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Relationship between white matter fractional anisotropy and other indices of cerebral health in normal aging: Tract-based spatial statistics study of aging

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White matter (WM) fractional anisotropy (FA) is thought to be related to WM integrity and decline in FA is often used as an index of decreasing WM health. However, the relationship of FA to other structural indices of cerebral health has not been well studied. We hypothesized that the decline in WM health will be associated with changes in several other indices of cerebral health. In this manuscript we studied the correlation between whole-brain/hemispheric/corpus callosum FA and gray matter (GM) thickness, sulcal span, and the volume of T2-hyperintense WM in a group of 31 healthy aging individuals (12 males/19 females) aged 57–82 years old. Individual subjects' FA measures were calculated from diffusion tracing imaging (DTI) data using tract-based spatial statistics—an approach specifically designed and validated for voxel-wise multi-subject FA analysis. Age-controlled correlation analysis showed that whole-brain average FA values were significantly and positively correlated with the subject's average GM thickness and negatively correlated with hyperintense WM volume. Intra-hemispheric correlations between FA and other measures of cerebral health had generally greater effect sizes than inter-hemispheric correction, with correlation between left FA and left GM thickness being the most significant ($r=0.6$, $p<0.01$). Regional analysis of FA values showed that late-myelinating fiber tracts of the genu of corpus callosum had higher association with other cerebral health indices. These data are consistent with the hypothesis that late-myelinating regions of the brain bear the brunt of age-related degenerative changes.

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Introduction and background

The cerebrum is a highly complex structure where aging trends among cerebral compartments are thought to be highly inter-related. A basic structural compartmentalization of the brain can be achieved by separating the cerebrum into cortical gray matter (GM) and sub-cortical white matter (WM) compartments. Each compartment may exhibit characteristic degenerative changes, some of which may be observed and quantified through non-invasive imaging (yielding specific quantitative indices of cerebral health). Histological and neuroimaging data suggest that structural integrity of both WM and GM compartments deteriorates with age, however, the interrelationship among compartmental aging trends have not been studied well. Age-related degenerative changes in human cerebrum are thought to be heterochronic and regionally heterogeneous with the multi-modal areas showing earlier and larger age-related alterations than unimodal sensory and motor areas (Flood and Coleman, 1988; Morrison and Hof, 1997). This heterochronicity and regional heterogeneity of aging are thought to be related to the development of cerebral myelination (Braak and Braak, 1996; Bartzokis et al., 2001, 2003, 2004; Royall et al., 2003; Bartzokis, 2004a,b). Myelination of associative areas is thought to follow a quadratic (inverted U) trajectory with age. Myelin sheaths of associative areas continue to develop into middle ages, which is then followed by a myelin breakdown and axonal loss which we will refer herein as “demyelination” (Yakovlev and Lecours, 1967; Miller et al., 1980; Benes et al., 1994; Bartzokis et al., 2001, 2003, 2004; Ge et al., 2002; Sowell et al., 2003; Bartzokis, 2004a,b; Allen et al., 2005; Jelsing et al., 2005;

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Table 1
 Gray matter thickness and sulcal span were calculated for 12 primary and secondary sulcal structures per hemisphere

Superior frontal sulcus
Inferior frontal sulcus
Pre-central sulcus
Post-central sulcus
Intraparietal fissure
Superior temporal sulcus
Cingulate sulcus
Lateral occipital, transverse occipital and lunata sulci
Calcarine fissure
Central sulcus
Parietoccipital fissure
Collateral sulci

Walhovd et al., 2005). This age-related demyelination of associative fibers is thought to be responsible for the degradation of cerebral network connectivity, and likely contributes to the age-related decline of higher cognitive function (Bartzokis et al., 2003). We hypothesized that age-related decline in WM

integrity will correlate with changes in other structural indices of cerebral health. We investigated whether reduction in WM integrity was associated with changes in cortical GM thickness, dilation and filling of cortical sulcal spaces with cerebro-spinal fluid (CSF) and increase of T2-hyperintense white matter (HWM) volume.

Cortical GM thickness can be defined as the distance from the outer cortical surface to the inner cortical WM–GM boundary. In aging, diminished cortical thickness is a neuroimaging index of declining cortical health that is thought to be related to regional reduction of neuronal density in the cortical mantle (Selemon et al., 1995; Jelsing et al., 2005; Lerch and Evans, 2005). Neuroimaging and histological studies report that GM thickness diminishes significantly during normal aging (Raz et al., 1997; Magnotta et al., 1999; Sowell et al., 2003). It is thought to decrease with age from an average thickness of ~2.6 mm at the age of 20 to about 2 mm for the age range of 80–90. The rate of cortical thickness reduction in abnormal aging and degenerative disorders was shown to be different from that in healthy aging (Thompson et al., 2003, 2004).

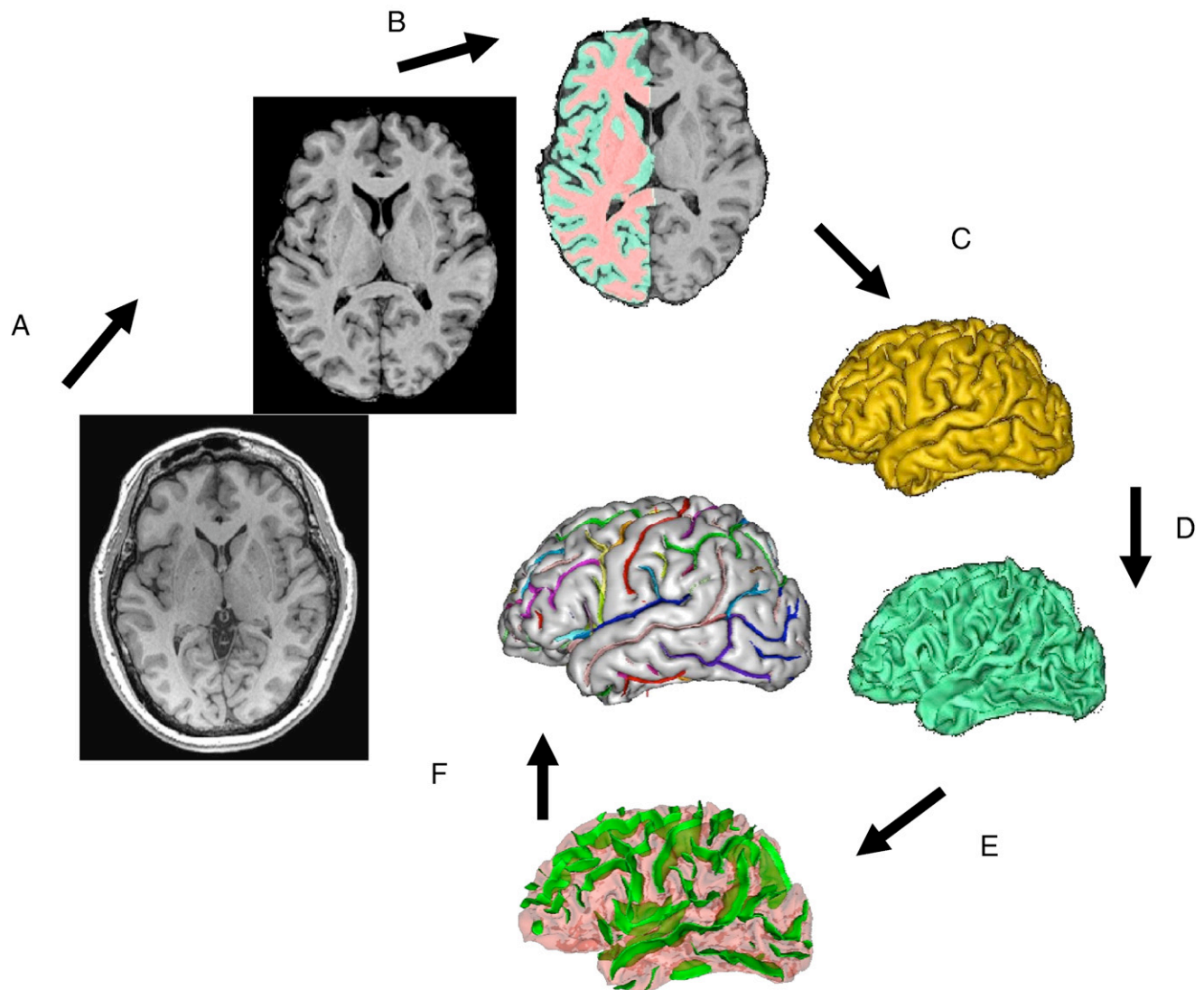


Fig. 1. Image processing pipeline for extraction of indices of cerebral health.

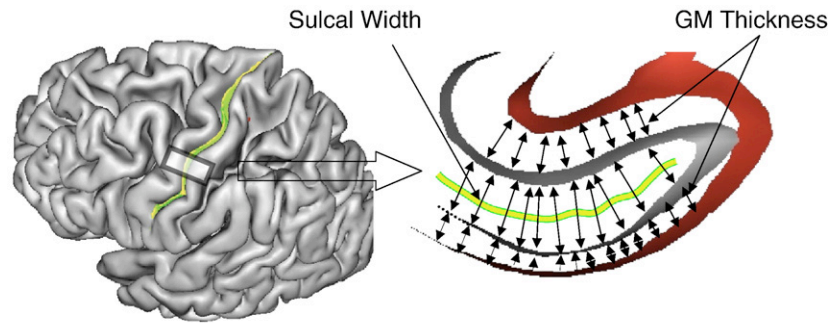


Fig. 2. Measurements of cortical cerebral health indices: average GM thickness average and average sulcal span.

Average sulcal span of cortical sulci is another readily measured neuroimaging index of cerebral health. Cerebral degeneration can result in dilation of cortical sulci and compensatory filling of freed space by CSF, increasing the sulcal span. This phenomenon is thought to be the combined result of the reduction of thickness of the gyral GM mantle and atrophy of gyral WM (Magnotta et al., 1999; Symonds et al., 1999; Jernigan et al., 2001; Kochunov et al., 2005a,b). The average sulcal span, specifically in the hippocampal, entorhinal and medial temporal cortices is correlated with neurocognitive decline in the course of mild cognitive impairment and dementia disorders (Bastos Leite et al., 2004).

Hyper-intense white matter (HWM) lesions observable on T2-weighted MR studies are a commonly used neuroimaging index of degeneration of sub-cortical WM. HWM regions in T2-weighted images in WM are a common finding in both normal and abnormal aging and neurodegenerative disorders. The T2-weighted signal is enhanced in cerebral regions where degradation of the myelin sheath results in a local accumulation of edema. The etiology of HWM is nonspecific and could be due to ischemia from small/large vessel pathology, trauma, inflammatory response and other causes (Pantoni and Garcia, 1995). The incidence of HWM lesions in normal aging is reported to be as high as 60–100% in normal subjects age 60 years old and above (Pantoni and Garcia, 1995; De Leeuw et al., 2001, 2005). As a marker for cerebral health, the increase in HWM lesion volume has been shown to correlate with: reduction in global WM and GM, volumes (Du et al., 2005; Wen et al., 2006); increase in intersulcal spaces (Kochunov et al., 2005a,b; Kochunov et al., in press); and severity of neurocognitive

deficits in the neuropsychiatric and neurological disorders (Pantoni and Garcia, 1995; Sachdev and Brodaty, 1999).

Fractional anisotropy (FA) of cerebral WM is often used as an index of decreasing WM health. FA of water diffusion describes directional selectivity of the random motion of water molecules within a tissue (Basser, 1994; Ulug et al., 1995; Conturo et al., 1996; Pierpaoli and Basser, 1996). Higher FA values (maximum theoretical value is 1.0) are observed along heavily myelinated WM tracts. High WM fractional anisotropy (FA), is thought to be due to the structure of the axonal cell membranes and myelin sheath which hinders the diffusion of water molecules in all but the direction along the fiber tract (Pierpaoli and Basser, 1996). If the water molecule environment is random, such as in GM and CSF compartments, water motion is random, yielding so-called isotropic diffusion with FA values close to zero. As an index of cerebral health, a decline in FA is thought to offer insight into degenerative changes in the micro-structural integrity of WM tracts. White matter FA was shown to be sensitive to the progression of various degenerative WM disorders that results in axonal loss and/or destruction of myelin sheath such as multiple sclerosis, leukoaraiosis, various dementias (Horsfield and Jones, 2002). FA has also been shown to decrease during the normal aging (Abe et al., 2002; Moseley, 2002; Sullivan and Pfefferbaum, 2003; Lehmebeck et al., 2006). The FA decline with age was shown to be due to an increase in the water diffusion in the direction perpendicular to the direction of the WM fibers (Horsfield and Jones, 2002; Smith et al., 2006) and this was interpreted as the degeneration of the axonal myelin sheath (demyelination) and/or replacement of axonal fibers with other cells (gliosis) (Mazziotta et al., 1995).

Previously, we reported age-related trends and interrelationships for several structural indices of cerebral health (Kochunov et al., 2005a,b; Kochunov et al., in press). We discovered significant ($p < 0.01$) changes with age for GM thickness and dilation of cortical sulcal sulci, but no significant age-corrected correlation for the increase in HWM volume. We found that dilation of cortical sulci was similarly and highly ($p < 0.01$) correlated with both reductions in the cortical GM thickness and increases in HWM

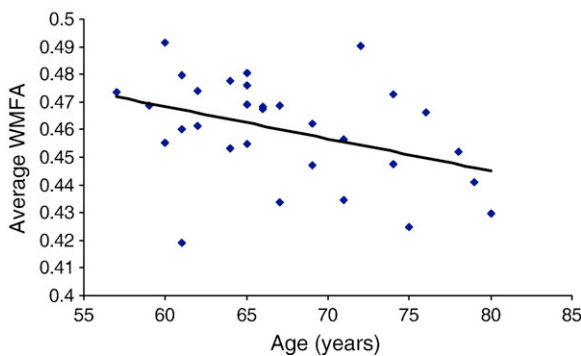


Fig. 3. Whole-brain average FA values plotted vs. subject's age.

Table 2
Correlation between global indices of cerebral health and age

	FA	GMT	SW	HWM
<i>r</i>	−0.39	−0.53	0.48	0.34
<i>p</i>	<0.05	<0.01	<0.01	>0.05

Table 3
Correlation between hemispheric indices of cerebral health and age

	L-FA	R-FA	L-GMT	R-GMT	L-SW	R-SW	L-HWM	R-HWM
<i>r</i>	-0.37	-0.39	-0.53	-0.54	0.47	0.48	0.33	0.32
<i>p</i>	<0.05	<0.05	<0.01	<0.01	<0.01	<0.01	>0.05	>0.05

volume, and that these correlations remained significant even when correcting for age. The current paper extends that work by examining whether these structural brain changes are associated with changes in white matter integrity assessed with diffusion-weighted imaging.

Materials and methods

Subjects

Thirty-one (12 males/19 females), normal, healthy subjects aged 57–82 years (average age=66.3±6.5 years old) were recruited as a part of the International Consortium for Brain Mapping (ICBM) (Mazziotta et al., 1995) (Mazziotta et al., 2001) project. Each subject's medical history was reviewed to rule out endocrinal, neurological and/or psychiatric illnesses. All subjects underwent a comprehensive neurological examination, had their blood pressure measured to rule out hypertension and were subjected to comprehensive neurocognitive testing, before qualifying for imaging. All experiments were performed with IRB approval and all subjects signed an informed consent.

Imaging

All imaging was performed at the Research Imaging Center, UTHSCSA, on a Siemens 3T Trio scanner using a high-resolution 8-channel head coil. An optimized, multimodality imaging protocol was used to acquire high-resolution DTI, T1- and T2-weighted images.

Diffusion-weighted imaging

Single-shot echo-planar gradient recalled echo, T2-weighted, sequence was used to acquire diffusion-weighted data with the spatial resolution of 1.7×1.7×3.0 mm. The sequence parameters were TE/TR=87/8000 ms, with 86 diffusion-weighted directions and two diffusion weighing *B* values of 0 and 700. The total sequence acquisition time was 12 min.

Table 4
Correlations between FA and whole brain average indices of cerebral health

	GMT	SW	HWM
FA	0.57 (0.46 ^a)	-0.42 (-0.29 ^a)	-0.47 (-0.41 ^a)

^a Indicates age-corrected partial correlation values.

T1-weighted imaging

High-resolution (isotropic 800 μm), high GM–WM contrast (~25%) T1-weighted images were acquired using a retrospective motion-corrected protocol (Kochunov et al., 2006, in press). With this protocol, six full-resolution volumes are acquired using a T1-weighted, 3D TurboFlash sequence with an adiabatic inversion contrast pulse with the following scan parameters: TE/TR/TI=3.04/2100/785 ms, flip angle=13°.

T2-weighted imaging

The T2-weighted data were acquired with a high-resolution (isotropic 1 mm), 3D turbo-inversion recovery Fluid Attenuated Inversion Recovery (FLAIR) sequence with the following parameters: TR/TE/TI/flip angle=5 s, 353 ms, 1.8 s, 180°. This sequence uses a non-selective inversion recovery pulse to prevent CSF pulsation artifacts (Bakshi et al., 2000).

Image processing

TBSS processing

We used a tract-based spatial statistics (TBSS) method that is distributed as a part of FSL package for multi-subject analysis of diffusion anisotropy (Smith et al., 2006). First, fractional anisotropy (FA) images were created by fitting the diffusion tensor to the raw diffusion data (Smith, 2002). During the next step, all FA images are nonlinearly aligned to a group-wise, minimal-deformation target (MDT) brain. The group's MDT brain is identified by warping all individual brain images in the group to each (Kochunov et al., 2001). MDT is selected as an image that minimizes the amount of the required deformation from other images in the group. Once the MDT brain is selected, all images in the group are normalized using this brain as a target.

Next, individual FA images are averaged to produce a group-average anisotropy image. This image is used to create a group-wise skeleton of white matter tracts. The skeletonization procedure is a morphological operation, which extracts the medial axis of an object. This procedure is used to encode the medial trajectory of the white matter fiber tracts with one-voxel thin sheaths.

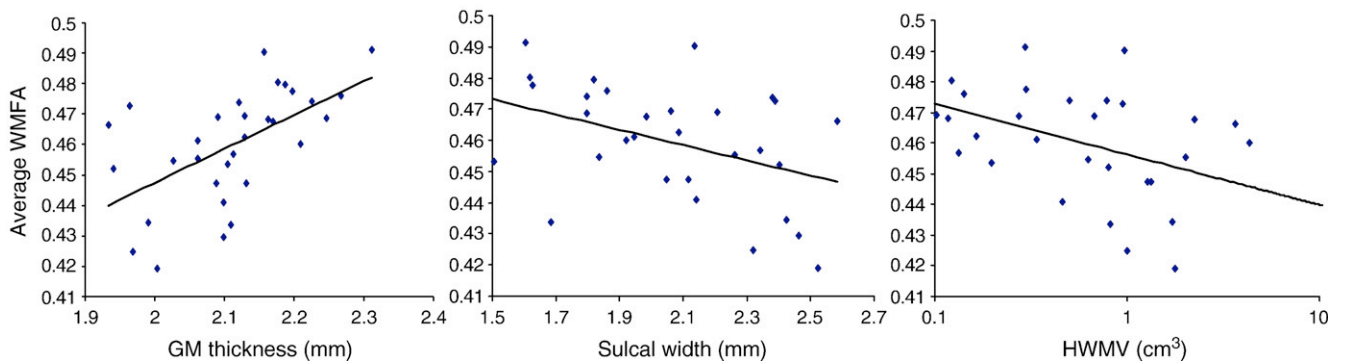


Fig. 4. Whole-brain average FA values plotted vs. whole-brain average GM thickness, sulcal span and HWM volume.

Table 5

Age-corrected correlations for L/R-hemispheric average FA and other indices of cerebral health

	L-FA	R-FA	L-GMT	R-GMT	L-SW	R-SW	L-HWM	R-HWM
L-FA	1	0.96	0.56	0.48	-0.29	-0.24	0.40	0.41
R-FA	0.96	1	0.49	0.53	-0.19	-0.33	0.39	0.41

Finally, FA images are projected onto the group-wise skeleton of white matter structures. This step accounts for residual misalignment among individual white matter tracts. For individual images, FA values are analyzed along the normal projection for each point of the skeleton image and the peak value is assigned to the skeleton. This step effectively corrects for misalignment of individual fiber tracts. 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 lines up the center of individual white matter tracts. The projection operation is performed under two constraints. A distance map is used to establish search borders for individual tracts. The borders are created by equally dividing the distance between two nearby tracts. Secondly, a multiplicative 20-mm full width at half-max Gaussian weighting is applied during the search to limit maximum projection distance from the skeleton.

T1-weighted images

Processing of T1-weighted images for extracting measures of cortical GM thickness and sulcal span was previously described in

Kochunov et al. (2005a,b) and Kochunov et al. (in press). The GM and sulcal span were measured concurrently for 12 primary and secondary sulcal structures per hemisphere (Table 1). Briefly, the processing was performed with the following steps: removal of non-brain tissue, registration to the Talairach frame, RF inhomogeneity correction, brain tissue partial volume segmentation, extraction of GM/WM pial surfaces, extraction and labeling and verification of sulcal surfaces and measurements of GM thickness and sulcal span (Fig. 1). The GM thickness and sulcal span were calculated in the same operation. The thickness of GM ribbon was sampled on both gyral banks of the sulcus (Fig. 2). The GM thickness and sulcal span values for individual sulci/gyri were averaged to obtain average whole-brain and hemispheric values.

T2-image processing

Processing of T2-weighted FLAIR images for HWM volume measurements was described in Kochunov et al. (in press). In short, FLAIR images were processed in the following steps: removal of non-brain tissue, registration to the T1-weighted images/Talairach frame, RF inhomogeneity correction and manual

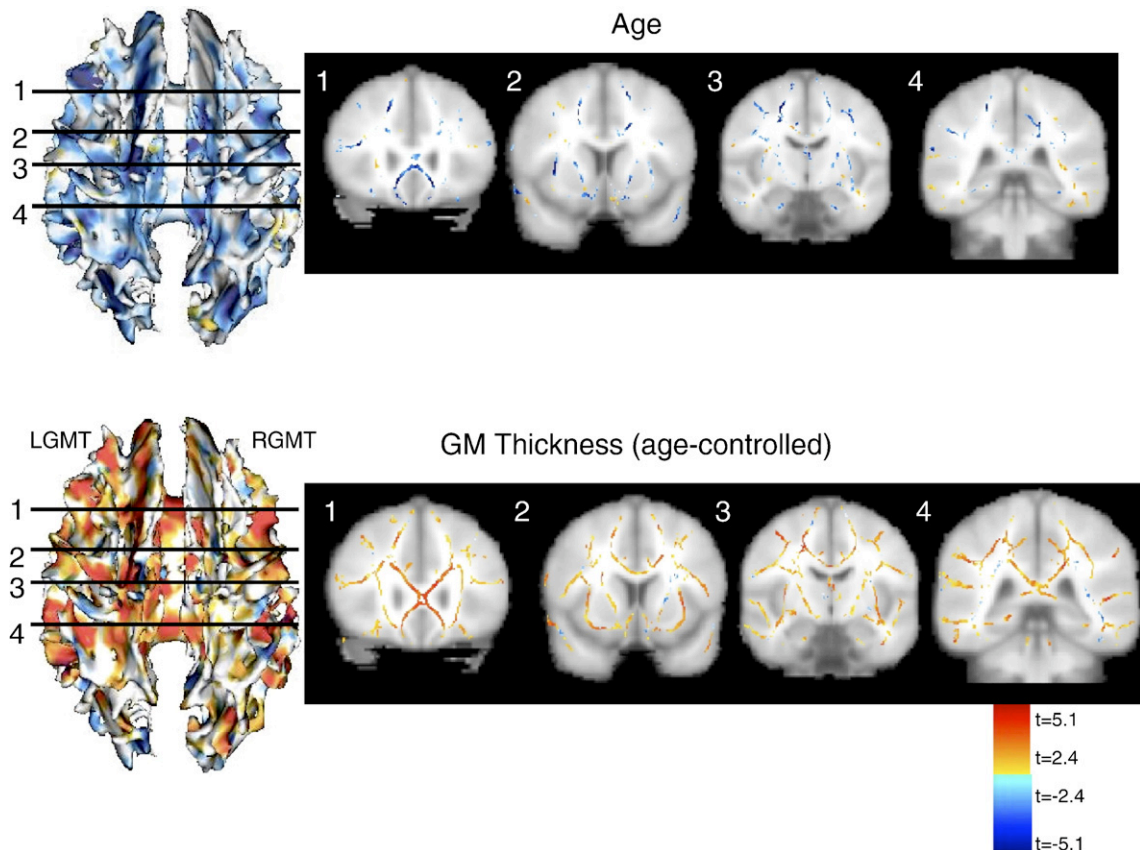


Fig. 5. Voxel-wise, correlation between FA and age (top) and age-corrected voxel-wise correlation between left/right hemispheric FA and left/right GM thickness (L/R GMT) rendered on the skeleton of cerebral WM tracts (right) and four coronal sections through corpus callosum.

delineation (painting) of hyper-intense lesions by two experienced neuroanatomists.

Results

Previously, we reported whole-brain age-related trends and the interrelationship among three cerebral health markers: average GM thickness, average sulcal span and HWM volume. The emphasis of this manuscript was to study correlations between the whole-brain/regional FA measurements and other indices of cerebral health.

FA correlation with age

Average FA was inversely related to age (i.e., 0.01 FA units/decade of life). This trend was significant ($r=-0.39$; $p<0.05$); see also Fig. 3 and Table 2. Previously, we reported that the whole-brain GM thickness measurements also decreased significantly with age while sulcal span increased significantly with age (Table 2) (Kochunov et al., in press). The correlation between HWM volume and age did not reach statistical significance (Table 2).

Inter-hemispheric age-related trends followed whole-brain trends (Table 3). For three cerebral health markers (FA, GM thickness and sulcal span), the correlation with age was numerically greater for the right than for the left hemisphere. However, these differences were slight and not statistically significant ($p\sim 0.2-0.3$). There were no inter-hemispheric differences for HWM volume trends.

Correlation between FA and other indices of cerebral health

Scatter plots (Fig. 4) and bivariate correlation analysis (Table 4) indicated a statistically significant ($p<0.05$) correlation between whole-brain FA and the three other cerebral health indices. Whole-

brain FA values had numerically greater correlation with the whole-brain average GM thickness, followed by HWM volume and average sulcal span (Table 4).

Age-controlled partial correlation analysis indicated that at the whole-brain level, the average FA values correlated significantly with the average GM thickness ($r=0.46$; $p<0.05$) and the HWM volume ($r=-0.41$; $p<0.05$) (Table 4). The correlation between FA and approached statistical significance ($r=-0.29$; $p\leq 0.1$).

The results of age-controlled partial correlations for the L/R hemispheric cerebral health indices are shown in Table 5. Higher correlation values were seen for the measurements from same hemisphere vs. measurements from opposite hemispheres. However, the difference in correlation coefficients was not significant ($z\text{-score}=2.1$, $p\sim 0.1$). The highest correlation was observed between left FA and left GM thickness ($r=0.57$, $p<0.01$), followed by right FA and right GM thickness ($r=0.52$, $p<0.01$). The correlation between FA and average sulcal span was also higher for the same-side measurements, but none were significant (Fig. 5). The correlation between HWM volume and FA was symmetric (Table 5).

Voxel-wise correlation between FA and other markers of cerebral degeneration

TBSS facilitated for a voxel-wise correlation analysis between regional FA values and external covariates. The correlation patterns were investigated for the whole brain, individual hemispheres and three regions of corpus callosum and fornix.

Correlation maps between FA voxels and age were 3D rendered on the skeleton of cerebral WM tracts (Fig. 6 top). The regional correlation pattern indicates an overall uniformly negative correlation between FA and age, with over 10% of the voxels showing a significant negative correlation and less than 2% of the FA voxels

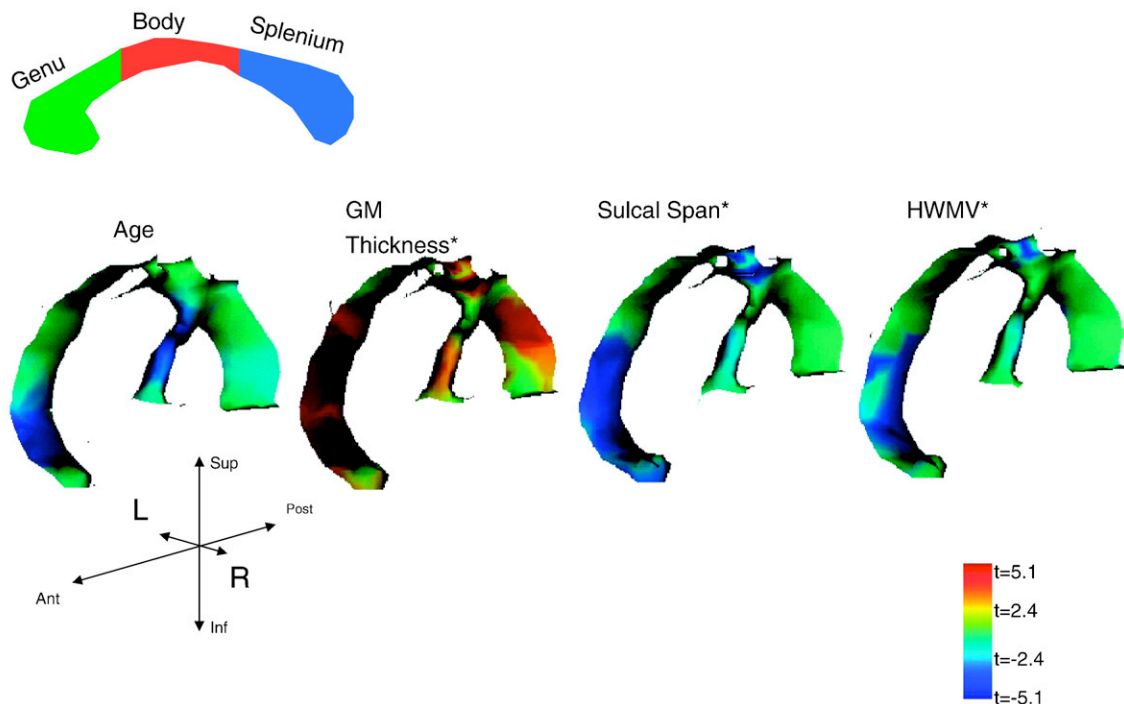


Fig. 6. Anterior-to-posterior subdivision of corpus callosum (top). Voxel-wise correlation between corpus callosum and body of fornix FA values and age, GM thickness, sulcal span and HWM volume. (*)Age-corrected correlations.

Table 6

The fractions of the FA voxels that showed statistically significant correlation between FA, age and whole brain and left/right hemispheric average health indices

	Age (whole brain; left; right) (%)	GM thickness ^a	Sulcal width ^a (left; right) (%)	HWM ^a (left; right) (%)
$r > 0.365$	1.4; 1.5; 1.2	22.2; 21.3	2.2; 2.1	2.5; 2.5
$r < -0.365$	9.3; 9.9; 11.5	1.9; 1.8	11.5; 11.0	9.1; 9.2

^a Indicates age-corrected correlations.

showing a significant positive correlation with age (Table 6). The age-controlled L/R partial correlation map between FA and GM is shown in Fig. 6 (bottom). Here, the spatial averages were performed across brain voxels within a hemisphere and correlated with GM thickness averaged over that same hemisphere. This figure indicates a predominantly positive correlation pattern with over 20% of FA voxels showing significant correlation ($r > 0.365$) with GM thickness (Table 6). The largest fraction of the significantly correlated FA was observed between left FA/left average GM thickness (~23%), followed by correlation between right FA and right GM thickness (~21%) (Table 6).

Age-controlled voxel-wise correlation between regions of corpus callosum (CC) and body of fornix (BF) FA values residing in the 10 mm wide band of median CC/BF was performed in the similar fashion. The whole-brain average GM thickness, sulcal span and HWM volume values were used to avoid the ambiguity of hemispheric division. The CC was subdivided into three regions: genu, body and splenium each occupying 1/3 on the anterior–posterior CC length (Kochunov et al., 2005a,b) (Fig. 6 top). The regional maps of correlations are shown in Fig. 6 and the fraction of statistically significant voxels is shown in Table 7. There were apparent and striking differences in the regional fractions of statistically significant correlations. The genu of the CC had the largest fractions of significantly correlated voxels for age and cerebral health indices with up to 67% of FA voxels showing statistically significant positive correlation with whole-brain GM thickness (Table 7). The body of the CC showed the smallest fractions of significantly correlated voxels.

Further, regional FA values in CC were correlated with the cortical health indices (GM thickness and sulcal span) calculated from the areas that roughly correspond to the anterior–posterior

subdivision of CC. GM thickness and sulcal span for the anterior cortical region were calculated from superior frontal, intermediate frontal and pre-central sulci. Likewise, posterior cortical health indices were calculated from post-central and intra-parietal sulci, and the central region was calculated within the central sulcus (Fig. 5). A partial correlation analysis was used to control for both age and global GM thickness trend. Controlling for global GM thickness was added to dissociate between the regional and global GM thickness trends. The resulting correlation pattern (Table 8), indicated that FA of the genu was highly correlated with GM thickness, independent of cortical area.

Regional sulcal span correlations were also performed while controlling for both age and global GM thickness. The sulcal span measurements are sensitive to both: reduction in GM thickness and the reduction in gyral WM volume (Kochunov et al., in press). Controlling for whole-brain GM thickness was done to emphasize the association between gyral WM volume and the FA of the tracts originating from these gyri. Regional correlation with sulcal span produced a pronounced regional correspondence between cortical and CC regions (Table 8). For the anterior sulcal span measurement the largest fraction of significantly correlated FA voxels was observed in the genu and the sulcal span measurement for the central region had the highest fraction of correlated voxels in the body of CC.

Discussion and conclusion

Our findings of age-related decline of FA with age and relationship among FA and other structural indices of cerebral health are consistent with a variety of findings published in the last 5–6 years. Pfefferbaum, Sullivan and colleagues were the first to utilize FA as an index of declining WM health in their reports on age-related FA trends in normal aging (Pfefferbaum et al., 2000; Sullivan et al., 2001). These reports were followed by other studies with similar findings regarding change in FA with age (Abe et al., 2002; Moseley, 2002; Sullivan and Pfefferbaum, 2003; Lehmbeck et al., 2006). All these studies interpreted their findings of age-related decline in cerebral FA as an indication of mild demyelination and/or axonal loss.

Of special interest are findings of differences in age-related trends for different regions of corpus callosum. Regional heterogeneity in rates of diminishing FA in the CC was first noted by Pfefferbaum et al. (2000). They reported that within the CC, FA values diminished most rapidly with age in the genu but age-related

Table 7

The fraction of voxels with significant age-corrected correlation between FA of CC/body of fornix and whole-brain average GM thickness, sulcal span and HWM volumes

	CC genu (%)	CC body (%)	CC splenium (%)	Fornix (%)
FA vs. Age				
Positive ($r > 0.365$)	0.1	10.3	2.6	1.7
Negative ($r < -0.365$)	24.7	7.6	12.3	18.7
FA vs. GMT ^a				
Positive ($r > 0.365$)	62.2	17.2	11.4	21.3
Negative ($r < -0.365$)	0	0	2.2	0
FA vs. SS ^a				
Positive ($r > 0.365$)	0	0.3	0	3.3
Negative ($r < -0.365$)	41.5	8.7	2.1	6.7
FA vs. HWM ^a				
Positive ($r > 0.365$)	0	0.2	0	2.9
Negative ($r < -0.365$)	40.2	11.2	10.1	5.3

^a Indicates age-corrected correlations.

Table 8

Voxel-wise correlation between CC FA values and GM/Sulcal span for anterior (superior frontal, intermediate and pre-central sulci), central (central sulcus) and posterior (post-central, intraparietal) is expressed as percentage of voxels with statistically significant correlation ($r > 0.369$) for GM thickness and ($r < -0.369$) for sulcal span

Region	GM thickness ^a			Sulcal span ^a		
	Genu (%)	Body (%)	Splenium (%)	Genu (%)	Body (%)	Splenium (%)
Anterior	29	14	18	28	4	3
Central	32	10	2	3	9	3
Posterior	26	4	5	5	7	6

^a Partial correlations were performed while controlling for both age and whole brain GM thickness.

FA changes in the mid-body and splenium were not significant. These findings were interpreted as micro-architectural differences between the genu and the midbody/splenium. The genu of CC is made up of densely packed, thinly myelinated frontal lobe commissural fibers, which continue to be myelinated into the 4th decade. The mid-body of the CC is composed of large and heavily myelinated commissural fibers that carry motor and proprioceptive information, which reach mature levels of myelination in the 1st to 2nd decades. Pfefferbaum, Sullivan and colleagues concluded that the smaller WM fiber bundles in the genu were especially vulnerable to age-related degenerative micro-structural changes (Pfefferbaum et al., 2000; Sullivan et al., 2001). The results of our ROI analysis of the CC for the age-related changes in FA agree with Pfefferbaum, Sullivan and colleagues (Fig. 7, Table 7).

Global relationship between FA and cerebral health markers

Clinical studies of WM disorders including multiple sclerosis (MS) and arterial leukoariosis (AL) often report significant association between decline in FA and increase in HWM volume (Horsfield and Jones, 2002). Recently, Vrenken and colleagues reported that the decrease in cerebral FA in MS patients was associated with an increased HWM volume and reduced GM/WM volumes (Vrenken et al., 2006). A longitudinal study of MS patients also indicated that decrease in cerebral FA was associated with an increase in HWM volume and a decrease in brain volume (Oreja-Guevara et al., 2005). We observed a similar pattern with decreasing FA, an increase in HWM volumes, an increase in sulcal span, and reduction in GM thickness. Our findings suggest that demyelination during cerebral aging in a normal population might be similar in nature and mechanisms to demyelination due to WM disorders. This suggestion is also supported by the high incidence of hyperintense WM lesions in both normal aging and demyelination disorders such as MS and LA. In fact, all our subjects had HWM lesions, which is consistent with a reported incidence rate of >90% in normal subjects older than 60 years old (De Groot et al., 2001; De Leeuw et al., 2001).

Regional relationship between FA and cerebral health markers

Thinly myelinated, associative fibers in the genu showed the strongest FA decline with age. These fibers also showed the strongest correlation with the whole-brain GM thickness, sulcal span and HWM volume, even when partial correlation analysis

was used to account for age. Correlations between FA of the thickly myelinated central CC with age and other cerebral health markers were much weaker. In fact, FA assessment of the central CC region revealed that a large fraction of voxels (>10%) was positively correlated with age. Pfefferbaum et al. (2000) observed a similar trend and hypothesized that this could be a remyelination trend with age.

Interestingly, FA within the CC did not indicate a significant regional correlation with GM thickness. However, FA of the genu was significantly correlated with GM thickness independent of cortical area, while FA of other CC regions did not appear to have a strong global or regional relationship (Table 8). This might suggest that changes in myelin levels in the thinly myelinated associative tracts of the genu could be an indicator of an overall decline in GM thickness.

Decreases in FA of the genu were strongly correlated with increases in sulcal span in the anterior cortical region, even when age and global GM thickness were controlled for. However, a definite relationship between FA and sulcal span was not seen for other regions of the CC. These findings indicate that a reduction of gyral WM volume in the anterior region, reflected as an increase in sulcal span, has a more direct regional association with the corresponding CC region. It also suggests that late-developing, thinly myelinated, associative fibers in the genu have a higher sensitivity to reduction in gyral WM, than earlier developing thickly myelinated fibers in other regions of the CC. Similar conclusions were made from post mortem and imaging data which showed that reduction in regional WM volume through myelin breakdown and axonal loss is first observed in the thinly myelinated regions of associative tracts and then progress to the thickly myelinated WM regions of motor and sensory tracts (Peters et al., 2000; Bartzokis et al., 2003, 2004).

Interpretation of correlation between FA to other degeneration markers

We interpret our findings based on the hypothesis of a differential WM aging proposed by Bartzokis et al. (2001, 2003,

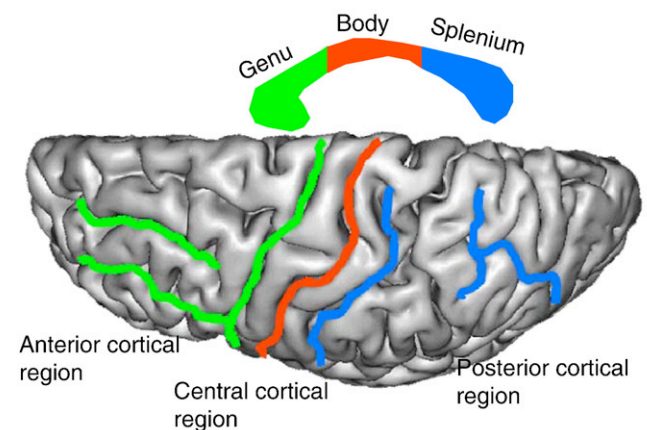


Fig. 7. Regional correlation between FA of CC and cortical indices of cerebral health. GM thickness and sulcal span for anterior cortical region were calculated from superior frontal, pre-central and intermediate frontal sulci. Likewise the indices for posterior region were calculated from post-central and intra-parietal sulci. GM thickness and average sulcal span for central region were calculated from the central sulcus.

2004). This hypothesis is based on the finding that oligodendrocytes of associative WM tracks are among the most metabolically active cells in the adult CNS and as such they are very vulnerable to the accumulation of metabolic damage. This damage is gradual in normal aging and more pronounced in demyelinating disorders such as MS and LA. The mechanism that makes GM thickness and sulcal span sensitive to this damage is not clear. It has been shown that myelin damage and axonal loss adversely affect neurons throughout the cortex due to increases in neuronal energy expenditures (Hildebrand et al., 1993) and the loss of neurotrophic factors (Dai et al., 2001; Wilkins et al., 2001, 2003). Further investigations that include indices of regional cortical metabolism such as glucose metabolism using PET are needed to address these questions.

Limitations

It is important to note that the measurements presented in this manuscript are cross-sectional. There are limitations to the conclusions that can be made about longitudinal processes, such as aging, from cross-sectional data as longitudinal studies often fail to confirm the age-related trends obtained from cross-sectional data. For example, longitudinal studies often report greater age effects on the slopes of non-verbal and visuo-spatial measures, suggesting the possibility of greater age effects on right hemisphere structures (Royall et al., 2005). However, no striking asymmetry could be confirmed from these cross-sectional data, although several appeared to favor the right hemisphere, and FA asymmetry correlated rather specifically with GM asymmetry (Tables 3, 5 and 6). Further research is needed to confirm the cross-sectional trends observed here using longitudinal study designs.

Summary

There is a significant interest in using diffusion tensor imaging as a measure of fiber integrity in aging, dementia, and other disease processes. We therefore examined the relationship between fiber integrity ascertained with DTI and other sensitive indices of cerebral health. The resulting data help to understand which of the correlations are mediated by age-dependent atrophy and which persist in the presence of age correction, and shed light on the differential value of various complementary imaging techniques in the assessment of brain aging.

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References

Abe, O., Aoki, S., et al., 2002. Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis. *Neurobiol. Aging* 23 (3), 433–441.

Allen, J.S., Bruss, J., et al., 2005. Normal neuroanatomical variation due to age: the major lobes and a parcellation of the temporal region. *Neurobiol. Aging* 26 (9), 1245–1260.

Bakshi, R., Caruthers, S.D., et al., 2000. Intraventricular CSF pulsation

artifact on fast fluid-attenuated inversion-recovery MR images: analysis of 100 consecutive normal studies. *AJNR Am. J. Neuroradiol.* 21 (3), 503–508.

Bartzokis, G., 2004a. Age-related myelin breakdown: a developmental model of cognitive decline and Alzheimer's disease. *Neurobiol. Aging* 25 (1), 5–18.

Bartzokis, G., 2004b. Quadratic trajectories of brain myelin content: unifying construct for neuropsychiatric disorders. *Neurobiol. Aging* 25 (1), 49–62.

Bartzokis, G., Beckson, M., et al., 2001. Age-related changes in frontal and temporal lobe volumes in men: a magnetic resonance imaging study. *Arch. Gen. Psychiatry* 58 (5), 461–465.

Bartzokis, G., Cummings, J.L., et al., 2003. White matter structural integrity in healthy aging adults and patients with Alzheimer disease: a magnetic resonance imaging study. *Arch. Neurol.* 60 (3), 393–398.

Bartzokis, G., Sultzer, D., et al., 2004. Heterogeneous age-related breakdown of white matter structural integrity: implications for cortical “disconnection” in aging and Alzheimer's disease. *Neurobiol. Aging* 25 (7), 843–851.

Basser, P., 1994. Focal magnetic stimulation of an axon. *IEEE Trans. Biomed. Eng.* 41 (6), 601–606.

Bastos Leite, A.J., Scheltens, P., et al., 2004. Pathological aging of the brain: an overview. *Top. Magn. Reson. Imaging* 15 (6), 369–389.

Benes, F.M., Turtle, M., et al., 1994. Myelination of a key relay zone in the hippocampal formation occurs in the human brain during childhood, adolescence, and adulthood. *Arch. Gen. Psychiatry* 51, 477–484.

Braak, H., Braak, E., 1996. Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. *Acta Neuropathol. (Berl)* 92 (2), 197–201.

Conturo, T.E., McKinstry, R.C., et al., 1996. Encoding of anisotropic diffusion with tetrahedral gradients: a general mathematical diffusion formalism and experimental results. *Magn. Reson. Med.* 35 (3), 399–412.

Dai, X., Qu, P., et al., 2001. Neuronal signals regulate neurotrophin expression in oligodendrocytes of the basal forebrain. *Glia* 34 (3), 234–239.

de Groot, J.C., de Leeuw, F.E., et al., 2001. Cerebral white matter lesions and subjective cognitive dysfunction: the Rotterdam Scan Study. *Neurology* 56 (11), 1539–1545.

de Leeuw, F.E., de Groot, J.C., et al., 2001. Prevalence of cerebral white matter lesions in elderly people: a population based magnetic resonance imaging study. The Rotterdam Scan Study. *J. Neurol. Neurosurg. Psychiatry* 70 (1), 9–14.

de Leeuw, F.E., Barkhof, F., et al., 2005. Progression of cerebral white matter lesions in Alzheimer's disease: a new window for therapy? *J. Neurol. Neurosurg. Psychiatry* 76 (9), 1286–1288.

Du, A.T., Schuff, N., et al., 2005. White matter lesions are associated with cortical atrophy more than entorhinal and hippocampal atrophy. *Neurobiol. Aging* 26 (4), 553–559.

Flood, D., Coleman, P., 1988. Neuron numbers and size in aging brain: comparison of human, monkey and rodent data. *Neurobiol. Aging* 9, 453–463.

Ge, Y., Grossman, R.I., et al., 2002. Age-related total gray matter and white matter changes in normal adult brain: Part I. Volumetric MR imaging analysis. *AJNR Am. J. Neuroradiol.* 23 (8), 1327–1333.

Hildebrand, C., Remahl, S., et al., 1993. Myelinated nerve fibres in the CNS. *Prog Neurobiol.* 40 (3), 319–384.

Horsfield, M.A., Jones, D.K., 2002. Applications of diffusion-weighted and diffusion tensor MRI to white matter diseases—A review. *NMR Biomed.* 15 (7–8), 570–577.

Jelsing, J., Rostrup, E., et al., 2005. Assessment of in vivo MR imaging compared to physical sections in vitro—A quantitative study of brain volumes using stereology. *NeuroImage* 26 (1), 57–65.

Jernigan, T.L., Archibald, S.L., et al., 2001. Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol. Aging* 22 (4), 581–594.

- Kochunov, P., Lancaster, J.L., et al., 2001. Regional spatial normalization: toward an optimal target. *J. Comput. Assist. Tomogr.* 25 (5), 805–816.
- Kochunov, P., Lancaster, J., et al., 2005a. Mapping structural differences of the corpus callosum in individuals with 18q deletions using targetless regional spatial normalization. *Hum. Brain Mapp.* 24 (4), 325–331.
- Kochunov, P., Mangin, J.F., et al., 2005b. Age-related morphology trends of cortical sulci. *Hum. Brain Mapp.* 26 (3), 210–220.
- Kochunov, P., Lancaster, J.L., Glahn, D.C., Purdy, D., Laird, A.R., Gao, F., Fox, P., 2006. Retrospective motion correction protocol for high-resolution anatomical MRI. *Hum. Brain Mapp.* 27 (12) (Dec.), 957–962.
- Kochunov, P., Thompson, P.M., Coyle, T.R., Lancaster, J.L., Kochunov, V., Royall, D., Mangin, J.F., Rivière, D., Fox, P., in press. Relationship among neuroimaging indices of cerebral health during normal aging. *Hum. Brain Mapp.*
- Lehmbeck, J.T., Brassens, S., et al., 2006. Combining voxel-based morphometry and diffusion tensor imaging to detect age-related brain changes. *Neuroreport.* 17 (5), 467–470.
- Lerch, J.P., Evans, A.C., 2005. Cortical thickness analysis examined through power analysis and a population simulation. *NeuroImage* 24 (1), 163–173.
- Magnotta, V.A., Andreasen, N.C., et al., 1999. Quantitative in vivo measurement of gyrification in the human brain: changes associated with aging. *Cereb. Cortex* 9 (2), 151–160.
- Mazziotta, J.C., Toga, A.W., et al., 1995. A probabilistic atlas of the human brain: theory and rationale for its development. The International Consortium for Brain Mapping (ICBM). *NeuroImage* 2 (2), 89–101.
- Mazziotta, J.C., Toga, A.W., et al., 2001. A probabilistic atlas and reference system for the human brain: International Consortium for Brain Mapping (ICBM). *Philos. Trans. R. Soc. Lond., B Biol. Sci.* 356 (1412), 1293–1322.
- Miller, A.K., Alston, R.L., et al., 1980. Variation with age in the volumes of grey and white matter in the cerebral hemispheres of man: measurements with an image analyser. *Neuropathol. Appl. Neurobiol.* 6 (2), 119–132.
- Morrison, J.H., Hof, P.R., 1997. Life and death of neurons in the aging brain. *Science* 278 (5337), 412–419.
- Moseley, M., 2002. Diffusion tensor imaging and aging—A review. *NMR Biomed.* 15 (7–8), 553–560.
- Oreja-Guevara, C., Rovaris, M., et al., 2005. Progressive gray matter damage in patients with relapsing–remitting multiple sclerosis: a longitudinal diffusion tensor magnetic resonance imaging study. *Arch. Neurol.* 62 (4), 578–584.
- Pantoni, L., Garcia, J.H., 1995. The significance of cerebral white matter abnormalities 100 years after Binswanger's report. A review. *Stroke* 26 (7), 1293–1301.
- Peters, A., Moss, M.B., et al., 2000. Effects of aging on myelinated nerve fibers in monkey primary visual cortex. *J. Comp. Neurol.* 419 (3), 364–376.
- Pfefferbaum, A., Sullivan, E.V., et al., 2000. Age-related decline in brain white matter anisotropy measured with spatially corrected echo-planar diffusion tensor imaging. *Magn. Reson. Med.* 44 (2), 259–268.
- Pierpaoli, C., Basser, P.J., 1996. Toward a quantitative assessment of diffusion anisotropy. *Magn. Reson. Med.* 36 (6), 893–906.
- Raz, N., Gunning, F.M., et al., 1997. Selective aging of the human cerebral cortex observed in vivo: differential vulnerability of the prefrontal gray matter. *Cereb. Cortex* 7 (3), 268–282.
- Royall, D.R., Roman, G.C., et al., 2003. Pathological determinants of dementia in Alzheimer's disease (AD). *Exp. Aging Res.* 29 (1), 107–110.
- Royall, D.R., Palmer, R., et al., 2005. Normal rates of cognitive change in successful aging: the freedom house study. *J. Int. Neuropsychol. Soc.* 11 (7), 899–909.
- Sachdev, P., Brodaty, H., 1999. Quantitative study of signal hyperintensities on T2-weighted magnetic resonance imaging in late-onset schizophrenia. *Am. J. Psychiatry* 156 (12), 1958–1967.
- Selemon, L.D., Rajkowska, G., et al., 1995. Abnormally high neuronal density in the schizophrenic cortex. A morphometric analysis of prefrontal area 9 and occipital area 17. *Arch. Gen. Psychiatry* 52 (10), 805–818 (discussion 819–820).
- Smith, S.M., 2002. Fast robust automated brain extraction. *Hum. Brain Mapp.* 17 (3), 143–155.
- Smith, S.M., Jenkinson, M., Johansen-Berg, H., Rueckert, D., Nichols, T.E., Mackay, C.E., Watkins, K.E., Ciccarelli, O., Cader, M.Z., Matthews, P.M., Behrens, T.E., 2006. Tract-based spatial statistics: voxelwise analysis of multi-subject diffusion data. *NeuroImage* 31 (4) (Jul. 15), 1487–1505.
- Sowell, E.R., Peterson, B.S., et al., 2003. Mapping cortical change across the human life span. *Nat. Neurosci.* 6 (3), 309–315.
- Sullivan, E.V., Pfefferbaum, A., 2003. Diffusion tensor imaging in normal aging and neuropsychiatric disorders. *Eur. J. Radiol.* 45 (3), 244–255.
- Sullivan, E.V., Adalsteinsson, E., et al., 2001. Equivalent disruption of regional white matter microstructure in ageing healthy men and women. *Neuroreport* 12 (1), 99–104.
- Symonds, L.L., Archibald, S.L., et al., 1999. Does an increase in sulcal or ventricular fluid predict where brain tissue is lost? *J. Neuroimaging* 9 (4), 201–209.
- Thompson, P.M., Hayashi, K.M., et al., 2003. Dynamics of gray matter loss in Alzheimer's disease. *J. Neurosci.* 23 (3), 994–1005.
- Thompson, P.M., Hayashi, K.M., et al., 2004. Mapping cortical change in Alzheimer's disease, brain development, and schizophrenia. *NeuroImage* 23 (Suppl. 1), S2–S18.
- Ulug, A.M., Barker, P.B., et al., 1995. Correction of motional artifacts in diffusion-weighted images using a reference phase map. *Magn. Reson. Med.* 34 (3), 476–480.
- Vrenken, H., Pouwels, P.J., et al., 2006. Altered diffusion tensor in multiple sclerosis normal-appearing brain tissue: cortical diffusion changes seem related to clinical deterioration. *J. Magn. Reson. Imaging* 23 (5), 628–636.
- Walhovd, K.B., Fjell, A.M., et al., 2005. Effects of age on volumes of cortex, white matter and subcortical structures. *Neurobiol. Aging* 26 (9), 1261–1270.
- Wen, W., Sachdev, P.S., et al., 2006. Gray matter reduction is correlated with white matter hyperintensity volume: a voxel-based morphometric study in a large epidemiological sample. *NeuroImage* 29 (4), 1031–1039.
- Wilkins, A., Chandran, S., et al., 2001. A role for oligodendrocyte-derived IGF-1 in trophic support of cortical neurons. *Glia* 36 (1), 48–57.
- Wilkins, A., Majed, H., et al., 2003. Oligodendrocytes promote neuronal survival and axonal length by distinct intracellular mechanisms: a novel role for oligodendrocyte-derived glial cell line-derived neurotrophic factor. *J. Neurosci.* 23 (12), 4967–4974.
- Yakovlev, P.I., Lecours, A.R., 1967. *Regional Development of the Brain in Early Life*. Blackwell Scientific Publications, Boston.