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Age-related effects in the neocortical organization of chimpanzees: Gray and white matter volume, cortical thickness, and gyrification

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ABSTRACT

Among primates, humans exhibit the most profound degree of age-related brain volumetric decline in particular regions, such as the hippocampus and the frontal lobe. Recent studies have shown that our closest living relatives, the chimpanzees, experience little to no volumetric decline in gray and white matter over the adult lifespan. However, these previous studies were limited with a small sample of chimpanzees of the most advanced ages. In the present study, we sought to further test for potential age-related decline in cortical organization in chimpanzees by expanding the sample size of aged chimpanzees. We used the BrainVisa software to measure total brain volume, gray and white matter volumes, gray matter thickness, and gyrification index in a cross-sectional sample of 219 captive chimpanzees (8–53 years old), with 38 subjects being 40 or more years of age. Mean depth and cortical fold opening of 11 major sulci of the chimpanzee brains were also measured. We found that chimpanzees showed increased gyrification with age and a cubic relationship between age and white matter volume. For the association between age and sulcus depth and width, the results were mostly non-significant with the exception of one negative correlation between age and the fronto-orbital sulcus. In short, results showed that chimpanzees exhibit few age-related changes in global cortical organization, sulcus folding and sulcus width. These findings support previous studies and the theory that the age-related changes in the human brain is due to an extended lifespan.

Introduction

Normal aging in humans is a complex process that brings about many structural changes in the brain. Research shows that normal brain aging in humans is characterized by particularly severe volume loss in regions involved in memory and executive functions, such as the hippocampus and frontal lobe (Abe et al., 2008; Peters, 2006; Raz et al., 1997; Rosen et al., 2002; Tisserand et al., 2004). The volumetric decline is associated with shrinkage of gray matter (GM) and white matter (WM) volumes and enlargement of the cerebrospinal fluid (CSF) spaces, resulting in an increase of the opening of cortical sulci (Ge et al., 2002; Lemaitre et al., 2012; Matsumae et al., 1996; Pfefferbaum et al., 1994; Sherwood et al., 2011; Sullivan et al., 1995). Evidence suggests that cerebral gray matter volume decreases at a linear rate with age in adulthood, whereas hippocampal volume is relatively stable until middle age, after which there is an accelerated rate of shrinkage (Ge et al., 2002; Good et al., 2001; Raz et al., 2005; Sherwood et al., 2011; Taki et al., 2011; Walhovd et al., 2005). White matter volume shows a quadratic change over the lifespan, in which it increases until the middle age period and then decreases with increasing age (Ge et al., 2002; Giorgio et al., 2010; Sowell et al., 2003; Walhovd et al., 2005; Westlye et al., 2010).

From a comparative perspective, previous studies have examined age-related changes in the brains of other mammals, and specifically primates. Nonhuman primates are of particular interest for studying the neurobiological correlates of aging because of their close phylogenetic relationship with humans (Finch and Austad, 2012). Nonhuman primates are often used as models to understand the effects of aging independent of the cellular changes that cause age-related neurodegenerative disorders commonly seen in humans such as Alzheimer's disease (Gearing et al., 1996; Kimura et al., 2003; Koo et al., 2012; Lemaitre et al., 2012; Sherwood et al., 2011; Squire et al., 1988). Characteristics of neurodegenerative diseases, such as diffuse plaques and vascular lesions, have been observed in the hippocampus and frontal lobes of aged macaque monkeys, chimpanzees, gorillas and orangutans

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(Gearing et al., 1997; Kimura, 2001; Poduri et al., 1994). At the present time there are only two reports of the existence of neurofibrillary tangles in great apes including one in a 41 year old chimpanzee (Rosen et al., 2008), and more recently in a sample of lowland gorillas (Perez et al., 2013). Finally, there is also evidence that apes and monkeys show age-related volumetric decline in the striatum and modest reductions in total brain volume (Alexander et al., 2008; Herndon et al., 1999; Matochik et al., 2000; Rapp and Amaral, 1992).

In terms of behavior and cognition, age-related decline in motor and cognitive functions have been described extensively in monkeys (Herndon et al., 1997; Lacreuse et al., 2005; Moss et al., 1988; Rapp and Amaral, 1989). In humans, the age-related volumetric reductions of the frontal lobe and the hippocampus are associated with decline in cognitive processes, including fluid reasoning, mental processing speed, episodic memory, and spatial ability (Park et al., 2001; Salthouse, 1996; Verhaeghen and Salthouse, 1997; Whalley et al., 2004). In aged nonhuman primates, there are impairments in delayed response tasks, delayed matching-to-sample tasks, delayed recognition span tasks, reversal learning tasks, and conceptual set-shifting task (Bartus et al., 1978; Hara et al., 2012; Moss et al., 1988). Far fewer data are available from great apes, including chimpanzees; however, a recent study by Lacreuse et al. (2014) reported a moderate but statistically significant decline in spatial memory in a sample of 4 chimpanzees over the age of 50 years old.

It has been hypothesized that a possible factor explaining the more pronounced pathological and cognitive changes found in humans compared to nonhuman primates is increased longevity (Hawkes, 2003; Herndon, 2009). Compared to other primates, humans have evolved an extended lifespan, particularly post reproductively, which has been proposed to increase the risk for the development of cognitive impairments and associated brain changes in later life (Herndon, 2009). The "grandmother hypothesis" suggests that human longevity resulted from selection for longer post-menopausal survival in women, who could contribute to the cooperative care of dependent offspring in their families (Finch and Sapolsky, 1999; Hawkes, 2003). According to Herndon (2009), chimpanzees' shorter post-menopausal lifespan might allow them to avoid cognitive impairments or neurodegenerative disorders that occur during the very latest stages of life in humans, such as Parkinson's or Alzheimer's disease.

To date, there are two studies on age-related changes in cortical organization in chimpanzee brains based on post-mortem or in vivo magnetic resonance imaging. Sherwood et al. (2011) examined age-related changes in cortical organization in chimpanzees compared to humans. They measured the volumes of brain regions in 69 chimpanzees and found that there was little evidence of marked age-related change. Specifically, chimpanzees did not show statistically significant volumetric age-related decline in gray and white matter volume for either the entire brain or frontal lobe or hippocampus. More recently, Chen et al. (2013) found that chimpanzees do show age-related declines in both gray and white matter, but the declines were much smaller than typically occur in older humans. One limitation of this prior research was the minimal number of very old or "aged" subjects, defined as those chimpanzees greater than 40 years of age. For instance, there were only 7 subjects over the age of 40 in the previous study by Sherwood et al., with only one being a male. Similarly, Chen et al. (2013) had only a small portion of chimpanzees over the age of 40 and the sample consisted entirely of females. Thus, both Chen et al. (2013) and Sherwood et al. (2011) may not have had enough statistical power to detect more robust age-related changes in cortical organization among the most geriatric chimpanzees, and particularly older males.

The aim of the current research was to further test for potential age-related decline in cortical organization in chimpanzees. This study differs from previous reports on age-related changes in the chimpanzee brain in two important ways. First, this study had a larger sample of male and female chimpanzees that included substantially more individuals representing the upper end of their lifespan. Second, we employed a different methodology and approach to the measurement of different dimensions of cortical organization. Here, we used the BrainVisa (BV) software to measure the organization and folding in the cerebral cortex. This software has been previously employed to assess age-related changes in human and baboon brains (Kochunov et al., 2005). Using the BV software, we measured the total brain volume, gray and white matter volumes, gray matter thickness, and gyrification index of 219 captive chimpanzees, with 38 subjects being 40 or more years of age, therefore considerably expanding the sample size in the oldest cohort of individuals. Furthermore, we measured the mean depth and cortical fold opening of 11 major sulci of the chimpanzee brains. We hypothesized that if age-related changes in the chimpanzee brain are reduced compared to humans, then age would account for a small proportion of variance in cortical organization, sulcus depth and fold opening in our sample.

Methods

Subjects

There were 219 captive chimpanzees (134 females, 85 males) in this study including 84 chimpanzees housed at the Yerkes National Primate Research Center (YNPRC) and 135 chimpanzees housed at The University of Texas M. D. Anderson Cancer Center (UTMDACC). Ages at the time of their magnetic resonance image scans ranged from 8 to 53 years ($Mean = 27.04$, $SD = 6.74$). In addition to analyzing the neuroanatomical variables against chronological age, we also classified the chimpanzees into 4 age groups including adolescent or sub-adult individuals ($\leq$15 years), young adults (16 to 25 years), middle-aged adults (26 to 39 years) and elderly (40 + years). The sample sizes in the sub-adult, young adult, middle-aged, and elderly groups were 33, 86, 62, and 38, respectively.

Magnetic resonance image collection

All chimpanzees were scanned in vivo during one of their annual physical examinations. Magnetic resonance image (MRI) scans followed standard procedures at the YNPRC and UTMDACC and were designed to minimize stress. Thus, the animals were first sedated with ketamine (10 mg/kg) or telazol (3–5 mg/kg) and were subsequently anesthetized with propofol (40–60 mg/kg/h). They were then transported to the MRI scanning facility and placed in a supine position in the scanner with their head in a human-head coil. Upon completion of the MRI, chimpanzees were briefly singly-housed for 2–24 h to permit close monitoring and safe recovery from the anesthesia prior to return to the home social group. All procedures were approved by the Institutional Animal Care and Use Committees at YNPRC and UTMDACC and also followed the guidelines of the Institute of Medicine on the use of chimpanzees in research. Seventy-six chimpanzees were scanned using a 3.0 T scanner (Siemens Trio, Siemens Medical Solutions USA, Inc., Malvern, Pennsylvania, USA). T1-weighted images were collected using a three-dimensional gradient echo sequence (pulse repetition = 2300 ms, echo time = 4.4 ms, number of signals averaged = 3, matrix size = 320 × 320, with 0.6 × 0.6 × 0.6 resolution). The remaining 143 chimpanzees were scanned using a 1.5 T G.E. echo-speed Horizon LX MR scanner (GE Medical Systems, Milwaukee, WI). T1-weighted images were collected in the transverse plane using a gradient echo protocol (pulse repetition = 19.0 ms, echo time = 8.5 ms, number of signals averaged = 8, matrix size = 256 × 256, with 0.7 × 0.7 × 1.2 resolution).

MRI processing

BrainVISA 4.0.1 (BV) is a freely distributed software (http://brainvisa.info) that can be used for a range of morphometrics, including