrontal cortical function; and the demyelination of callosal fibers in Region II are related to performance.

Peters and Sethares (2002) also reported changes in the myelin of the CC were related to cognition in aged macaques. Specifically, they reported age-related myelin changes in area 46 (prefrontal cortex) and Region V of the CC, but did not report data on myelin changes in Regions I or II. We found correlations between Region II and cognitive performance. These two studies utilized different tests of cognitive performance: delayed nonmatch to sample (Peters and Sethares, 2002) and the detoured reach task (present study). Delayed nonmatch to sample is considered a test of working memory, whereas the detoured reach task is considered a task of executive function. While working memory, attention, and executive function are all interrelated cognitive processes, they may have different neural underpinnings.

While both young adult marmosets performed similarly on the detoured reach task, the geriatric marmosets showed more variability in performance. Three of the four geriatric marmosets performed poorly on the task compared to the young adult individuals, never reaching criterion. One geriatric marmoset performed quite well on this task (and actually better than the young adult subjects), reaching criterion in only three test sessions. While assessments of executive function typically have been found to decline with aging, however, even in humans there are individual differences in cognitive aging with some geriatric individuals maintaining high levels of cognitive function. As evidenced in this study, marmosets also display variability in cognitive aging, with both "good" and "poor" cognitive agers.

The current study has the obvious limitation of small sample size. Nonetheless, the pattern of decreased myelin integrity seen in geriatric individuals, and the age-related changes in cognitive performance, suggest an association between structural brain changes and cognitive aging that is worth further investigation. We plan to further examine this (including additional measures of cognitive performance and additional measure of age-related brain changes) with additional subjects as they become available.

The availability of geriatric marmosets for study is currently rather limited in the US. As interest in using marmosets for investigations of aging continues to increase, we hope that there is an associated increase in the numbers of geriatric marmosets. The development and maintenance of this resource will undoubtedly shed light on cognitive and brain aging and be invaluable in meeting therapeutic needs of aging-related neurological disease.

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