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Brain aging in humans, chimpanzees (*Pan troglodytes*), and rhesus macaques (*Macaca mulatta*): magnetic resonance imaging studies of macro- and microstructural changes

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ABSTRACT

Among primates, humans are uniquely vulnerable to many age-related neurodegenerative disorders. We used structural and diffusion magnetic resonance imaging (MRI) to examine the brains of chimpanzees and rhesus monkeys across each species' adult lifespan, and compared these results with published findings in humans. As in humans, gray matter volume decreased with age in chimpanzees and rhesus monkeys. Also like humans, chimpanzees showed a trend for decreased white matter volume with age, but this decrease occurred proportionally later in the chimpanzee lifespan than in humans. Diffusion MRI revealed widespread age-related decreases in fractional anisotropy and increases in radial diffusivity in chimpanzees and macaques. However, both the fractional anisotropy decline and the radial diffusivity increase started at a proportionally earlier age in humans than in chimpanzees. Thus, even though overall patterns of gray and white matter aging are similar in humans and chimpanzees, the longer lifespan of humans provides more time for white matter to deteriorate before death, with the result that some neurological effects of aging may be exacerbated in our species.

1. Introduction

Among primates, humans appear to be particularly susceptible to neurodegenerative diseases such as Alzheimer's disease, Parkinson`s disease, and Huntington's disease (Gearing et al., 1994; Gerlach and Riederer, 1996; Hof et al., 2002; Olson and Varki, 2003; Rosen et al., 2008; Rosen et al., 2011; Walker and Cork, 1999). The neurological basis for this important species difference remains uncertain. However, we may glean insight into human vulnerability by comparing patterns of age-related changes in brain structures between humans and other primates.

Human aging is accompanied by alterations in brain morphology. One post-mortem study found a decline in brain weight that begins at about 45 to 50 years of age and reaches a minimum after 86 years of age, by which time mean brain weight has decreased by about 11% relative to its maximum in young adulthood (~19 years of age) (Dekaban, 1978). This trend was confirmed by another autopsy study (Miller et al., 1980), which found that mean hemisphere volume changed little between the ages of 20 and 50 years, after which mean volume in both sexes fell at about 2% per decade. In vivo magnetic resonance imaging (MRI) studies have similarly revealed global brain volume decline as well as selective regional shrinkage with age in humans. There is consensus that gray matter (GM) volume decreases with age, and that this decline begins early in life (as early as ~4 years of age) (Allen et al., 2005; Bartzokis et al., 2001; Pfefferbaum et al., 1994; Raz and Rodrigue, 2006; Walhovd et al., 2005). Overall cortical

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volume shows a pronounced linear decrease with age, but the rate of decline of different cortical regions is highly heterogeneous (Allen et al., 2005; Fjell et al., 2009; Walhovd et al., 2005; Walhovd et al., 2011). Inconsistent findings have been reported for the relationship between age and white matter (WM) volume (Abe et al., 2008; Allen et al., 2005; Blatter et al., 1995; Courchesne et al., 2000; Giedd et al., 1999b; Good et al., 2001; Guttmann et al., 1998; Jernigan et al., 1991; Jernigan et al., 2001; Pfefferbaum et al., 1994; Walhovd et al., 2005), which may be partially attributable to variation in sample ages, inconsistent segmentation methods and inconsistent structural demarcations (Walhovd et al., 2011). Recent studies demonstrate that age differences in cerebral WM volume followed a nonlinear (quadratic or cubic) trajectory and that volumetric reductions are not evident until middle age (fifth or sixth decade) (Allen et al., 2005; Walhovd et al., 2005). Although most brain aging studies are based on cross-sectional rather than longitudinal data, some of the above findings have been validated in longitudinal studies (Giedd et al., 1996; Giedd et al., 1999a; Giedd et al., 1999b; Raz et al., 2005; Resnick et al., 2000). These volumetric age-related changes have functional consequences. For example, age-related declines in both GM and WM volume, especially in the anterior regions, are linked to decreased performance on attention and executive function tasks (Brickman et al., 2007; Zimmerman et al., 2006).

Fewer studies have examined age-related changes in non-human primate brains, and findings have been somewhat inconsistent. Neuroimaging studies of the macaque brain found that both overall brain volume and the GM volume significantly decrease with age (Andersen et al., 1999; Wisco et al., 2008). On the other hand, a post-mortem study did not find a reduction in brain weight with age in macaques (Herndon et al., 1998). Although some neuroimaging studies found a positive correlation between age and WM volume (Andersen et al., 1999; Lacreuse et al., 2005), another found a negative correlation (Wisco et al., 2008). An autopsy study of chimpanzee brains (Herndon et al., 1999) reported a marginal decrease of brain weight with age; however, a recent MRI study reported that neither GM nor WM volume changed with age in chimpanzees (Sherwood et al., 2011).

Although volumetric alterations are a hallmark of brain aging, they may be preceded by less obvious changes, particularly in the WM. The advent of diffusion MRI opens a new window into the investigation of age-related microstructural changes in WM. With the tensor model of diffusion MRI, several different indices, including fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD), can be derived. Among these diffusion tensor imaging (DTI) indices, FA characterizes the degree of anisotropic water diffusion in a voxel (Basser et al., 1994; Pierpaoli et al., 1996) and is thought to reflect microstructural features of WM such as fiber density, axon diameter, fiber coherence, and myelination (Buchel et al., 2004; Pfefferbaum and Sullivan, 2003). FA is highly variable within WM. FA values are typically high in regions with highly ordered parallel fibers and are low in regions with less coherent fiber orientations or where fiber bundles cross. Significant decreases in WM FA are associated with certain disease states such as Alzheimer`s disease, Parkinson`s disease, and multiple sclerosis (Filippi et al., 2001; Hess, 2009; Horsfield and Jones, 2002; Matsui et al., 2007; Rose et al., 2000) and with normal, physiological aging in humans (Pfefferbaum and Sullivan, 2003; Sullivan et al., 2006b; Sullivan and Pfefferbaum, 2006; Westlye et al., 2010). FA in the frontal WM is more susceptible to aging effects than are the more posterior regions (Salat et al., 2004; Salat et al., 2005; Sullivan and Pfefferbaum, 2006).

Several studies have also examined age-related changes in other DTI indices such as AD and RD, which refer respectively to the magnitude of diffusion along and perpendicular to the principal diffusion direction. The neurobiological interpretation of AD and RD, however, is complicated by many factors (Wheeler-Kingshott and Cercignani, 2009). Assaf and Pasternak (Assaf and Pasternak, 2008) suggested that conjoint analysis of all measures derived from the diffusion tensor should yield a more comprehensive picture of different elements of WM microstructure. By analyzing FA and MD conjointly with other DTI indices, for example, RD, AD, and the mode of the diffusion tensor, it may be possible to distinguish between diffusivity patterns with different neurobiological foundations (Groves et al., 2012). Although neurobiological interpretations should be made with caution, RD changes are generally thought to be sensitive to changes in myelination (Song et al., 2002; Tyszka et al., 2006), whereas AD changes may be related to changes in fiber density and/or axonal caliber (Song et al., 2003; Tyszka et al., 2006). Age-related changes of these DTI indices have been correlated with decrements in working memory, interhemispheric transfer, balance, attention shifting, and reaction time (Bucur et al., 2008; Charlton et al., 2008; Fjell et al., 2011; Janowsky et al., 1996; Madden et al., 2009; Madden et al., 2004; Sullivan et al., 2001; Sullivan et al., 2010).

In the only published non-human primate brain aging study using diffusion MRI of which we are aware, WM FA of rhesus monkeys reportedly decreases with age, particularly within anterior regions and along cortico-cortical association tracts such as the superior longitudinal fasciculus and anterior cingulum bundle (Makris et al., 2007). In parallel with these changes in FA, histological studies have demonstrated local splitting of myelin and spherical cytoplasmic cavities or balloons within the myelin sheaths of elderly macaques (Feldman and Peters, 1998; Peters, 2002a; Peters, 2002b; Peters et al., 2000).

There are no published studies examining age-related changes in the WM microstructure in our closest living primate relative, the chimpanzee. Here, for the first time, DTI data were acquired from a large sample of chimpanzees (*Pan troglodytes*); and age-related changes in several DTI indices, including FA, RD, AD, and MD, were measured and compared between chimpanzees and rhesus macaques (*Macaca mulatta*) and contrasted with published data from humans (Westlye et al., 2010).

2. Methods

Both T1-weighted and diffusion-weighted MRI (dw-MRI) scans were collected from 32 chimpanzees (13.9–56.7 years) and 20 female rhesus macaques (9.2–26.6 years) on a Siemens 3T Trio Scanner (Siemens Medical System, Malvern, PA, USA). All chimpanzees and macaques were housed at Yerkes National Primate Research Center (YNPRC) in Atlanta, Georgia. All procedures were carried out in accordance with protocols approved by the YNPRC and the Emory University Institutional Animal Care and Use Committee (approval no. YER-2001206). T1-weighted images were used to compare age-related changes in brain size, as well as GM and WM volume, in chimpanzees and macaques. Diffusion-weighted images were used to compare age-related changes in WM microstructure in chimpanzees, macaques and human females (20.7–85.0 years). The human data consisted of 178 scans, representing a subsample from a previously published, large-scale human aging study (Westlye et al., 2010). In addition, to evaluate the effect of diffusion weighting (i.e., b value) on estimation of diffusion parameters, as well as to perform cross-species comparisons, diffusion-weighted images were collected from an additional 39 human females (21.0–61.0 years) with interspecies-matched b value on the Siemens 3T Trio. All human procedures were approved by the Emory University Institutional Review Board.