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The marmoset as an important primate model for longitudinal studies of neurocognitive aging.

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Abstract

Age-related cognitive decline has been extensively studied in humans, but the majority of research designs are cross-sectional and compare across younger and older adults. Longitudinal studies are necessary to capture variability in cognitive aging trajectories, but are difficult to carry out in humans and long-lived nonhuman primates. Marmosets are an ideal primate model for neurocognitive aging as their naturally short lifespan facilitates longitudinal designs. In a longitudinal study of marmosets tested on reversal learning starting in middle-age, we found that, on average, the group of marmosets declined in cognitive performance around 8 years of age. However, we found highly variable patterns of cognitive aging trajectories across individuals. Preliminary analyses of brain tissues from this cohort also shows highly variable degrees of neuropathology. Future work will tie together behavioral trajectories with brain pathology and provide a window into the factors that predict age-related cognitive decline.

Graphical Abstract

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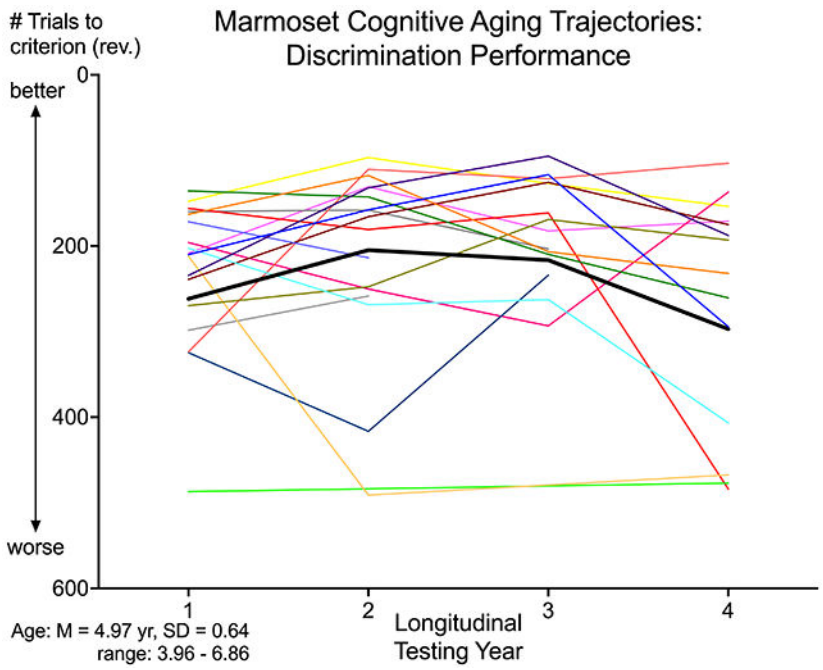

Keywords

Marmoset; aging; longitudinal study; reversal learning; neuropathology

Introduction

Age-related cognitive decline is well documented in humans; however, the bulk of the literature is based on cross-sectional studies that compare the performance of old adults and younger adults in the same tasks. These studies have highlighted differences between young and older participants in a range of cognitive abilities sometimes referred to as “fluid abilities”, such as episodic memory, speed of processing and working memory (Hedden & Gabrieli, 2004; Park & Schwarz, 2000; Salthouse, 2010). However, cross-sectional studies are subject to cohort effects and often over-estimate age effects (Schaie, 2009 but see Salthouse, 2010). Although longitudinal studies possess their own challenges, due to nonrandom attrition and practice effects (e.g. Lindenberger et al., 2002; Rabbitt et al., 2004; Salthouse, 1996), they are necessary to capture true age-related change and examine whether between-individual differences in age-related change are correlated across different aspects of brain and behavior (Lindenberger, 2014). In addition, longitudinal studies can determine normative and non-normative influences on lifespan cognitive trajectories (Steinerman, 2010). Longitudinal studies in humans have highlighted the heterogeneity of cognitive and brain trajectories, with some people showing little or no change, while others display marked changes with advancing age (Nyberg et al., 2020). This individual variability likely results from differences in brain maintenance, brain compensation and cognitive reserve (Cabeza et al., 2018; Stern et al., 2020), under the influence of various biological (e.g., genetic) and environmental (e.g., lifestyle) factors (Nyberg et al., 2020).

Due to the complexity of these interactions in humans (different lifestyles, diet, medications, exercise, etc.), it is crucial to study cognitive and brain aging in animal models for which these sources of variation can be better controlled (McQuail et al., 2021). Nonhuman primates (NHP) are arguably the best animal models of human cognitive aging due to their phylogenetic proximity and overlap with humans in many aspects of brain function and behavior (Baxter, 2001; Emery Thompson et al., 2020; Hara et al., 2012; Herndon et al., 1997; Lacreuse & Herndon, 2009; Voytko & Tinkler, 2004). To date, several NHP species have been used as models for human cognitive aging (Shively et al., this issue), but longitudinal studies remain remarkably rare (Hopkins et al., 2020; Lacreuse et al., 2014; Pifferi & Aujard, 2019; Suomi et al., 1996). A major challenge to longitudinal approaches in NHPs is their long lifespan; our closest great ape relatives, the chimpanzees, have a life expectancy in captivity of 28.3 years at birth, that increases to 34.6 for animals who reach one year of age, with an estimated maximum lifespan of 74 years (Havercamp et al., 2019). Likewise, the most common NHP used in biomedical research, rhesus macaques, have an average life expectancy of approximately 26 years, with a maximum lifespan of 40 years (Colman, 2018).

The common marmoset (*Callithrix jacchus*) is gaining attention as an ideal model for translational neuroscience research (Abbott et al., 2003), including for aging research (Ross, 2019; Tardif et al., 2011). First, marmosets are ideally suited for longitudinal investigations because they have a relatively short life expectancy; captive laboratories report average lifespan between 5 and 9 years for females and 5 and 13 years for males (Nishijima et al., 2012; Ross, 2019). Maximum lifespan was previously reported to be about 16 years (Tardif et al., 2011) , but increased to 21 years in a Japanese colony (Nishijima et al., 2012). Extended maximum lifespans may be found in marmosets colonies with reduced exposure to potential pathogens (see Ross, 2019). Second, this small-bodied species (300-500 g) is easier to handle than larger primates and easier to group-house in captivity. Third, they have a rich behavioral repertoire, are highly social (Miller, 2017; Miller et al., 2016), are able to perform a range of cognitive tasks (Nakamura et al., 2018; Nummela et al., 2019; Spinelli et al., 2004) and have a brain organization typical of anthropoid primates (Fukushima et al., 2018; Liu et al., 2019; Miller et al., 2016). Aging studies in the marmoset are only in their infancy, but have documented age-related changes in a number of biological systems between ages 5 and 8 (Ross et al., 2012), including weight loss (Tardif et al., 2011), hearing loss (Harada et al., 1999) and cartilage aging (Berkovitz & Pacy, 2000). With regards to the brain, some age-related changes are similar to those observed in humans and include age-related deposition of amyloid-β protein in cortical areas, which has been found in marmosets as early as ages 8 (Geula et al., 2002, Freire Cobo et al., this issue) to 10 (Maclean et al., 2000; Rodriguez-Callejas et al., 2016), reduced neurogenesis in the dentate gyrus (Leuner et al., 2007), accumulation of dystrophic and activated microglia in specific regions (Rodriguez-Callejas et al., 2016; Freire Cobo et al., this issue) and age-related alterations of the corpus callosum (Phillips et al., 2019).

In contrast, studies of age-related cognitive decline in the marmoset remain extremely sparse. Three cross-sectional studies have recently documented age differences in executive function (Munger et al., 2017; Sadoun et al., 2019) working memory (Sadoun et al., 2019) and detour reaching (Phillips et al., 2019) in this species, suggesting that aging

influences cognitive domains that are also sensitive to aging in other primates (see Baxter, 2001; Lacreuse & Herndon, 2009). Yet, one of the main advantages of the marmoset over traditional primate models of human aging such as macaque monkeys, is their much shorter lifespan of about 10 years, particularly well-suited to longitudinal designs. In the first study of this type (Rothwell et al., 2021), our group tested marmosets on reversal learning, a task of executive function, starting in middle-age (about 5 years old) until the marmosets were about 9 years old. In order to examine associations between cellular and pathological changes in the brain and the observed behavioral changes, brain tissues were collected post-behavioral assessments for the analysis of prefrontal cortex (PFC) and hippocampal neuropathology.

Variability in Marmoset Cognitive Aging Trajectories

Age-related decline in cognitive performance appeared around age 8, consistent with Sadoun et al.'s cross-sectional study of marmosets (2019). In addition, sex differences were observed, with females exhibiting an earlier and steeper decline than males. Importantly, highly variable patterns of cognitive aging trajectories were seen in both sexes (Figure 1). The existence of substantial individual variability in cognitive aging patterns has been recognized for a long time, both in humans (Hedden & Gabrieli, 2004) and NHP (Rapp & Amaral, 1992). Cognitive variability not only includes differences across individuals – not all individuals will exhibit robust cognitive deficits with age – but also within-individual differences across time (MacDonald et al., 2009) and across tasks (Roalf et al., 2016). The consideration of such indices are critical for assessing cognitive decline (Hultsch et al., 2008; MacDonald et al., 2006), in particular for identifying individuals at risk for dementia (Roalf et al., 2016) or those exhibiting brain pathology (Ferreira et al., 2017).

Variability in Marmoset Neuropathology

The analysis of brain tissues from the marmosets at the end of the longitudinal study indicates that the extent of neuropathology is highly variable across individuals. Our preliminary investigations based on 12 marmoset brains revealed large individual differences in loss of dendritic spine densities in dorsolateral prefrontal cortex (dlPFC) and hippocampus and degrees of amyloid-β deposition in dlPFC layer III of area 8b/9 (Freire Cobo et al., this issue) and hippocampus CA1 (Figure 2). Along with the amyloid-β burden, we also observed individual differences in microglial activation (Figure 3) and morphology (Figure 4). Some marmosets showed an increased activation state of microglial cells, in both dlPFC layer III of area 8b/9 and hippocampus CA1 with an increase of the atrophic microglial phenotype (Garaschuk & Verkhratsky, 2019). As our sample sizes increase, we will be able to determine whether neuropathology is more severe in marmosets characterized as cognitively impaired, as well as in females, as would be predicted from sex differences in cognitive trajectories (Rothwell et al., 2021).

Discussion

Few studies to date have leveraged the advantages of small, short-lived NHP (Fischer & Austad, 2011) for longitudinal investigations of neurocognitive aging (Pifferi & Aujard, 2019; Rothwell et al., 2021). Longitudinal assessments of cognitive, behavioral and

biological parameters, combined with multiple neuroimaging assessments (Laclair et al., 2019; Nephew et al., 2020) and post-mortem neuropathology in the aging marmoset will provide invaluable insight into healthy and pathological aging, including Alzheimer's disease (AD). While transgenic rodent models have advanced our understanding of AD, clinical trials have routinely failed for almost two decades (King, 2018). A need exists to study animal models that naturally undergo cerebral and behavioral changes more similar to humans to understand the development of AD-like neuropathology better. Furthermore, individual variability in susceptibility or resistance to AD-like neuropathology can only be understood with longitudinal studies. In this context it is therefore crucial to ensure that marmosets are made readily available for aging research (Miller & Lee, 2019; Servick, 2018; Shively, this issue), as we expect that the marmoset will become a major NHP model in which to address these fundamental questions.

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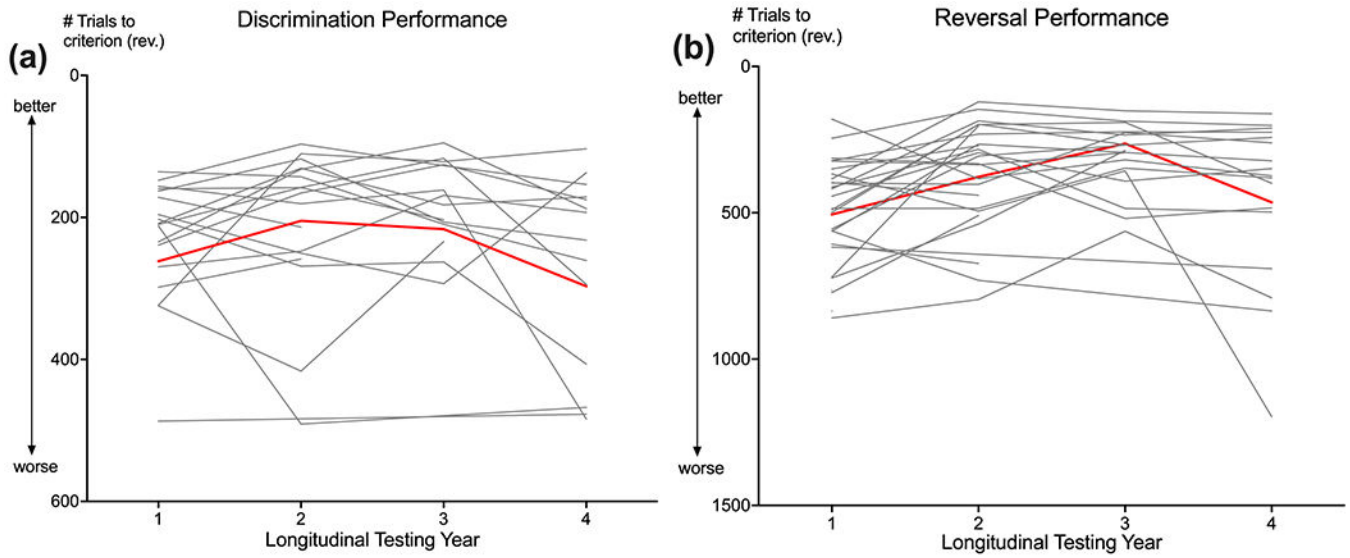

Figure 1. Cognitive aging trajectories.

Trajectories of cognitive performance on trials to criterion for (a) discrimination and (b) reversal testing across a 4-year longitudinal study spanning middle to old age. Performance is measured by the number of trials to criterion, with fewer trials representing better performance. Red lines represent the average aging trajectories for all marmosets (N=27) and gray lines represent individual marmosets. Average age at Testing Year 1 was 4.97 years old (SD = 0.64; 3.96 to 6.86 years).

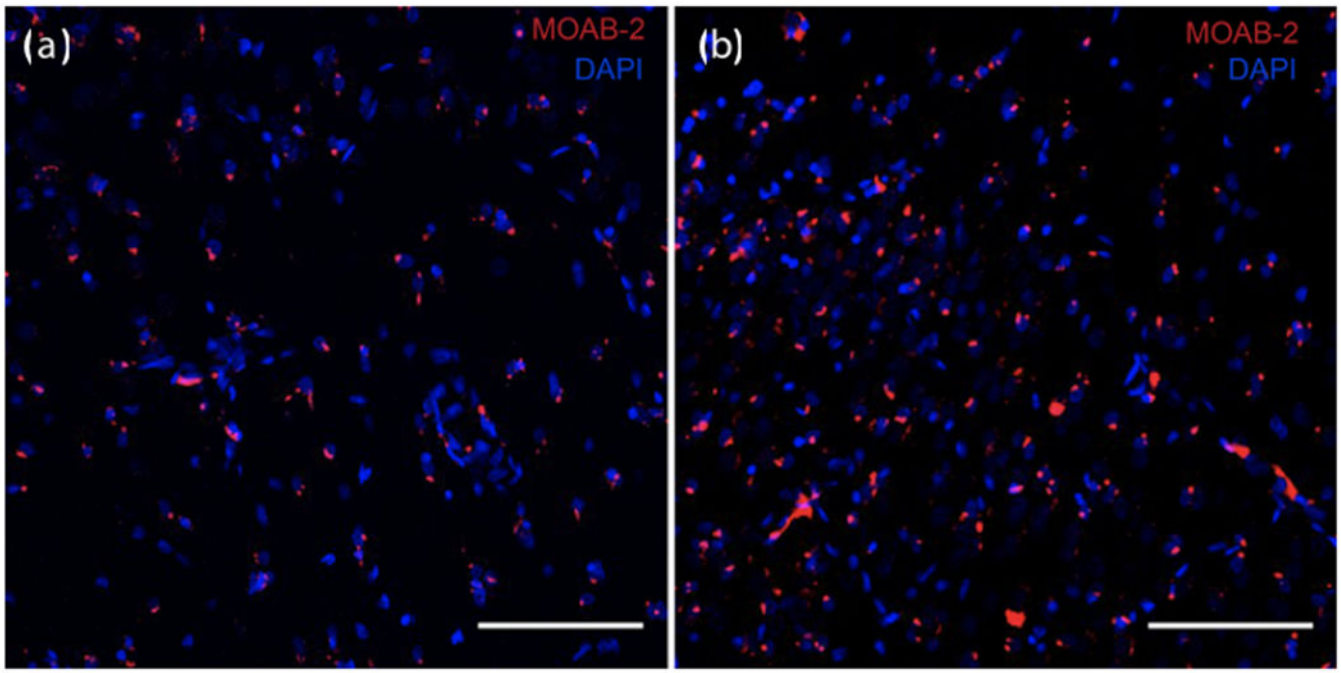

Figure 2. Amyloid deposits in hippocampus.

Varying degrees of amyloid deposits in CA1 of old marmosets. Amyloid-β peptide detected by MOAB-2 antibody (red); cell nuclei stained with DAPI (blue). Scale bar = 100 μm. Amyloid burden in two male marmosets: (a) low burden, 9 years old and (b) high burden 8 years old.

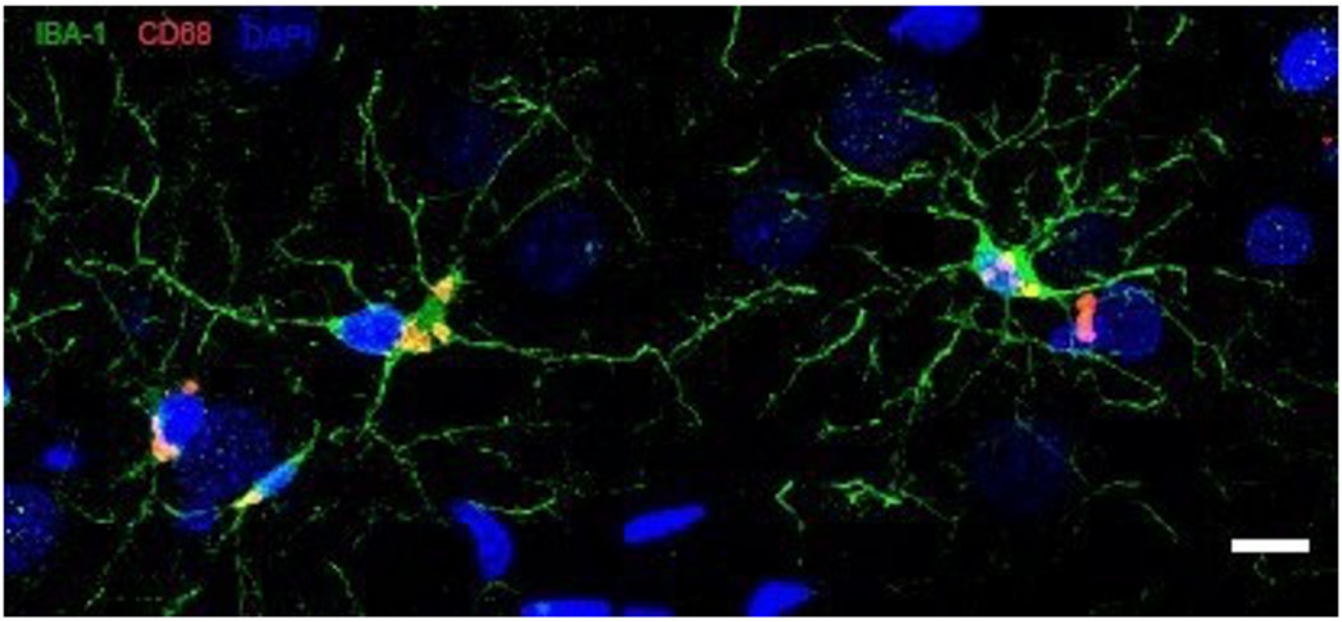

Figure 3. Microglia activation in hippocampus.

Activated microglia in CA1 of an old marmoset. Confocal images of microglia expressing Iba-1 (green) and CD68 (red). Nuclei are stained with DAPI (blue). Scale bar = 10 μm.

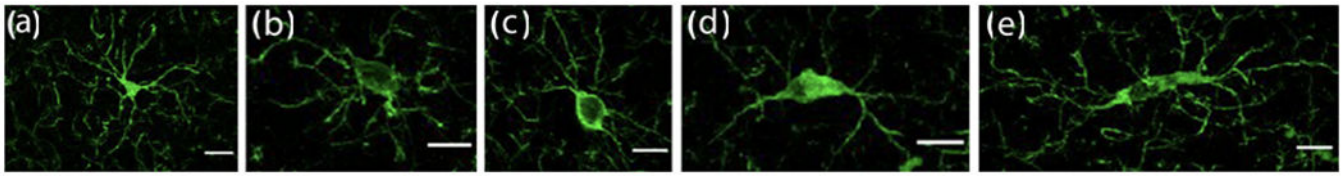

Figure 4. Microglia morphology in dlPFC.

Microglia detected by Iba-1 expression (green). (a) Highly ramified morphology with small cell soma and fine processes; (b-c) intermediate morphology with enlarged cell soma and thick, short processes; (d-e) ameboid and dystrophic microglia, with extensive loss of processes. Scale bars = 10 μm.