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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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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, 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.

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# 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.

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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  $\sim$ 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 nonhuman 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. Diffusionweighted 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 interspeciesmatched b value on the Siemens 3T Trio. All human procedures were approved by the Emory University Institutional Review Board.

# 2.1. Data acquisition

#### 2.1.1. Chimpanzees

Chimpanzee MRI scans were performed on the Siemens 3T Trio scanner with a standard birdcage coil routinely used for human head imaging. Chimpanzees were immobilized with ketamine (2-6 mg/ kg, i.m.) before being anesthetized with an intravenous propofol drip (10 mg/kg/h). Animals were under constant observation by the veterinary staff before, during, and after the scan. Head motion was minimized by stabilizing with foam cushions and elastic straps. A single-shot (SS), spin-echo (SE), echo planar imaging (EPI) sequence was used to acquire the dw-MRI from chimpanzees. A dual spin-echo technique combined with bipolar gradients was used to minimize eddy current artifacts (Alexander et al., 1997). Diffusion-weighting gradients were applied in 60 directions with a b value of 1000 s/ mm<sup>2</sup>, repetition time/echo time (TR/TE) of 5900/86 ms, field of view (FOV) of 130  $\times$  230 mm<sup>2</sup>, matrix size of 72  $\times$  128, partial Fourier option of 5/8, spatial resolution of  $1.8 \times 1.8 \times 1.8 \text{ mm}^3$ , 41 contiguous slices covering the whole brain. Margosian reconstruction (Margosian et al., 1986) was used to overcome the phase distortions in diffusion-weighted partial Fourier acquisitions. Diffusionweighted images with phase-encoding directions (left-right) of opposite polarity were acquired to correct for susceptibility distortion (Andersson et al., 2003). Eight averages of dw-MRI were collected to boost the signal noise ratio (SNR). For each average of diffusion-weighted images, 5 images without diffusion weighting  $(b = 0 \text{ s/mm}^2)$  were also acquired with matching imaging parameters. The total diffusion MRI scan time was approximately 60 minutes. High-resolution T1-weighted images were also acquired using a 3D magnetization-prepared rapid gradient-echo (MPRAGE) sequence. The T1 scan protocol, optimized for 3T, used the following imaging parameters: a repetition time/inversion time/echo time (TR/TI/TE) of 2600/900/3.06 ms, flip angle of 8°, volume of view of  $205 \times 205 \times 154$ mm, matrix of 256  $\times$  256  $\times$  192, and resolution of 0.8  $\times$  0.8  $\times$ 0.8 mm<sup>3</sup>, with 2 averages. Total T1 scan time was approximately 17 minutes.

# 2.1.2. Rhesus macaques

MRI scans of rhesus macaques were performed on the Siemens 3T, using the human knee coil. Macaques were immobilized with ketamine (2-6 mg/kg, i.m.) before being anesthetized with isoflurane (1%). Animals were under constant observation by the veterinary staff before, during, and after the scan. Head motion was minimized by stabilizing with foam cushions and elastic straps. A similar SS-SE EPI sequence was used to acquire the dw-MRI for macaques with identical diffusion directions and b values but a slightly different protocol. Diffusion-weighting gradients were applied in 60 directions with a b value of 1000 s/mm<sup>2</sup>; repetition time/echo time of 7000/108 ms, field of view of 141  $\times$  132 mm<sup>2</sup>, matrix size of 128  $\times$ 120, resolution of  $1.1 \times 1.1 \times 1.1 \text{ mm}^3$ , 43 slices with no gap, covering the whole brain. Averages of 10 sets of diffusion-weighted images with phase-encoding directions (left-right) of opposite polarity were acquired. For each average of diffusion-weighted images, 5 images without diffusion weighting ( $b = 0 \text{ s/mm}^2$ ) were also acquired, with matching imaging parameters. The total diffusion MRI scan time was approximately 86 minutes. High-resolution T1weighted images were also acquired using a 3D MPRAGE sequence. The acquisition parameters were as follows: TR/TI/TE of 2600/900/ 3.37 ms, flip angle of  $8^\circ$ , volume of view of  $160 \times 160 \times 88$  mm, matrix of  $320 \times 320 \times 176$ , and resolution of  $0.5 \times 0.5 \times 0.5$  mm<sup>3</sup>, with 3 averages. Total T1 scan time was approximately 25 minutes.

#### 2.1.3. Human subjects

A total of 39 human females underwent MRI scanning in Emory on a Siemens 3T with a 12-channel parallel imaging phase-array coil. Foam cushions were used to minimize head motion. Diffusion MRI data were collected with a diffusion-weighted SE-EPI sequence (Generalized Autocalibrating Partially Parallel Acquisitions [GRAPPA] factor of 2). A dual spin-echo technique combined with bipolar gradients was used to minimize eddy-current effects (Alexander et al., 1997). The parameters used for diffusion data acquisition were as follows: diffusion-weighting gradients applied in 60 directions with a b value of 1000 s/mm<sup>2</sup>; TR/TE of 8500/95 ms; FOV of 216  $\times$  256 mm<sup>2</sup>; matrix size of 108  $\times$  128; resolution of 2  $\times$  $2\times2$  mm^3; and 64 slices with no gap, covering the whole brain. Averages of 2 sets of diffusion-weighted images with phaseencoding directions of opposite polarity (left-right) were acquired to correct for susceptibility distortion (Andersson et al., 2003). For each average of diffusion-weighted images, 4 images without diffusion weighting ( $b = 0 \text{ s/mm}^2$ ) were also acquired with matching imaging parameters. The total diffusion MRI scan time was approximately 20 minutes. T1-weighted images were acquired with a 3D MPRAGE sequence (GRAPPA factor of 2) for all participants. The scan protocol, optimized at 3T, used a TR/TI/TE of 2600/ 900/3.02 ms, flip angle of 8°, volume of view of  $224 \times 256 \times 176$ mm<sup>3</sup>, matrix of 224  $\times$  256  $\times$  176, and resolution of 1  $\times$  1  $\times$  1 mm<sup>3</sup>, with 1 average. Total T1 scan time was approximately 4 minutes.

The 178 previously acquired human female scans were performed using a 12-channel head coil on a 1.5-T Siemens Avanto scanner (Siemens Medical Solutions, Erlangen, Germany) at Oslo University Hospital Rikshospitalet, Oslo, Norway. A single shot dual spin-echo EPI sequence was used for the diffusion-weighted MRI scan with 30 diffusion directions and a b value of 700 s/mm<sup>2</sup>. Further imaging technical details are described elsewhere (Westlye et al., 2010).

#### 2.2. Data processing

Both anatomical and diffusion MR data were analyzed using tools from the Oxford Center for Functional Magnetic Resonance Imaging of the Brain's software library (FSL, http://www.fmrib.ox. ac.uk/fsl/) (Smith et al., 2004).

#### 2.2.1. T1 structural image

T1-weighted images were preprocessed with skull stripping (BET with occasional manual intervention when necessary (Smith 2002)), intensity bias correction (FAST) (Zhang et al., 2001), noise reduction (SUSAN) (Smith and Brady, 1997), and contrast enhancement (squaring the images and then dividing by the mean). The preprocessed T1 was then classified into 3 tissue types, namely, GM, WM, and cerebrospinal fluid (CSF), using FAST. The volume of each tissue type was then estimated and brain size was calculated as the sum of GM plus WM. Pearson correlation coefficients between the GM/WM/brain volumes and age were calculated for both chimpanzees and macaques using SPSS (SPSS Inc., Chicago, IL, USA). Recent studies suggest that higher order polynomials are superior to straight line fits in describing the aging effect in humans, particularly for WM (Allen et al., 2005; Walhovd et al., 2005; Walhovd et al., 2011). For this reason, we also performed quadratic and cubic regressions to explore aging effects on GM and WM in chimpanzees. The best model was determined by evaluating the statistical significance of higher-order polynomial regression terms (Allen et al., 2005). Polynomial regressions were not performed on macaque data due to the lack of middle-aged macaques in our sample and the resulting discontinuous age distribution.

# 2.2.2. Diffusion-weighted MRI

*2.2.2.1. Preprocessing.* Diffusion MR data were first corrected for eddy-current distortion and for susceptibility distortion following the method of Andersson et al., using Matlab (Matlab7, Mathworks,

Needham, MA, USA) codes incorporated in SPM5 (http://www.fil. ion.ucl.ac.uk/spm/). DTIFIT was used to independently fit diffusion tensors to each voxel. Maps of FA, RD, AD, and MD were calculated accordingly for each subject.

2.2.2.2. Voxelwise analysis using tract-based spatial statistics. Voxelwise statistical analysis of the diffusion MR data was carried out for each species using tract-based spatial statistics (TBSS) implemented in FSL 4.1 (FMRIB, Oxford. http://www.fmrib. ox.ac.uk/fsl/). TBSS scripts were tailored to the needs of chimpanzee and macaque data processing. The primary modification to the scripts is the replacement of the FA template for the non-human primates (detailed below).

Each subject's FA data were first aligned into a common space using the nonlinear registration tool FNIRT (Andersson et al., 2007a; Andersson et al., 2007b), which uses a b-spline representation of the registration warp field (Rueckert et al., 1999). The common space, defined by an FA template, is specific to each species. For both chimpanzees and macaques, population-specific FA templates were respectively derived from previously acquired images on the same animals collected using a slightly different protocol. The template resolution is 0.8 mm isotropic for chimpanzees and 0.5 mm isotropic for rhesus macaques. The details of the protocol and the template generation can be found elsewhere (Li et al., 2011). For human subjects, the FSL self-contained FMRIB58\_FA template was used as the common space. These individual FA images were then averaged to create a mean FA image, which was thinned to generate an FA skeleton that represents the centers of tracts common to all individuals. The mean FA skeleton was thresholded and binarized at FA > 0.3 so as to include major white-matter pathways but to exclude minor tracts in which there was substantial intersubject variability and/or partial volume effects. Subsequently, individual FA maps were projected onto this mean skeleton mask by searching perpendicular from the skeleton for maximum FA values. Using maximum FA from the centers of the tracts further minimizes confounding effects due to partial voluming (Smith et al., 2006). The resulting tract-invariant skeletons for each individual were used in subsequent voxelwise cross-subject statistics. Similar warping and analyses were used on RD, AD, and MD data, yielding RD, AD, and MD skeletons sampled from voxels with FA > 0.3. The voxelwise cross-subject statistical analysis were performed using permutation-based inference (Nichols and Holmes, 2002), as implemented in the "randomize", part of FSL. We tested for linear and quadratic effects of age on FA, RD, AD, and MD with general linear models (GLMs). Threshold-free cluster enhancement (Smith and Nichols, 2009) was used to avoid the arbitrariness involved in setting smoothing levels and thresholds for cluster size inference. A total of 5000 permutations were performed for each contrast. Statistical *p* value maps were thresholded at p < 0.05, corrected for multiple comparisons across space.

2.2.2.3. Whole-skeleton analysis. After averaging the 4 DTI indices (FA, RD, AD, and MD) across the entire TBSS skeleton of each individual brain, we estimated the aging trajectory for both chimpanzees and macaques by regressing each mean DTI index against age with either a linear or a quadratic model. The preferred model was selected based on the Akaike Information Criterion (AIC; the lower the better) (Akaike, 1974; Bozdogan, 1987). Given the small sample sizes for chimpanzees (n = 32) and macaques (n = 20), a more lenient threshold of significance level (p < 0.1) was used for the model significance. We also compared the chimpanzee trajectory with that for 2 different samples of human females. One sample was restricted to the same absolute age range as chimpanzees (referred to as "Human<sub>R</sub>" below), whereas the other (Human<sub>C</sub>) spanned the entire human age range, except for individuals

younger than 20.7 years. An age of 20.7 years is the approximate human lifespan equivalent of the youngest chimpanzee in the sample, who was 13.9. We arrive at 20.7 by multiplying a scaling factor of 1.5 to 13.9. We choose 1.5 based on species differences in longevity and age of puberty onset. Chimpanzees in the wild normally die before age 45 (Hill et al., 2001), whereas human huntergatherers who survive to age 45 can expect to live an additional 20 years (Kaplan et al., 2000), with some surviving into their 80s (Blurton Jones et al., 2002). Chimpanzee puberty occurs around age 8 (Herndon, 2009), whereas human puberty begins around 12.5 years in modern, industrialized nations. However, the latter has decreased by 2 years or more over the last 150 years because of improvements in nutrition and public health, and the typical onset of menarche in traditional hunter-gatherer societies can be as late as age 17 (Howell, 1979). Thus, we believe that 1.5 is a conservative estimate of the extent to which chimpanzee lifespan must be stretched to match that of humans. Similarly, a scaling factor of 3 can be used in rhesus macaques for an equivalent human age because 1 year in the life of the macaque is commonly equated to 3 human years (Herndon, 2009; Tigges et al., 1988). We explored both human samples, restricted and complete, partly because it is still controversial as to whether human longevity results from the uniform expansion of typical hominid lifespan or the selective extension of the terminal part of the lifespan. Human<sub>R</sub> consists of 136 females aged 13.9-56.7 years. Human<sub>C</sub> consists of 178 women between the ages of 20.7 to 85 years. The aging trajectories for each DTI index were statistically compared pairwise across species using hypothesis tests. In comparing linear trajectories, the slope ( $\beta_1$ , assuming the model of  $Y = \beta_1 X + \beta_0$  difference between the regression lines was statistically tested using an "interaction" model, a 3-term linear model that includes species (dummy variable), age, and the interaction of species\*age. The slopes are considered different if the interaction term coefficient is significant. In the comparison of 2 quadratic trajectories, the curvature ( $\beta_2$ , assuming the model of  $Y = \beta_2^* X^2 + \beta_1^* X + \beta_0$ ) difference between the regression lines was statistically tested using a 5-term linear model that consists of species (dummy variable), age, the linear interaction term of species\* age, age<sup>2</sup>, and the quadratic interaction term of species\* age<sup>2</sup>. Curvature is considered different if the quadratic interaction term is significant. The curvature reflects the overall acceleration of the trajectory. For the quadratic trajectory, the extremum  $(-\beta_1/2\beta_2)$  as well as its 95% confidence interval (CI) were also estimated using the Delta method (Casella and Berger, 2002; Cramér, 1946). The extremum is thought to reflect the age when WM is most mature before senescence. Given that fitting of quadratic models may sometimes be substantially affected by seemingly irrelevant factors (Fjell et al., 2010), the same data were also fit with local smoothing spline to validate the quadratic fits and corresponding estimation of minima and maxima. This nonparametric spline fitting technique self-adaptively takes advantage of the local information and is thought to yield more robust results than fitting with quadratic curve, a global fit model. The technical details of local smoothing spline fitting can be found elsewhere (Fjell et al., 2010).

In addition, we explored the effect of diffusion MRI parameters, particularly the b value on the estimation of global mean DTI indices, and we compared the DTI indices across all 3 species. Different b values were used for our human (b = 700 s/mm<sup>2</sup>) and non-human primate scans (b = 1000 s/mm<sup>2</sup>), which raises a potential confound for the observed species differences. To address this concern, we added a smaller sample (39 females) of human scans (refer to as "Human<sub>b1000</sub>" below) acquired with b = 1000 s/mm<sup>2</sup> to match the b value of the nonhuman scans. To match the age range, we limited the sample of Human<sub>C</sub> to the age range 21.0 to 61.0 years, resulting in a new sample (Human<sub>b700</sub>) of 121

females. The effect of b value was then explored by performing a 2sample t test between human samples with different b values (Human<sub>b1000</sub> vs. Human<sub>c</sub>; Human<sub>b1000</sub> vs. Human<sub>b700</sub> respectively). We also performed cross-species (rhesus macaques vs. chimpanzees vs. Human<sub>b1000</sub>) comparison of DTI indices using 1-way analysis of variance (ANOVA) with Tukey adjustment.

All statistical tests were implemented using SPSS, along with customized Matlab scripts.

# 3. Results

# 3.1. Brain size versus age for chimpanzees and macaques

Fig. 1 illustrates age-related changes in the global brain, GM and WM volumes, respectively, for macaques (left column) and chimpanzees (right column). For both species, there was a marginally significant negative correlation between age and brain volume (chimpanzees r = -0.28 (p = 0.06), macaques r = -0.32 (p = 0.09)). Linear regression slopes indicate that female chimpanzee brains lose 0.74 cc ( $\sim 0.2\%$ ) per year, whereas female rhesus macaque brains lose 0.28 cc ( $\sim 0.3\%$ ) per year. Although there was no significant linear decrease in WM volume with age in either macaques or chimpanzees, GM volume significantly decreased in both species (for macaques, r = -0.45 (p = 0.023), slope = -0.29 cc/y ( $\sim 0.6\%$ ); for chimpanzees, r = -0.46 (p = 0.004), slope = -0.94 cc/y ( $\sim 0.4\%$ )). Given the evidence that human WM aging follows

a curvilinear trajectory (Allen et al., 2005; Walhovd et al., 2005; Walhovd et al., 2011), we also fit both cubic and quadratic models to chimpanzee WM volume. This revealed a marginally significant cubic trend (p = 0.08) in which WM began decreasing at the age of 44.4 years (~78% of the lifespan) (Fig. S1).

# 3.2. Age-related changes in mean DTI indices across entire brain WM skeleton

Fig. 2 illustrates the aging trajectories of FA, RD, AD, and MD, averaged across the entire WM skeleton, for rhesus macaques, chimpanzees, Human<sub>R</sub>, and Human<sub>C</sub>. Table 1 summarizes the estimations of the slope (if linear model is fit), or the curvature, extrema and its 95% CI (if quadratic model is fit) of the aging trajectories. Additional parameters of all aging models are summarized for each group in Table S1. The fits of local smoothing spline are illustrated in Fig. S3. Estimations of minima and maxima were compared between quadratic fits and local smoothing spline fits (Table S2).

# 3.2.1. FA trajectories

For rhesus macaques, mean FA decreases with age. For chimpanzees and both human samples, an inverted U-shaped curve better described the relationship between FA and age. For the restricted human sample (Human<sub>R</sub>), there was no difference between humans and chimpanzees in either the age of FA maximum, both species peaking at  $\sim$ 30 years (31.0 years for



Fig. 1. Age-related changes in whole brain, gray matter, and white matter volumes for rhesus macaques and chimpanzees.



**Fig. 2.** Aging trajectories of fractional anisotropy (FA; first row), radial diffusivity (RD; second row), axial diffusivity (AD; third row), and mean diffusivity (MD; fourth row) for rhesus macaques (first column), chimpanzees (second column), humans with same absolute age range as chimpanzee (third column), and humans with complete age range (fourth column). In the plots of rhesus macaques and chimpanzees, the equivalent human age (multiplying chimpanzee age by 1.5 and rhesus macaque age by 3.0) is given at the top of each plot.

chimpanzees, 29.9 years for Human<sub>R</sub>), or in the curvature (i.e., acceleration) of age-related change (Table 1). For the complete human sample (Human<sub>C</sub>), there was again no significant difference between human and chimpanzee FA maxima or acceleration (Table 1 and Supplementary Table S1 for details). Crucially, however, if the chimpanzee FA age maximum is rescaled by  $1.5 \times$  to predict the human FA age maximum based on the extended human lifespan, the rescaled chimpanzee maximum ( $31.0 \times 1.5 = 46.5$ ) lies above the Human<sub>C</sub> 95% CI [19.1–40.1], implying that deterioration of human WM microstructural integrity begins relatively earlier

(i.e., after a smaller proportion of the individuals' longer lifespan has been completed). In other words, the chimpanzee maximum is reached at approximately 55% of the captive lifespan (i.e., 57 years, the age of the oldest chimpanzee in our sample), whereas the human maximum is reached at about 35% of the lifespan (i.e., 85 years, the age of the oldest human participant in our sample). The peak age estimations using local spline fits are similar to those using quadratic fits for both chimpanzees and humans. For each species, the spline fit estimation falls into the 95% CI of corresponding quadratic fit estimation (Table S2).

Table 1
Summary of the quadratic model on the diffusivity change as a function of the age across species

	Macaque	Chimpanzee			Human <sub>R</sub>			Human <sub>C</sub>	
	$\beta_1~(\times 10^{-5})$	$\beta_1~(\times 10^{-5})$	$\beta_2~(\times 10^{-5})$	Extrema (95% CI)	$\beta_1~(\times 10^{-5})$	$\beta_2~(\times 10^{-5})$	Extrema (95% CI)	$\beta_2~(\times 10^{-5})$	Extrema (95% CI)
FA	-232.2	_	-5.239	30.97 [25.34–36.60]	_	-3.589	29.94 [26.03-33.84]	-1.957	29.59 [19.11-40.06]
RD	8505	_	611.0	31.94 [26.41-35.52]	_	275.1	32.02 [26.15-37.88]	516.3	39.66 [36.14-43.18]
AD	-22610	-3611	_	_	_	-190.7	15.62 [-12.34-43.59]	527.4	49.63 [47.50-51.76]
MD	-1883	_	457.0	33.55 [25.79-36.15]	-1334	_	—	519.1	43.02 [40.38-45.66]

Key: AD, axial diffusivity; FA, fractional anisotropy; MD, mean diffusivity; RD, radial diffusivity.

Linear model was used for macaques for all 4 parameters. Values of  $\beta_1$  or  $\beta_2$  are listed for chimpanzee and human, depending on the model selected ( $\beta_1$  for linear,  $\beta_2$  for quadratic).

Quadratic model:  $Y = \beta_2^* X^2 + \beta_1^* X + \beta_0$ . Linear model:  $Y = \beta_1^* X + \beta_0$ .

#### 3.2.2. RD trajectories

For rhesus macaques, mean RD increases with age. For chimpanzees and both human samples, a U-shaped curve better describes the relationship between RD and age. There is no difference between chimpanzees and the Human<sub>R</sub> group in the age at which RD is minimized (both ~32 years of age), or in the acceleration of age-related change (Tables 1 and S1). However, for Human<sub>C</sub>, RD is minimized at a later age (39.7 [36.1–43.2], ~47% of lifespan) than for chimpanzees (31.9 years, ~56% of lifespan). Nevertheless, the rescaled chimpanzee minimum (47.9 years) also lies above the Human<sub>C</sub> confidence interval, again suggesting that WM decline begins at a proportionally earlier age in humans. The peak age estimations of RD using local spline fits are similar to those using quadratic fits for both chimpanzees and humans (Human<sub>C</sub>). For each species, the spline fit estimation falls into the 95% CI of corresponding quadratic fit estimation (Table S2).

There was no significant difference in the acceleration of RD change between humans and chimpanzees.

# 3.2.3. AD trajectories

For rhesus macaques, mean AD decreases with age. For chimpanzees, there is no significant linear or quadratic relationship with age. For Human<sub>R</sub>, an inverted U-shape curve better models the relationship between AD and age, with peak AD at age ~ 15.6 years. For Human<sub>C</sub>, a U-shape curve better models the relationship between AD and age, with a minimum at ~49.6 years (~58% of lifespan).

#### 3.2.4. MD trajectories

Neither linear nor quadratic models were significant for chimpanzees' or rhesus macaques' MD trajectories, nor is either model significant for Human<sub>R</sub>. For Human<sub>C</sub>, a U-shape curve better describes the relationship between MD and the age, with a minimum at ~43.0 years.

# 3.3. Voxelwise analysis of age-related changes in DTI indices

# 3.3.1. Chimpanzees

Voxelwise TBSS analyses revealed very limited decreases in FA with age. Of the 36,778 skeleton voxels, only 350 (1.0%) voxels, concentrated in bilateral corticospinal tracts (CSTs)/superior corona radiata (SCR), show a significant linear decrease with age. In addition, 540 (1.5%) voxels, concentrated in right CST/SCR, superior longitudinal fasciculus (SLF), and left rostrum of the corpus callosum, exhibit a significant quadratic (inverted U-shape) relationship with age. Only 34 voxels, concentrated in the right CSTs/SCR, exhibit both linear and quadratic relationship with age (Fig. 3A, Supplementary videos).

In contrast to FA, age-related changes in RD were widespread, including the bilateral superior longitudinal fasciculus (SLF)/ arcuate fasciculus (AF), corticospinal tract (CST), splenium and rostrum of the corpus callosum, and the inferior longitudinal fasciculus (ILF) (Fig. 3B, Supplementary videos). Of the 36,778 skeleton voxels, 5887 (16.0%) showed a significant positive linear relationship with age, and 7771 (21.1%) voxels showed a significant U-shape relationship with age. A total of 2681 (7.3%) voxels showed both significant linear and significant quadratic age effects.

No significant linear or quadratic effects of age were found for either AD or MD.

Increases in RD, in the absence of significant changes in AD, should lead to decreases in FA. However, of 5887 voxels the RD of which linearly increases with age, only 349 (5.9%) voxels also demonstrate significant linear FA decrease. Furthermore, of 7771 voxels exhibiting quadratic RD age relationships, only 537 (6.9%) voxels also demonstrate significant quadratic FA age relationships.



**Fig. 3.** Voxelwise linear age-related changes in (A) chimpanzee fractional anisotropy (FA), (B) chimpanzee radial diffusivity (RD), (C) macaque FA, (D) macaque RD, (E) macaque axial diffusivity (AD), and (F) macaque mean diffusivity (MD). Blue and light blue indicate significant negative correlation, whereas red and yellow indicate positive correlation. Significant (TFCE corrected p < 0.05) voxels overlaid on the FA skeleton (green). The coordinate system is similar to Montreal Neurological Institute (MNI) space, with the anterior commissure as the origin. Significant clusters were dilated for improved visual clarity.

Thus, we repeated the FA analysis with a more liberal uncorrected threshold of p < 0.05. This revealed the expected widespread decreases in FA with age that overlap extensively with the significant changes in RD (4304 voxels for linear, 6461 voxels for quadratic; Fig. S2).

#### 3.3.2. Rhesus macaques

Voxelwise TBSS analysis in rhesus macaques revealed widespread age-related linear decreases in FA across most WM tracts, including most of the corpus callosum, extreme capsule (EC), anterior limb as well as the posterior limb of the internal capsule, SLF, fronto—occipital fasciculus (FOF), uncinate fasciculus (UF), ILF (Fig. 3C, Supplementary videos). Of 32,246 skeleton voxels, 15,221 (47.2%) showed a significant negative linear relationship with age. This pattern is similar to what has been previously reported in humans (Westlye et al., 2010). No significant quadratic age effects on FA were found for rhesus macaques, likely because of the absence of middle-aged rhesus macaques in our sample.

TBSS analysis also revealed widespread age-related increases in RD across most WM tracts, including the corpus callosum (except the rostrum), EC, posterior limb of the internal capsule, SLF, FOF, UF, and ILF (Fig. 3D, Supplementary videos). Of a total of 32,246 skeleton voxels, 9819 (30.4%) showed a significant positive linear relationship with age, and these overlapped extensively with significant decreases in FA. Consistent with the FA findings, however, no significant quadratic age effect on RD was found.

Only 1592 of 32,246 (4.9%) of the skeleton voxels showed a significant linear AD decrease with age, with most of them concentrated in the anterior limb of the internal capsule (Fig. 3E, Supplementary videos). Finally, 1069 of 32,246 skeleton voxels showed a significant MD decrease with age, with 1053 overlap with the significant AD voxels, indicating that AD is the driving force behind the MD changes (Fig. 3F, Supplementary videos). Like FA and RD, no significant quadratic age effect on AD or MD was found.

# 3.4. Species differences in global mean DTI metrics

Irrespective of age, there were species differences in DTI metrics that might shed light on species differences in WM organization. The observed species differences may have been exaggerated by differences in anatomical resolution and diffusion weighting. For example, our primary human sample was acquired with b = 700 s/mm<sup>2</sup>, whereas both chimpanzee and macaque scans were acquired with  $b = 1000 \text{ s/mm}^2$ . To quantify the influence of this discrepancy, we acquired a second but smaller sample of human subjects with  $b = 1000 \text{ s/mm}^2$ . In humans, increasing the b value from 700 s/mm<sup>2</sup> to 1000 s/mm<sup>2</sup> significantly reduced mean DTI metrics over the entire brain skeleton for all 4 indices (Fig. 4, dash line). Therefore, interspecies comparisons of global DTI metrics were conducted on all data with  $b = 1000 \text{ s/mm}^2$ . Collapsing across age, average FA was highest in humans, followed by chimpanzees and then rhesus macaques, although the difference between the latter 2 species was only marginally significant. Although both chimpanzees and humans had higher AD than rhesus macaques, they did not differ from each other in terms of AD. RD was highest in chimpanzees, followed by humans and then rhesus macaques (Fig. 4).

#### 4. Discussion

In this comparative study of brain aging, both chimpanzees and rhesus macaques exhibited significant decreases in GM volume with age. Although there was no change in macaque WM with age, there was a trend for a cubic effect involving late-life WM decline in chimpanzees. In both chimpanzees and humans, average FA across the entire WM skeleton had an inverted U-shaped relationship with age, whereas average RD had a U-shaped relationship. Both the FA maximum and the RD minimum for humans occurred earlier in the human lifespan than expected, based on the relative position of these events in the chimpanzee lifespan. In addition, humans but



**Fig. 4.** Comparisons of fractional anisotropy (FA), radial diffusivity (RD), axial diffusivity (AD), and mean diffusivity (MD) as a function of species and b value. *p* Values of the statistical tests are listed. Abbreviations: M, Rhesus macaques; C, Chimpanzees; H<sub>c</sub>, Human<sub>c</sub>; H<sub>b700</sub>, Human<sub>b700</sub>; H<sub>b1000</sub>, Human<sub>b1000</sub>.

not chimpanzees showed a U-shaped relationship between age and AD. Voxelwise TBSS revealed both widespread decreases in FA and widespread increases in RD in rhesus macaques. Chimpanzees also showed widespread increases in RD with age, with less pronounced but still widespread FA decreases with age (using uncorrected thresholds).

#### 4.1. Brain volume and age

For both chimpanzees and rhesus macaques, brain volume decreased marginally with age, and GM volume decreased significantly with age. Rhesus macaque brain volume declined at an annual rate of 0.28 cc, whereas GM declined at a rate of 0.29 cc. These findings are consistent with another macaque brain aging study (Andersen et al., 1999), in which brain volume was reported to decrease  $\sim 0.28$  cc/y whereas GM decreased at  $\sim 0.38$  cc/y. Andersen et al. also found a significant age-related linear increase in WM volume; however we found no such relationship in our data. One possible reason is that the significant linear increase of WM volume reported in (Andersen et al., 1999) was primarily driven by lower WM volumes in the younger, 5- to 7-year-old rhesus macaques, which, unfortunately, are missing in our sample.

A recent MRI study concluded that neither GM nor WM volume decreases with age in chimpanzees (Sherwood et al., 2011). In contrast, our results indicate significant age-related decreases in GM in female chimpanzees, a trend for late-life WM decline, as well as a trend for a decrease in total brain volume with age. Similarly, Herndon et al. (Herndon et al., 1999) found post-mortem brain weight to decrease with age in chimpanzees. Specifically, female chimpanzee brains lost weight at a rate of 0.79 g/y. Here, we found that female chimpanzees lost volume at a rate of 0.74 cc/y, which is equivalent to 0.77 g/y (0.74 \* 1.036 g/cc [the specific gravity of fresh brain tissue]). These 2 slope values, from 2 independent samples of chimpanzees, are statistically indistinguishable (p = 0.95). Sherwood et al. (Sherwood et al., 2011) suggest that the discrepancy between their results and those of Herndon et al. are likely due to Herndon et al.'s inclusion of very old chimpanzees, in their 50s. Indeed, when we remove all 3 chimpanzees in their 50s from our data set, the r value changes from -0.28 to -0.14, and the trend for a decline in overall brain volume is lost (the *p* value increases from 0.06 to 0.23). Moreover, the cubic trend in chimpanzee WM is driven by these 3 chimpanzees in their 50s. However the significant decline in GM persists even after removal of these 3 animals (r changes from -0.46 to -0.39, and p value increases from 0.004 to 0.018). Sherwood et al. pooled data from chimpanzees scanned at both 3T and 1.5T and then appropriately included scanner type as a confounding variable in their regression model. All of our scans were acquired at 3T. The 3T scans afford better contrast to noise, and may yield more accurate segmentations on which volumetric measures are based. When we re-analyze their data (provided in their supplementary spreadsheet) from female chimpanzees scanned at 3T only, we also observe a significant age-related decrease in GM with a slope (-0.86 cc/y) similar to ours (-0.94 cc/y). This trend is not observed among the Sherwood et al. chimpanzees scanned at 1.5T. The discrepancy in results could thus be due to differences in field strength and the resulting segmentation. We believe that the similar findings of Herndon et al. (Herndon et al., 1999), the reanalysis of the Sherwood et al. 3T data, and our own data support the conclusion that there is an age-related linear decrease in GM volume in chimpanzees. If very old chimpanzees in their 50s are included, there may also be a decline in WM and overall brain volume. Female chimpanzee WM decline begins at age ~44.4 years. However, in the wild, few if any chimps live that long. Human female decline begins in the early 50s (Allen et al., 2005; Westlye et al., 2010). If human decline occurred at the same relative

lifespan position as chimpanzees, it would be expected to start at about age 66.6 years (44.4\*1.5). Thus, WM decline begins at a relatively earlier age in humans, resulting in more time for atrophy before death (Fig. 5).

Further analysis of the Sherwood et al. database also reveals a statistically significant decrease in brain volume among male chimpanzees scanned at 3T, even in the absence of animals in their 50s (n = 14, p = 0.011), with a loss of 2.10 cc/y. This rate of decline is significantly greater (p = 0.04) than for their 3T female sample (slope = -0.80 cc/y). These data suggest that male chimpanzees are more susceptible to age-related brain atrophy than are female chimpanzees. This may be a more general characteristic of chimpanzee aging, as the life expectancy of male chimpanzees is shorter than that of female chimpanzees (Herndon et al., 1999).

#### 4.2. Whole-skeleton DTI metrics and age

Although humans have a longer lifespan than chimpanzees (Hawkes, 2004; Herndon, 2009; Kaplan et al., 2000), reproductive senescence occurs at about the same absolute age in the 2 species (Herndon, 2009). Similarly, we find that FA begins its decline at about the same absolute age in the 2 species ( $\sim$  30 years). Although



**Fig. 5.** Schematic representation of macro and microstructural brain aging for (A) chimpanzees and (B) humans. Red triangle indicates the onset of age-related decline. Trajectories of chimpanzee gray matter (GM)/ white matter (WM)/ fractional anisotropy (FA) are based on fitted equations from our study. Trajectory of human FA is also based on the fitted equations from our study. Trajectories of human GM/WM are based on equations from Allen et al., 2005. We use 80 years as the life expectancy of modern humans (Oeppen and Vaupel, 2002; Vaupel et al., 1998). We adopted 41 years as a liberal estimate of the life expectancy of chimpanzees that survive to adulthood. Although the median lifespan of captive chimpanzees is 26 years, in 1 sample of 89 captive chimpanzees, 20 lived into their 40th year (Herndon, 2009). Using a more conservative (lower) estimate of the chimpanzee life expectancy would further strengthen our conclusions.

RD begins increasing at a later age in humans (40 years vs. 32 years for chimpanzees), the human decline begins at a proportionally earlier point in lifespan (46.7% vs. 56.3%). FA decreases and RD increases are well-documented correlates of human aging that are believed to reflect a decrease in WM integrity (Buchel et al., 2004; Pfefferbaum and Sullivan, 2003; Sullivan et al., 2006a; Sullivan and Pfefferbaum, 2006; Westlye et al., 2010). RD increases, in particular, have been linked with age-related myelin loss (Song et al., 2002; Tyszka et al., 2006, but see Wheeler-Kingshott and Cercignani, 2009). Our finding that these 2 markers of WM integrity begin their decline at a relatively earlier point in the human as compared to the chimpanzee lifespan implies that humans have more time to accumulate damage before death (Fig. 5). Thus, the oldest humans may experience more myelin loss, and therefore greater neural transmission delays, than the oldest chimpanzees. Sherwood et al. (Sherwood et al., 2011) suggest that GM and WM volume decrease in humans only after the age at which the chimpanzee lifespan ends. The situation is different for the measures of WM integrity used here, particularly FA, which begins its decline in humans at a time point before the end of the chimpanzee lifespan. In light of the above, one hypothesis as to why neurodegenerative diseases are rare in non-human primates is that the shorter chimpanzee life expectancy does not leave sufficient time for WM to deteriorate to the extent that neurodegenerative disease is explicitly manifest. Interestingly, several genes involved in synaptogenesis are expressed at higher levels in human compared with non-human primate prefrontal cortex (Caceres et al., 2007; Liu et al., 2012). Increased synaptogenesis entails higher metabolic rates, which may lead to greater oxidative stress and myelin damage (Bartzokis, 2004; Kregel and Zhang, 2007; Preuss, 2011).

Unlike FA and RD, the quadratic AD trajectories estimated for Human<sub>R</sub> and Human<sub>C</sub> have opposite curvatures, which likely reflects the sensitivity of the quadratic model to the sampled age span. Local spline fits generated more consistent results in the 2 human samples, exhibiting AD decline during the early portion of the lifespan and increase during the later portion (Fig. S3). The AD trajectory of chimpanzees is similar to that of the humans, except that the late increase of AD was absent. The cellular significance of these AD changes is unclear at this time, although AD has been hypothesized to track both fiber density and diameter (Kumar et al., 2012; Song et al., 2003; Tyszka et al., 2006).

For rhesus macaques, the linear model fit the data better in all cases. However, this could well be attributed to the lack of middle-aged as well as young adult (aged <8 years) rhesus macaques in our sample, as extrapolations from humans and chimpanzees led us to expect WM quality to peak in middle-age. Nevertheless, like humans (Pfefferbaum and Sullivan, 2003; Sullivan et al., 2006a; Sullivan and Pfefferbaum, 2006; Westlye et al., 2010), and as reported previously (Makris et al., 2007), rhesus macaques show clear decreases in FA and increases in RD with age. These findings are consistent with histological studies that have demonstrated local splitting of myelin and spherical cytoplasmic cavities or balloons within the myelin sheaths of elderly rhesus macaques (Feldman and Peters, 1998; Peters, 2002b; Peters et al., 2000).

#### 4.3. Voxelwise analysis of age-related changes in DTI metrics

Similar to humans, rhesus macaques showed widespread agerelated decreases in FA and increases in RD. Two region-specific patterns of age-related changes, reported in previous human studies (Bennett et al., 2010; Burzynska et al., 2010), were also found in our rhesus macaque sample. More than half of the voxels showing age-related decreases in FA are accompanied by increases in RD only. A mere 106 of 15,221 (0.7%) voxels, concentrated on anterior limb of the internal capsule, exhibit a second pattern characterized by simultaneous RD increase and AD decrease. Chimpanzees also showed widespread age-related increases in RD, but did not show widespread significant decreases in FA at a conservative statistical threshold that corrects for multiple comparisons. However, when the threshold was relaxed to p < 0.05 uncorrected, the expected age-related decreases in FA were widespread. Only 1 pattern (increased RD without significant change in AD) was observed in chimpanzees. We speculate that the RD increases found in both rhesus macaques and chimpanzees reflect age-related myelin loss and myelin damage.

# 4.4. Species differences in average DTI metrics

Increasing the b value from 700 s/mm<sup>2</sup> to 1000 s/mm<sup>2</sup> significantly reduced mean DTI metrics over the entire brain skeleton for all 4 indices. These findings (for FA and MD at least) are consistent with previous in vivo human DTI calibration studies (Bisdas et al., 2008; Farrell et al., 2007; Hope et al., 2012) as well as predictions from some theoretical studies primarily based on simulations (Anderson, 2001; Jones and Basser, 2004). Indeed, both b value and SNR will affect DTI metrics (Anderson, 2001; Farrell et al., 2007; Jones and Basser, 2004). Specifically, within the range of the moderate b values (b  $< 1000 \text{ s/mm}^2$ ), FA is predicted to decrease with the increasing b value and SNR (Hope et al., 2012; Jones and Basser, 2004). Acquired on a 3T with 60 directions, 2 averages and a b value of 1000 s/mm<sup>2</sup> in about 20 minutes, our Human<sub>b1000</sub> data have not only higher b value but also higher SNR compared with the Human<sub>b700</sub> data, which were acquired on a 1.5T with 30 directions, 2 averages and a b value of 700 s/mm<sup>2</sup> in about 11 minutes (Westlye et al., 2010). Hence our observation of lower FA for Human<sub>b1000</sub> confirmed this simulation–based prediction. On the other hand, although MD is relatively robust to the variation of SNR (Farrell et al., 2007; Hope et al., 2012), it changes with the b value. The b value effect on MD is primarily driven by the variation of the component with high diffusivity values (Jones and Basser, 2004). Higher b value predicts reduced MD. This prediction is consistent with the lower MD observed in Human<sub>b1000</sub>. Given that MD is significantly reduced for Human<sub>b1000</sub>, we believe that the b value played a more dominant role here than SNR in affecting the diffusivity metrics.

Collapsing across age, average FA was highest in humans, followed by chimpanzees and then rhesus macaques, although the difference between the latter 2 species was only marginally significant. Although both chimpanzees and humans had higher AD than rhesus macaques, they did not differ from each other in terms of AD. RD was highest in chimpanzees, followed by humans and then rhesus macaques (Fig. 4). One possible explanation for these findings may relate to species difference in brain size. Brain size increases from rhesus macaques to chimpanzees to humans. One cost of increasing brain size is that axons must propagate action potentials over a greater distance (Harrison et al., 2002), which slows transmission time (Ringo, 1991; Ringo et al., 1994). This can be overcome to some extent by either increasing axonal caliber (cross-sectional area) or increasing myelination (Changizi, 2001; Harrison et al., 2002; Wang et al., 2008). Average axon crosssectional area steadily increases with increasing brain size (Wang et al., 2008). Given that rhesus macaques have the smallest brain, they can afford smaller-caliber axons, which results in low AD. The insignificant AD difference between chimpanzee and human may reflect the lack of a difference in axon caliber between the 2 species. Instead, the human brain may compensate for its increased size by increasing myelination which results in lower RD than that found in chimpanzees. Following this interpretation, it is somewhat surprising that rhesus macaques have the lowest mean RD even though they have the smallest brain volume. This might be because the slim axons are more densely packed in the rhesus macaque brain. Assuming an average axon diameter of 1 µm (Wang et al., 2008), a mean RD of 40  $\times$  10<sup>-5</sup> mm<sup>2</sup>/s, and a diffusion time of 50 ms, a rudimentary estimation indicated that water molecules can diffuse over a distance spanning the cross section of 6 axons and encounter several dozens of myelin sheaths and membranes over the given diffusion time (Beaulieu and Allen, 1994). Thus, even if the axons in rhesus macaque brains have less myelination than chimpanzees and humans, it is still possible that water molecules experience more hindrance due to more compact axon packing, resulting in overall lower RD. We acknowledge, however, that the neural basis of the anisotropic water diffusion in the brain is highly complex, being influenced by myelin sheath, axon caliber, axon density, extracellular spacing, and various membrane permeability (Beaulieu, 2002) that may all vary greatly across the 3 species. The explanations that we suggest for species differences in DTI metrics are necessarily speculative and require histological validation.

As SNR of the diffusion MRI data (rhesus macaques, chimpanzees, and Human<sub>b1000</sub>) are similar across the 3 species (SNR ~ 30 for diffusion-weighted images), it is unlikely to be the source of the cross-species differences in the DTI measures.

#### 5. Study limitations and conclusions

In this study, for practical reasons, we used a cross-sectional rather than a longitudinal design. Thus, our study reveals differences between individuals of various ages rather than age-related changes within individuals. In addition, the effects of age on brain anatomy should be studied as a continuous process, and only a part of the story is captured if distinct age ranges are compared. In our study, the chimpanzee sample has a relatively continuous age distribution, but the rhesus macaque sample lacked middle-aged as well as young adult individuals. Moreover, rearing history can have an impact on brain development and subsequent anatomy (Sanchez et al., 1998; Schenker et al., 2005). Hence our findings based on captive primates may be confounded by the effect of various rearing histories and should be extrapolated to wild primates with caution. Finally, the quadratic models relied upon in this study assume a constant curvature or rate of brain aging. This assumption may not necessarily be true in the real world. Very likely, brain aging may be "characterized by steep increase in development, slow decline during adulthood, and then a sharper decline in older age" (Fjell et al., 2010). Quadratic model fits will not be able to fully describe such changes. More sophisticated models, such as the local smoothing spline (Fjell et al., 2010), can extract more relevant information. Nevertheless, we provide both quadratic and local smoothing spline models, and show that these differ little in their estimation of the age at which DTI metrics reach their minima or maxima, although exceptions exist.

With respect to the MR imaging techniques, although it is ideal to acquire the diffusion MR data with as high resolution as possible, the voxel dimensions for rhesus macaques (1.1 mm isotropic), chimpanzees (1.8 mm isotropic) and humans (2.0 mm isotropic) were chosen as a compromise between scanner hardware, brain anatomy of each species, and scan time permitted by Yerkes veterinarians. To equate partial volume effects (PVE) to those of human data with 2.0-mm isotropic voxels, the resolutions are estimated to be 1.4 mm isotropic for chimpanzees and 0.8 mm isotropic for rhesus macaques. However, acquiring diffusion data with such spatial resolution and sufficient SNR is too challenging with our current hardware. Fortunately, the major aims of the study are (1) to derive the changes in DTI-based measures (e.g., FA, RD) with age within each species; and (2) to compare the trends of the aging process across species instead of the absolute values.

Furthermore, TBSS takes FA (and other DTI metrics) from the tract skeleton in a way that claims to be unaffected by PVE, which is strictly true for those main tracts wider than the relevant voxel dimension (Smith et al., 2006). For thinner tracts, the skeleton FA will be somewhat affected by the PVE. However, with an elevated FA threshold of 0.3 (the threshold that we used in the study), the proportion of PVE affected tracts will not likely be sufficiently high to significantly alter our major findings in cross-species comparison. Hence, although the observed species differences may have been exaggerated by inconsistent PVE in the worst possible scenario, major conclusions in our study should not be significantly altered.

To summarize, similar to results from previous human brain aging studies, both chimpanzees and rhesus monkeys exhibited significant decreases in GM volume with age. On the other hand, WM volume did not decrease with age in either species as assessed by linear models. However, when high-order polynomial models were fit, there was a suggestion that, like humans, chimpanzees show a late-life decline in WM volume. This decline occurs relatively earlier in the human as compared to the chimpanzee lifespan. Also similar to previous human studies, voxelwise analysis of diffusion MRI data revealed widespread age-related decreases in FA and increases in RD in both chimpanzees and rhesus macaques, although FA effects were more pronounced in rhesus macaques. In both chimpanzees and humans, average FA across the entire WM skeleton had an inverted U-shaped relationship with age, whereas average RD had a U-shaped relationship. Similar to WM volume findings, both the FA maximum and the RD minimum for humans occurred earlier in the human lifespan than expected based on the relative position of these events in the chimpanzee lifespan, suggesting that humans have more time for WM to deteriorate before death. Thus, even though overall patterns of GM and WM aging are similar in humans and chimpanzees, the longer lifespan of humans provides more time for WM to deteriorate before death (Fig. 5), with the result that some neurological effects of aging may be exacerbated in our species.

### **Disclosure statement**

No authors have any actual or potential conflicts of interest to disclose.

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#### Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neurobiolaging. 2013.03.028.

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