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Fractional Anisotropy of Cerebral White Matter and Thickness of Cortical Gray Matter across the Lifespan

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Abstract

We examined age trajectories of fractional anisotropy (FA) of cerebral white matter (WM) and thickness of cortical gray matter (GM) in 1,031 healthy human subjects (aged 11-90 years). Whole-brain FA and GM thickness values followed quadratic trajectories with age but the relationship between them was linear, indicating that a putative biological mechanism may explain the non-linearity of their age trajectories. Inclusion of the FA values into the quadratic model of the whole-brain and regional GM thickness changes with age made the effect of the age² term no longer significant for the whole-brain GM thickness and greatly reduced its significance for regional GM thickness measurements. The phylogenetic order of cerebral myelination helped to further explain the intersubject variability in GM thickness. FA values for the early maturing WM were significantly better ($p=10^{-6}$) at explaining variability in GM thickness in maturing (aged 11-20) subjects than FA values for the late maturing WM. The opposite trend was observed for aging subjects (aged 40-90) where FA values for the late maturing WM were better ($p=10^{-16}$) at explaining the variability in GM thickness. We concluded that the non-linearity of the age trajectory for GM thickness, measured from T1-weighted MRI, was partially explained by the heterogeneity and the heterochronicity of the age-related changes in the microintegrity of cerebral WM. We consider these findings as the evidence that the measurements of age-related changes in GM thickness and FA are driven, in part, by a common biological mechanism, presumed to be related to changes in cerebral myelination.

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Introduction

The human cerebrum is a complex, multi-compartmental structure that undergoes continuous, nonlinear changes over the lifespan and its age-related trends follow a specific anatomic sequence and (Gogtay et al., 2004; Kochunov et al., 2010b; Sowell et al., 2003; Yakovlev and Lecours, 1967). A basic structural compartmentalization of the brain can be achieved by separating the cerebrum into white matter (WM) and gray matter (GM) compartments. Each compartment exhibits characteristic age-related changes, some of which may be measured using non-invasive imaging, yielding quantitative indices of cerebral integrity. Integrity of cerebral WM is commonly assessed using fractional anisotropy (FA) of water diffusion, while the integrity of cortical GM is assessed using cortical GM thickness. FA, calculated from diffusion tensor imaging (DTI) data, describes the directional selectivity of the random diffusion of water molecules (Beaulieu, 2002). Absolute WM FA values are sensitive to many parameters including myelin content, intra-voxel axonal crossing and axonal fiber density and diameter (Beaulieu, 2002). Even so, changes in regional FA values during lifespan are presumed to be due to changes in cerebral myelin levels and myelin packing (Madler et al., 2008; Song et al., 2003; Song et al., 2005). GM thickness is calculated as the distance from the outer cortical surface to the inner cortical WM-GM boundary (Fischl and Dale, 2000), or a related symmetric measure (Lerch and Evans, 2005). GM thickness is an indirect measure of a complex cortical architecture with changes in cortical myelination, synaptic pruning and cell density being the candidate cellular events responsible for its age-related changes during normal maturation and aging (Huttenlocher and Dabholkar, 1997).

Cerebral FA and cortical GM thickness follow quadratic, inverse-U, trajectories with age, indicating that at some point cerebral maturation is overtaken by effects of cerebral aging (Gogtay et al., 2004; Kochunov et al., 2010b; Salthouse, 2009; Sowell et al., 2003). These age trajectories are regionally heterochronic, proceeding largely in the phylogenetic order (i.e. the sequence in which they appear during evolution) with the maturation of the motor and sensory areas preceding the maturation of the associative areas (Gogtay et al., 2004; Kochunov et al., 2010b; Westlye et al., 2010a). In his 1901 manuscript (Flechsig, 1901), Fleschig suggested that cerebral myelination plays an important role in heterochronicity of the developmental and aging processes. He identified that the areas responsible for primary motor and sensory functions are the earliest to begin myelination, achieve full myelination in childhood and show little age-related decline during aging. In contrast, cerebral areas responsible for higher order cognitive function reach peak myelination in the adulthood and show signs of age-related decline soon thereafter. Fleschig's findings were later confirmed by cross-sectional and longitudinal DTI studies. The early developing, sensory and motor WM areas were shown to reach asymptotic FA values soon after birth, while the FA values for the multimodal WM continued to increase until the 3rd-to-4th decades of life (Gao et al., 2009; Kochunov et al., 2010b; Lebel et al., 2010; Lebel et al., 2008). During aging, FA values for the multimodal WM declined at much higher rates than these for the sensory and motor areas (Fjell et al., 2008; Flechsig, 1901; Hasan et al., 2009b; Kochunov et al., 2010b; Lebel et al., 2010; Lebel et al., 2008).

Several recent studies that analyzed changes in cortical GM thickness with age during maturation and aging suggested that changes in WM integrity are potentially responsible for both the non-linearity of its trajectory with age and phylogenetic order of cortical maturation (Kochunov et al., 2008; Sowell et al., 2004; Westlye et al., 2010a). Yet, this relationship has not been tested directly. Additionally, peak GMT occurs near puberty, preceding the peak of cerebral myelination by two decades (Gogtay et al., 2004), making the relationship between gray-matter thickness and white matter microintegrity unclear.

We attempted to clarify this relationship in a large population of subjects ranging in age from 11 to 90. The first hypothesis was that the age-related changes in microstructural integrity of cerebral WM is responsible for the non-linearity of age-related trajectory of GMT. Further, we hypothesized that the phylogeny of WM development is responsible for heterochronicity of GMT trends. We tested if the FA values of early maturing WM tracts could explain more intersubject variability in GMT than the FA values for late-maturing WM tracts in younger individuals. Likewise, we tested if that the average FA values for would have higher explanatory power for understanding variability in GMT among older individuals.

Materials and Methods

Subjects

Analyses were performed on data from 1,031 (416 males/615 females) healthy subjects recruited from the San Antonio, Texas, metro area. Subject's age ranged from 11 to 90 years, average age = 38.4 ± 19.1 years (Figure 1). Among them, 710 subjects (average age = 43.2 ± 15.6 , aged 11 to 85 years) were from 127 families with the average family size = 5.6 ± 6.9 subjects per family, ranging from 2 to 37 individuals. Subjects were excluded for MRI contraindications, history of psychiatric or neurological illnesses, substance abuse, stroke or other major neurological event. All experiments were performed with IRB approval from the University of Texas Health Science Center at San Antonio (UTHSCSA). All subjects signed an informed consent. For minors, children and their parents signed assents and informed consents, respectively.

MR imaging—Imaging data were collected using a Siemens 3T Trio scanner located at the Research Imaging Institute, UTHSCSA.

T1-weighted imaging: This study used an MRI protocol specifically optimized for GM thickness measurements (Kochunov and Davis, 2009). The average GM thickness of the human cerebral cortex is approximately 2.5mm, regionally variable from 1.8-3.2 mm, and therefore high spatial resolution is necessary for accurate mapping of the intersubject GM thickness differences (Fischl and Dale, 2000). The protocol was designed to collect data to resolve the cortical ribbon across to cortex using isotropic spatial resolution of 0.8mm, voxel size = 0.5mm^3 . T1-weighted contrast was achieved using a magnetization prepared sequence with an adiabatic inversion contrast-forming pulse (scan parameters: TE/TR/TI = 3.04/2100/785 ms, flip angle = 11 degrees). A retrospective motion-correction technique (Kochunov et al., 2006) was used to reduce subject motion-related artifacts.

Diffusion tensor imaging: Diffusion tensor images were collected using a single-shot, echo-planar, single refocusing spin-echo, T2-weighted sequence with a spatial resolution of $1.7 \times 1.7 \times 3.0\text{mm}$. The sequence parameters were: TE/TR = 87/8000ms, FOV = 200mm, axial slice orientation with 50 slices and no gaps, 55 isotropically distributed diffusion weighted directions, two diffusion weighing values $b=0$ and 700 s/mm^2 and three $b=0$. These parameters were calculated using an optimization technique that maximizes the contrast to noise ratio for FA measurements (Jones et al., 1999).

Data Processing

Processing of T1-weighted images—Details for the processing of the T1-weighted images are discussed elsewhere (Figure 2) (Kochunov et al., 2007). Briefly, the processing consisted of removing non-brain tissues, global spatial normalization and radio frequency (RF) inhomogeneity correction. Non-brain tissues such as skin, muscle and fat were removed using an automated skull stripping procedure and images were corrected for radio-

frequency (RF) inhomogeneity (Smith et al., 2004). Next, images were imported into a freely distributed, structural analysis package, BrainVisa (<http://www.nitrc.org/projects/brainvisa>) and processed using its cortical extraction and parcellation pipelines, as described by Kochunov and colleagues (2005). This pipeline extracts the pial and GM/WM interface surfaces, performs extraction, labeling and verification of sulcal surfaces as described by Mangin and colleagues (Mangin et al., 2004), and segments the cortical landscape into 15 cortical regions using the primary sulcal structures (Cachia et al., 2003; Kochunov et al., 2009b). For the frontal lobe these regions included: superior, intermediate, inferior frontal and pre-central gyri and orbitofrontal area. Parietal lobe was segmented into the post-central gyrus and superior and inferior parietal lobules. Temporal lobe was segmented into superior, intermediate and inferior temporal gyri and the fusiform gyrus. Occipital lobe was segmented into lateral and medial occipital areas. Limbic lobe was segmented into the cingulate and parahippocampal gyri.

Measurements of cortical gray matter thickness

GM thickness (GMT) is commonly defined as the distance from the outer cortical surface to the inner cortical WM-GM boundary (Figure 2 D,H). Computationally, cortical thickness is determined by measuring the distance between two polygonal meshes, one representing the pial cortical surface and the other the white-gray interface. Multiple GMT measurements algorithms have been proposed to deal with the complex topography of the cerebral cortex. We used a GMT measurement tool distributed as a plug-in for BrainVisa (http://www.nitrc.org/projects/brainvisa_ext). This tool uses a “normal-average” algorithm that has been reported to be a good compromise between accuracy and performance (Lerch and Evans, 2005). The GMT is measured as the Euclidian distance from an inner mesh vertex to the outer mesh along the direction normal to the inner mesh polygon. The measurement is repeated, inward, along the direction normal the outer mesh and the two distances are averaged (Kochunov et al., 2008). The consistency of the distance measurements is insured by a verifying that the line that connects the two surfaces does not intersect any other polygons, inner or outer, along the way. GMT measurements were averaged for individual cortical areas for both hemispheres; the whole-brain GMT measurement was obtained by averaging bilateral gyral GMT measurements.

Processing of diffusion-weighted images—Details for the processing of DTI scans are discussed elsewhere (Kochunov et al., 2007). In short, the tract-based spatial statistics (TBSS) software (Smith et al., 2006) was used for multi-subject analysis of fractional anisotropy images. FA images were created by fitting the diffusion tensor to the raw diffusion data (Smith SM, 2002). All FA images were nonlinearly aligned to a group-wise, minimal-deformation target (MDT) brain (Kochunov et al., 2001). Next, individual FA images were averaged to produce a group-average anisotropy image. This image is used to create a group-wise skeleton of WM tracts which encodes the medial trajectory of the WM fiber-tracts. Finally, FA values from each image were projected onto the group-wise skeleton of WM structures. This step accounts for residual misalignment among individual WM tracts. FA values are assigned to each point along a skeleton using the peak value found within a 20mm distance perpendicular to the skeleton. The FA values vary rapidly perpendicular to the tract direction but very slowly along the tract direction. By assigning the peak value to the skeleton, this procedure effectively maps the center of individual WM tracts on the skeleton.

Tract-based analysis

Whole-brain average FA values were calculated by averaging values for the entire total WM skeleton. Average FA values were also calculated for eleven major WM tracts (Table 1) as described elsewhere (Kochunov et al., 2010a; Kochunov et al., 2010b). Briefly, the

population-based, 3D, DTI cerebral WM tract atlas developed in John Hopkins University (JHU) and distributed with FSL (Wakana et al., 2004) was used to calculate population average diffusion parameter values along eleven major WM tracts (Table 1, Figure 3). The JHU atlas was non-linearly aligned to the MDT brain and labels for individual tracts transferred to the MDT brain using nearest-neighbor interpolation. Per-tract average values were calculated by averaging the values along the tracts in both hemispheres. The overall average FA values were calculated by averaging values for the entire WM skeleton.

Selection of early and late maturing WM tracts

We made the selection of early versus late maturing WM tracts based on the rates of age-related maturation (FA/year) reported in (Kochunov et al., 2010b) (Table 1). These rates were calculated by fitting FA measurements between the 2nd and 4th decades of life using a simple linear model (Kochunov et al., 2010b). The rates of age-related decline were calculated in a similar way. The rates of age-related maturation are significantly correlated with the rate of age-related decline ($r=0.74$; $p=.01$) (Kochunov et al., 2010b) indicating that the late maturing WM tract show larger age-related decline in FA values.

Statistical analysis

A large number (710) of our subjects had relatives who also participated in this study. Familial similarity among subjects can violate the assumption of sample independence underlying many statistical techniques. Accordingly, the effects of familial aggregations were modeled using a general linear mixed effects (GLME) model. A GLME model partitions the intersubject variance into (1) effects of covariates or fixed effects and (2) mixed effects associated with familial dependencies. Theoretically, modeling familial aggregations using the GLME model makes the results representative of those that would be obtained using a sample of unrelated subjects.

The fixed effects of age and gender for FA and GMT measurements were modeled using a model proposed by Westlye and colleagues (Westlye et al., 2010a). This model includes the effects of age, age², sex, and sex*age interactions and can account for a potential second order or quadratic trend by age. We tested the hypothesis by nesting the quadratic model for GM thickness with FA values and evaluating the significance of the goodness of fit between the base and nested models. The goodness of fit was assessed using the logarithm of the likelihood (Λ) values (Simel et al., 1993). The difference in fit quality between the base and nested models was assessed using the likelihood ratio test or D-test (McGee, 2002). D-values were calculated as twice the difference between the logarithms of likelihood values for each model. Their significance was tested using a chi-square reference distribution (Simel et al., 1993).

GLME models—First, the whole-brain-average and regional FA and GM thickness values were modeled as a quadratic function of age and sex (as in equation 1).

$$X_{i,j} = \tilde{A} + \beta_{age} Age_{i,j} + \beta_{age^2} Age_{i,j}^2 + \beta_{sex} Sex_{i,j} + \beta_{age,sex} Age_{i,j} \cdot Sex_{i,j} + \alpha_{i,j} \quad (1)$$

Here $X_{i,j}$ is the dependent variable, $FA_{i,j}$ or GM thickness i,j , for the “jth” subject from the “ith” family, $\tilde{A}$ is the constant (mean) term, the β s are the covariate regression coefficients for each covariate and $\alpha_{i,j}$ is a coefficient that accounts for random effects. This modeling was performed with the [R] package (R-Development-Core-Team, 2009) using the linear mixed effects model library and the maximum likelihood estimation algorithm (Pinheiro et

al., 2008). Next, a nested model was created by expanding the base model to include the effects of the individual differences in the $FA_{i,j}$ values, equation 2.

$$GMT_{i,j} = \alpha + \beta_{age} Age_{i,j} + \beta_{age^2} Age_{i,j}^2 + \beta_{sex} Sex_{i,j} + \beta_{age,sex} Age_{i,j} \cdot Sex_{i,j} + \beta_{FA} FA_{i,j} + \alpha_{i,j} \quad (2)$$

The nested model was also used to evaluate statistical effects of the FA from early-versus late-maturing WM for predicting the whole-brain-and regional summaries of GM thickness. For both models, the subjects' sex was coded as (0:1; F:M). The results of the modeling are the standardized regression coefficients (β) for and their standard errors. These estimate linear associations between criterion variables (FA) and fixed and interaction effects of age and sex. The level of statistical significance was set at $p \leq 10^{-4}$ throughout the manuscript to reduce the probability of Type 1 errors associated with multiple comparisons.

Results

Fixed effects

Quadratic models provided an excellent fit for the whole-brain (WB) FA and GM thickness measurements (Figure 4) (Table 2). The quadratic age and sex model was significant for all regional FA measurements (Table 2) and for all regional GM thickness measurements; the sole exception was the inferior parietal lobe (Table S1, see supplement). For regional GM thickness measurements, the largest quadratic age effect was observed for the superior parietal lobule, while the age-related trajectories for the post-and-pre-central gyri were linear (Figure 5, top; Table S1). Linear rates of maturation and decline were calculated for the early-and-late maturing WM using a piece-wise linear regression (Figure 5, bottom). The rates of age-related change were for the late maturing WM were two-to-three higher than these for the early maturing WM.

The FA and GM thickness showed a significant positive relationship across the lifespan and in the maturing and aging groups ($r=0.47, 0.28$ and 0.58 , respectively; $p \leq 10^{-4}$) (Figure 6). These correlations remained significant and positive even when corrected for age (partial $r=0.34, 0.33$ and 0.40 ($p \leq 10^{-4}$), across the lifespan, maturing and aging groups, respectively). Testing of the first hypothesis showed that the GM thickness model, nested with the WB FA values (eq. 2), was significantly better ($\chi^2 > 15$; $p < 10^{-16}$) at explaining intersubject variability than the base (eq. 1), age and gender, model (Tables 3 and S2). The FA term was a significant ($t = 9.8$; $p \leq 10^{-16}$) covariate for the WB and all regional ($t \geq 7.5$; $p \leq 10^{-12}$) GM thickness measurements (Tables 3 and S2). Inclusion of WB-FA values in the model caused the quadratic age term to be no longer significant for the WB-GM thickness (Table 3). For regional GM thickness measurements, inclusion of WB-FA values produced a three fold reduction in the magnitude of the beta-coefficient for the age² term (from 0.13 ± 0.08 to 0.04 ± 0.06 mm/year²) with a corresponding decline in its statistical significance (from $t = 7.0 \pm 3.2$ to 3.7 ± 1.9) (Tables 3 and S2).

Testing of the second hypothesis revealed that the GM thickness model nested with FA values from early maturing WM was significantly better ($\Delta\Lambda = 12.3$; $p < 10^{-6}$) at explaining intersubject variability in the WB GM thickness measurement areas, in maturing subjects (aged 11-20) (Table 4). This was observed for all regional GM thickness measurement with the exception of the cingulate and parahypocampal gyri (Table S3). In aging subjects (aged 40-90 years), the opposite trend was observed. The GM thickness model nested with FA values from the late developing WM was significantly better at explaining intersubject variability than the model nested with FA values from early maturing WM ($\Delta\Lambda = 79.1$; $p < 10^{-16}$) (Table 4). Regionally, the model nested with FA values from late maturing WM

showed significantly higher explanatory power for ten cortical areas (Table S3). In remaining five areas, the FA values from late maturing areas continued to show higher explanatory power but the $\Delta\Lambda$ value was not statistically significant ($p=10^{-1}$ - 10^{-3}) (Table S3).

Significant ($p\leq 10^{-4}$) sex effects were observed for the whole-brain and for the six regional GM thickness measurements while a significant age*sex interaction was observed for the whole-brain and four regional measurements (Table 2). The sign of the sex effect and interaction coefficients indicated that the males had slightly higher GM thickness values and slightly higher rates of GM thickness decline with age. Regional FA values calculated for the late maturing tracts showed higher rates of age-related changes than the FA values for early maturing tracts (Figure 4, bottom, Table 2). There were no significant gender effects observed for the regional FA measurements (Table 2).

Mixed effects

Significance of the within-group dependence due to familial aggregations was tested by modeling mixed-effects parameters using a Markov-Chain Monte-Carlo method (Baayen et al., 2008) provided by [R] statistical analysis software (R-Development-Core-Team, 2009). The effects of the familial aggregation was highly statistically significant ($p=10^{-6}$) indicating a shared genetic contribution to intersubject variability.

Discussion

The relationship between age trajectories of FA and cortical GM thickness was analyzed in a large ($N=1,031$) group of healthy individuals, aged 11 to 90 years. The whole-brain (WB) average FA and GM thickness age trajectories closely matched previously trends observed in smaller cross-sectional and longitudinal cohorts (Gogtay et al., 2004; Hasan et al., 2009a; Raz et al., 2005; Sowell ER et al., 2003; Tamnes et al., 2010; Westlye et al., 2010a, b). The peak WB-GM thickness occurred about two decades earlier than the peak WB-FA however, the relationship between GM thickness and FA was linear and positive across the lifespan. Our first hypothesis was that a common, putative mechanism is responsible for the non-linearity of FA and GM thickness age-trajectories. Nesting of the quadratic-age GM thickness model with the WB-FA term significantly improved the model's explanatory power made the effect of the age² term no longer statistically significant. Our second hypothesis was that the phylogeny of WM development is responsible for the heterochronicity of GM thickness trends. Assessing the explanatory power that FA values from the early and late maturing WM confirmed that the heterochronicity of regional cerebral WM development was an important factor in explaining the intersubject variability in GM thickness.

We believe that age-related change in cortical myelin and/or glial cell density is a potential cause of the linear relationship between the FA and GM thickness. GM thickness is regularly measured from T1-weighted (T1w) images and there is a strong relationship between the levels of intra-and-extra cortical axonal myelination and T1w imaging signal (Barbier et al., 2002; Clark et al., 1992; Westlye et al., 2010a). The T1w imaging signal is a weighted summation of cellular properties and patterns of fiber connections in the cerebral cortex (Walters et al., 2003). Histological studies that compared GM thickness measured from MRI with that from the corresponding myelin-stained sections observed that the MR signal was highly sensitive to inter-and inter-layer myelination and the intra-and inter-layer density of the glial cells (Eickhoff et al., 2005; Walters et al., 2003). In fact, the profile of the cortical T1w signal was more similar to the myelo-profile rather than to the cytoarchitectonic profile of the cortical ribbon (Eickhoff et al., 2005). Likewise, intersubject differences in the regional WM FA values have been reported to be predominantly due to

the regional intersubject differences in myelination levels and density of the glial cells (Kochunov et al., 2009a; Madler et al., 2008; Song et al., 2005). The age-related changes in regional axonal myelin, reflected by variability in FA values in white matter, are likely to be similar to age-related changes in cortical myelin (Abe et al., 2002; Gao et al., 2009). Therefore, the sensitivity of the T1w-imaging contrast to cortical myelin levels leads to shifts in the GM/WM tissue boundaries and can influence the GMT measurements (Westlye et al., 2010a).

The shape of the age trajectory for the cerebral WM integrity has been explained by difference in the maturation and aging trends for glial cells that myelinate early and late developing WM (Pfefferbaum et al., 2000; Sullivan et al., 2001; Wood P. and Bunge RP., 1984). An oligodendrocyte in the primary motor and sensory areas myelinates a single axonal segment (Wood P. and Bunge RP., 1984), while each oligodendrocyte in associative WM ensheathes up to 50 axons (Lamantia and Rakic, 1990; Wood P. and Bunge RP., 1984). Oligodendrocytes in the motor and sensory areas have much higher rates of myelin production (per segment) reaching the peak myelination in the 1st decade of life (Gao et al., 2009; Hof et al., 1990; Lamantia and Rakic, 1990; Wakana et al., 2004). This is evident from the high explanatory power that FA values from the early maturing WM areas offered for the GM thickness in the maturing (aged 11-20 years) subjects, where the largest improvements in the explanatory power was observed for the primary sensory and motor cortical areas. Oligodendrocytes of the associative WM have much lower rates of myelin production, turn over and repair (Flechsig, 1901; Hof et al., 1990; Kochunov et al., 2010b; Wakana et al., 2004). This leads to prolonged rise in the FA values of the associative cortical areas when compared to the motor and sensory area (Gao et al., 2009; Gogtay et al., 2004). Oligodendrocytes of the associative WM are also highly susceptible to accumulation of metabolic damage, specifically to iron-mediated injury, and their density declines sharply in later decades (Bartzokis, 2004; Bartzokis et al., 2004; Kochunov et al., 2007; Kochunov et al., 2010b; Pfefferbaum et al., 2000). This can explain the higher explanatory powers that the offered by FA measurements from these areas in predicting age-related decline in GM thickness. This relationship was the strongest for the superior frontal and orbitofrontal cortices whose GM thickness is known to decline rapidly in aging (Kochunov et al., 2008; Raz N et al., 1997; Westlye et al., 2010a). However, the FA of the early maturing WM remained to be a good predictor of the GM thickness for the primary motor and sensory areas, including pre-central, post-central gyri and inferior parietal areas even in the aging individuals.

Our study demonstrated that the age trajectory for GMT measured from high (voxel size=500=μm³) spatial resolution T1w MRI was partially explained by the age-related variability in the micro-integrity of cerebral WM. Cortical myelination should be considered as one of the core candidates for the age-related GM thickness change. The sensitivity of the T1w signal to cortical myelin levels leads to shifts in the GM/WM tissue boundaries and to a positive relationship between GMT and FA across the life-span. Further studies that examine the changes in the biophysical properties of the MRI signal with age are necessary to elaborate the findings reported by this study as changes in these properties may provide highly valuable biomarkers in the study of neurodevelopment, healthy aging and disorders.

A large number of our subjects (710 out of 1,031) had relatives who also participated in this study. The effects of this familial aggregation were highly statistically significant, indicating that there was a significant within-family dependence of GM thickness measurements. This finding was expected as over 50% of the intersubject variability in the GMT is attributable to genetics (Winkler et al., 2009). Individual genetic factors also strongly influence the age trajectories of GMT (Peper et al., 2009; Wallace et al., 2006). The finding of a common biological mechanism that influences the age trajectories of GMT and FA is of importance

to genetic studies. A bivariate genetic analysis can reveal genetic factors that contribute jointly to both traits and this improves the power of genetic discovery compared to univariate analyses (Turner et al., 2005). Therefore, bivariate whole-genome linkage and association analysis of the FA and GMT measurements can lead to identification of specific genetic factors responsible for intersubject differences in cortical myelination (manuscript in review).

Limitations

The measurements presented here are cross-sectional; inevitably, a study of the whole human lifespan cannot assess the same subjects over the full age range. The conclusions that are made about longitudinal processes, such as aging, from cross-sectional data as longitudinal studies occasionally fail to confirm the age-related trends obtained from cross-sectional data (Royall et al., 2005).

Another potential limitation is the use of the quadratic age and gender model to approximate the age trajectories of FA and GMT. More advanced statistical models, such as the nonparametric smoothing and spline-fitting techniques, can provide a more robust fit for an age trajectory than the quadratic model (Fjell et al., 2010). Specifically, these advanced models provide more robust estimates for the age-of-peak than a quadratic model in the situations where the age-range is incompletely sampled (Fjell et al., 2010). We consider this a minor limitation. The primary aim of this manuscript was to study the relationship between GMT and FA and the quadratic model provided an excellent fit ($r^2 > .90$) for these measurements.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Subject's distribution stratified in 5 year intervals

Figure 2.

T1-w image processing pipelines. A T1-w image is skull-stripped, globally spatially normalized, and RF-inhomogeneity corrected (A). Next, cerebral hemispheres and cerebellum are identified and tissue classified (B); cortical surfaces for GM and WM are calculated (C;D) and homotopic erosion operation and crevasse detector are used to reconstruct sulcal surface as the medial surface of the two opposing gyral banks (E). Sulcal identification pipeline uses a congregation of 500 artificial neural network-based pattern classifiers to identify (F) sulcal landmarks and to perform gyral segmentation of the cortex (G). GM thickness was calculated as the distance between the pial (C) and GM/WM interface surfaces (H)

Figure 3.

Skeletonized, average FA values are shown on the population average FA image. WM-tract labels for eleven major tract are taken from Johns-Hopkins DTI WM atlas. The average FA values were calculated for the following tracts: CR(corona radiata), SLF (superior longitudinal fasciculus), Cingulate, EC (external capsule), IC (internal capsule), FO (fronto-occipital), CST (cortico-spinal), SS (sagittal striatum) and the Genu, Body and Splenium of Corpus Callosum

Figure 4.

Age-related trajectory for the whole-brain average GM thickness and FA values. Solid and dashed lines are the result of linear regression for GM thickness ($-.001 \cdot \text{age}^2 - 0.0003 \cdot \text{age} + 2.41$; $r=0.99$) and FA ($-.00001 \cdot \text{age}^2 + 0.0018 \cdot \text{age} + 0.52$; $r=0.98$), respectively.

Figure 5.

Age-related trajectory for regional GM thickness measurements (top) varied from a linear decline for the post-central gyrus ($-0.01 \cdot \text{age} + 2.2$; $r=0.99$) to a quadratic (inverse-U) trajectory for the superior temporal lobule ($-0.0002 \cdot \text{age}^2 + 0.005 \cdot \text{age} + 2.2$; $r=0.97$). The linear rates of age-related increase and decline were calculated for the FA values from the early-and-late maturing WM by piece-wise fitting of the data on the opposite sides from the age-of-peak (bottom).

Figure 6.

Whole-brain average GM thickness versus whole-brain average FA value plotted for all subjects (top; GM thickness = $3.07 \cdot \text{FA} + 0.61$; $r=0.47$), maturing (middle; GM thickness = $1.40 \cdot \text{FA} + 1.69$; $r=0.28$) and aging groups (bottom; GM thickness = $3.12 \cdot \text{FA} + 0.49$; $r=0.58$)

Table 1

Early and late maturing white matter tracts.

Early maturing tracts	Fiber Type	Connections	Maturation rate (FA/year)*	Aging rate (FA/year)*
Cortico-Spinal (CS)	P	Cortical/Spinal Cord	$0.2 \cdot 10^{-4}$	$0.5 \cdot 10^{-4}$
External Capsule (EC)	A/P	Frontal/Temporal/ Occipital	$0.3 \cdot 10^{-4}$	$-9.7 \cdot 10^{-4}$
Corona Radiata (CR)	P	Cortical/Subcortical	$2.5 \cdot 10^{-4}$	$-12.0 \cdot 10^{-4}$
Internal Capsule (including thalamic radiation) (IC)	P	Subcortical/Brainstem /Cortex	$4.7 \cdot 10^{-4}$	$-6.5 \cdot 10^{-4}$
Late maturing tracts				
Corpus Callosum (Genu, Body and Splenium)	C	Cerebral Hemispheres	$14.8 \cdot 10^{-4}$	$-21.0 \cdot 10^{-4}$
Cingulum	A	Cingulate Gyrus/Hippocampus	$13.6 \cdot 10^{-4}$	$-12.0 \cdot 10^{-4}$
Sagittal Stratum (SS)	A/P	Subcortical/Temporal /Occipital	$12.4 \cdot 10^{-4}$	$-6.7 \cdot 10^{-4}$
Superior Longitudinal Fasciculus	A/P	Frontal/Temporal/ Occipital	$6.8 \cdot 10^{-4}$	$-9.4 \cdot 10^{-4}$
Superior/Inferior Fronto-Occipital Fasciculi (FO)	A	Frontal/Parietal/Occipital	$10.9 \cdot 10^{-4}$	$-14.5 \cdot 10^{-4}$

* Rates of average rate of change were taken from (Kochunov et al., 2010b).

C=Commissural, P=Projection, A=Association;

Results (value± sd (t-value, p-value)) of the modeling of the intersubject variability in fraction anisotropy (FA) and gray matter thickness (GM thickness) using the base, quadratic age and sex model (eq. 1). Bolded values are significant at p≤1E-4.

Table 2

Measurement	Average	$\beta_{age} \pm sd \cdot 10^{-3}$ (t; p)	$\beta_{age}^2 \pm sd \cdot 10^{-3}$ (t;p)	$\beta_{sex} \pm sd$ (t;p)	$\beta_{age,sex} \pm sd \cdot 10^{-3}$ (t;p)	Λ_{base} (p)
Whole Brain FA	0.52±0.31	2.0±0.3 (7.2, 1E-8)	-0.03±0.00 (9.3, 1E-11)	-0.5±0.4(0.14, 0.9)	-0.00±0.00 (0.31, 0.8)	2264.4 (1E-16)
Early Maturing WM FA	0.51±0.28	1.5±0.3 (9.0; 1E-9)	0.02±0.00 (10.9, 1E-11)	-0.00±0.00(0, 1.0)	0.00±0.00 (1.2, 0.22)	2361.1 (1E-16)
Late Maturing WM FA	0.57±0.38	2.4±0.2 (10.0; 1E-9)	-0.04±0.00 (13.6, 1E-16)	0.3±3.6 (0, 1.0)	-0.00±0.00 (0.31, 0.8)	2253 (1E-16)
Whole Brain GM thickness	2.21±0.17	1.1±1.3 (0.9; 0.39)	-0.09±0.001 (5.5; 1E-8)	0.09±0.02 (4.2; 1E-5)	-2.5±0.6 (4.9; 1E-6)	431.0 (1E-16)

Results (value± sd (t-value, p-value)) of the modeling of the intersubject variability in gray matter thickness (GM thickness) using the nested model that included the whole-brain FA values (eq. 2). D-test ($\chi^2 = -2 \cdot (\Lambda_{\text{base}} - \Lambda_{\text{nested}})$) was used to ascertain the significance in the difference in the explanatory for the expanded (quadratic age and sex and FA) versus base (quadratic age and sex) models. Bolded values are significant at $p \leq 10^{-4}$.

Table 3

Measurement	$\beta_{\text{age}} \pm \text{sd} \cdot 10^{-3}$ (t; p)	$\beta_{\text{age}}^2 \pm \text{sd} \cdot 10^{-3}$ (t; p)	$\beta_{\text{sex}} \pm \text{sd}$ (t; p)	$\beta_{\text{age,sex}} \pm \text{sd} \cdot 10^{-3}$ (t; p)	$\beta_{\text{FA}} \pm \text{sd}$ (p) (t; p)	$\Lambda_{\text{nested}}(\text{p})$	χ^2 (p), d.f.=1
Whole Brain GM thickness	-5.2±1.4 (4.4; 1E-5)	- .00±0.001 (1.5; .10)	0.09±0.02 (4.3; 1E-5)	-2.5±0.6 (5.0; 1E-6)	1.8±0.2 (9.8; E-16)	477.1 (1E-16)	92.2 (1E-16)

Results (value± sd (t-value, p-value)) of the modeling of the intersubject variability in gray matter thickness (GM thickness) versus FA values for early (FA_{em}) and late (FA_{lm}) maturing cerebral WM using general linear mixed effects model in eq 2. Bolded values are significant at p≤10⁻⁴.

Table 4

Measurement	Maturing group (Age=11-20; N=252, df=225)			Aging group (Age=40-90; N=483, df=399)		
	$\beta_{FAem} \pm sd$ (p) (tp)	$\beta_{FAlm} \pm sd$ (p) (tp)	$\Delta\Lambda$ (p)	$\beta_{FAem} \pm sd$ (p) (tp)	$\beta_{FAlm} \pm sd$ (p) (tp)	$\Delta\Lambda$ (p)
Whole Brain GM thickness	3.46±0.48 (7.1; 1E-11)	1.53±0.31 (4.9; 1E-5)	12.3 (1E-6)	1.55±0.33 (4.7; 1E-5)	1.92±0.20 (8.9; 1E-16)	-79.1 (1E-16)