Relationship Among Neuroimaging Indices of Cerebral Health During Normal Aging

Peter Kochunov,^{1*} Paul M. Thompson,² Thomas R. Coyle,³
Jack L. Lancaster,¹ Valeria Kochunov,¹ Donal Royall,⁴ Jean-François Mangin,⁵
Denis Rivière,⁵ and Peter T. Fox¹

¹Research Imaging Center, University of Texas Health Science Center at San Antonio, Texas

²Laboratory of Neuroimaging, Department of Neurology, UCLA School of Medicine, Los Angeles, California

³Department of Psychology, University of Texas at San Antonio, Texas

⁴Department of Psychiatry, University of Texas Health Science Center at San Antonio, Texas

⁵Service Hospitalier Frédéric Joliot, CEA, Orsay, France

Abstract: Sensitive measures of brain aging show great promise for gauging factors that affect aging and degenerative processes, such as risk genes or therapy. Here we examined age-related trends for three indices of cerebral health: gyral gray matter (GM) thickness, dilation of sulcal spaces with CSF, and the volume of T2-hyperintense white matter (HWM) lesions. The study involved 31 healthy adults age 57–82 years old. Measurements of average GM thickness, average sulcal span and HWM volume were performed using high-resolution 3D T1- and T2-weighted brain MR images. Age-related trends for the three cerebral health indices were consistent with previously published work though the analysis of their covariance led to a previously unreported relationship. Simultaneous multiple regression found that dilation of cortical sulci were primarily ($t = 2.59$, $P < 0.01$) related to the increases in HWM volume and secondarily related ($t = -2.51$, $P < 0.01$) to the reductions of the cortical GM thickness. The are-corrected correlation between reduction in GM thickness and increases in HWM volume, was not significant ($P = 0.34$). These findings are of interest in designing quantitative measures of brain aging for monitoring individual patients and in large-scale clinical trials. *Hum Brain Mapp* 29:36–45, 2008. © 2007 Wiley-Liss, Inc.

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*Correspondence to: Peter Kochunov, University of Texas Health Science Center at San Antonio, Research Imaging Center, 7703 Floyd Curl Drive, San Antonio, Texas 78284. E-mail: kochunov@uthscsa.edu

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INTRODUCTION

In next decades, the proportion of population aged 65 years and above will increase from 12% in 2003 to over 20% by 2030 [He et al., 2005]. The increase in population, in which the disability rates from the dementias could be as high as 10–20%, mandates the development of research tools that could help detect early signs of abnormal cerebral aging and track the progression of neurodegenerative disorders. There is an urgent need for sensitive quantitative measures of the cerebral aging process to understand the trajectory of age-related change, and also for clinical trials that assess how well anti-dementia drugs are resisting degenerative changes. In clinical studies, it is also beneficial to develop

the normal range of variation for morphometric parameters during normal aging, to better detect deviations from normal that may signal the onset of mild cognitive impairment, Alzheimer's disease, or other dementias. Consequently, noninvasive imaging of age-related cerebral alterations is an extremely active area of research, where advances in high-resolution, multimodal, structural MR imaging are paving the way for systematic, quantitative studies of regional morphology of cerebral aging.

Age-related trends and the interrelationship were investigated among three well-established neuroimaging indices of cerebral health: (i) cortical gray matter (GM) thickness, (ii) dilation and filling of sulcal and ventricular spaces with CSF, and (iii) volume of T2-hyperintense white matter (HWM) lesions. These indices complement more traditional volumetric assessments of the hippocampus, entorhinal cortex, and medial temporal lobe structures that show the earliest changes in Alzheimer's disease [Csernansky et al., 2005; Du et al., 2006; Ezekiel, 2004]. Other indices include measuring the cerebral boundary shift to estimate global cerebral atrophy in longitudinal studies [Smith et al., 2002] and tensor-based morphometry or surface-based anatomical modeling to visualize the region and rate of age-related volume loss [Studholme et al., 2004; Thompson et al., 2001, 2004a].

Cortical GM thickness can be defined as the 3D distance from the outer cortical surface to the inner cortical WM–GM boundary. Cortical thickness undergoes significant age-related changes [Sowell et al., 2003] and diminished cortical thickness is thought to be related to regional neuronal density in the cortical mantle [Jelsing et al., 2005; Lerch and Evans, 2005; Selemon et al., 1995]. During normal aging, the average thickness of the GM mantle is reported to decrease linearly with age from an average thickness of ~2.6 mm at the age of 20 to <2 mm at the age of 80–90 by both neuroimaging and histological studies [Magnotta et al., 1999; Raz et al., 1997]. The rate of cortical GM thickness reduction in abnormal aging could be different from that in healthy aging and this difference could be an important diagnostic factor [Thompson et al., 2003, 2004b]. In both normal and abnormal aging the rate of GM volume loss has been shown to be correlated with progression of neuropsychological deficits.

A substitute parameter called regional GM density (GMD) has been introduced and widely used [Good et al., 2001; Wright et al., 1995] because of difficulties in measuring GM thickness directly. Regional GMD is defined as the proportion of voxels classified as GM relative to voxels of other tissue types as analyzed within a sphere of a fixed radius, usually 5–15 mm. Since the average thickness of GM mantle is only ~2–3 mm, the GM ribbon folds cannot be fully spatially resolved even on high-resolution ($1 \times 1 \times 1$ mm) 3D MR images, a limitation known as buried cortex [Fischl and Dale, 2000; Magnotta et al., 1999]. Buried cortex is related to the inability to resolve details of finer cortical folds due to insufficient spatial resolution. Unless corrected for, it can greatly influence the calculation of re-

gional GM thickness. A number of approaches have been proposed to calculate GMD [Fischl and Dale, 2000; Magnotta et al., 1999]. Sowell et al. [2002, 2003] were the first group to use regional GMD to study effects of cortical aging in a group of 176 subjects aged 7–87 years old while Gogtay and colleagues used GMD to study regional effect of cerebral maturation in subjects age 4–22 years [Gogtay et al., 2004]. The trends of age-related GMD decline were analogous to the trends in GM thickness reported by Raz et al. [1997] and Magnotta et al. [1999].

Average sulcal span is another readily measurable neuroimaging marker of cerebral health. While cortical GM thickness undergoes relatively small changes during normal aging, the average span of sulcal spaces increases from less than 1 mm for subjects in their 20s, to 5–10 mm in older (70–80 years old) subjects [Kochunov et al., 2005] with the compensatory filling-in of freed space by CSF. This is a well-described phenomenon and visual assessments of regional “widening” of cortical sulci, specifically in the hippocampal, entorhinal, and medial temporal cortices are correlated with neurocognitive decline in the course of mild cognitive impairment and dementia disorders [Bastos Leite, et al., 2004]. The cause of this phenomenon is unknown but it is thought that reduction of gyral thickness and degeneration of gyral GM mantle results in dilation of cortical sulci [Jernigan et al., 2001; Magnotta et al., 1999; Symonds et al., 1999]. Recently, we developed an automated analysis method to study age-related changes in sulcal span in the primary and secondary cortical sulci [Kochunov et al., 2005]. This analysis utilizes the fact that the MRI contrast between GM and cerebrospinal fluid (CSF) remains more stable through life-span than the GM/WM contrast [Kochunov et al., 2005]. We used this method to study age-related trends in sulcal span and depth in 14 prominent sulcal structures in a group of 90 healthy volunteers aged 20–82 years. Both average sulcal span and depth showed significant changes with age. The age-related increase in sulcal span was as high as 0.9 mm/decade for sulcal structures associated with multimodal cortical areas such as the superior frontal sulcus. However, that manuscript did not elaborate on the underlying cause of sulcal dilation. An important finding was that observed regional rates of increase in sulcal span (~0.5–0.7 mm/decade) and reduction in sulcal depth (~0.3–0.4 mm/decade) could not be fully explained by the reduction in thickness (<0.1 mm/decade) [Magnotta et al., 1999] of the cortical mantle alone. This indicated that other processes—such as reduction in gyral WM volumes—must also be considered, in order to account for the high-rates of sulcal span.

The volume of HWM observable on T2-weighted MR studies is also a very commonly used marker of cerebral health. Regions of high signal intensity on T2-weighted images in WM are a very common finding in both normal and abnormal aging and neurodegenerative disorders. The T2-weighting mechanism leads to a voxel intensity increase for areas with longer spin–spin (T2) relaxation times, e.g. water. Healthy cerebral WM tracts are covered

(myelinated) with compounds containing long-chain fatty acids with very short T2-relaxation time and thus appear dark on T2-weighted images. Local edema, often associated with degradation of the myelin sheath, results in localized accumulation of extracellular water. This lengthens a voxel's average T2 relaxation time and results in increased signal intensity of edema on a T2-weighted image. The etiology of HWM is nonspecific and could be due to ischemia from small vessel disorder, trauma, inflammatory response, and other causes [Pantoni and Garcia, 1995]. The prevalence of HWM regions in normal aging were reported for a large group of subjects (>1000) in the Rotterdam study. This study showed that the HWM incidence rate could be as high as 60–100% in normal subjects aged 60 years and above [de Leeuw et al., 2001, 2005]. As a cerebral health index, the increase in HWM volumes has been shown to be correlated with reduction in cerebral WM and GM, volumes [Du et al., 2006; Wen et al., 2006], and with severity of neurocognitive deficits in the neuropsychiatric and neurological disorders [Sachdev and Brodaty, 1999].

The cortical GM thickness and sulcal span can be used as the indices of cortical health, while the HWM volume can be used as an index of subcortical health. While these indices have been studied individually and in pairs in both normal and abnormal aging, no combined studies of these indices' trends and their interrelationship have yet been performed. We investigated the global trends and interrelationship for three indices of cerebral health in a group of 31 normally aging subjects aged 57–82. The imaging protocol was modified from our previously published work [Kochunov et al., 2005], by inclusion of T2-weighted study and increasing spatial resolution of T1-weighted study to isotropic 800 μm .

MATERIALS AND METHODS

Subjects

Thirty-one (11 males/20 females), normal, healthy subjects aged 57–82 (average age = 67.3 ± 6.7 years old) were recruited as a part of the International Consortium on Brain Mapping (ICBM) [Mazziotta et al., 1995, 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 subjects signed an informed consent.

Imaging

All imaging was performed at the Research Imaging Center, UTHSCSA, using a Siemens 3T Trio scanner and a high-resolution 8-channel head coil. An optimized, multi-

modality imaging protocol was used to acquire high-resolution T1- and T2-weighted imaging data.

T1-weighted imaging

High-resolution (isotropic 800 μm), T1-weighted images were acquired using a retrospective motion-corrected protocol [Kochunov et al., 2006]. Under 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° . This sequence was chosen because its adiabatic contrast-establishing pulse and linear phase encoding schema lead to a uniform tissue contrast across the imaging volume, being less affected by B1-inhomogeneity/RF penetration artifacts. The sequence control parameters—TI, TR, and flip angle—were adjusted to produce GM/WM contrast of 25% based on T1/T2 relaxometry measurements in a group of seven, young (average age = 23.4 ± 3.5 years) healthy subjects [Deichmann et al., 2000]. The acquisition time per full resolution segment is kept at 4.2 min by using a GRAPPA [Griswold et al., 2002] parallel imaging acceleration factor of 2 along the phase encoding direction.

T2-weighted imaging

The T2-weighted data was acquired with a high-resolution (isotropic 1 mm), 3D turbo-inversion recovery Fluid Attenuated Inversion Recovery (FLAIR) with the following parameters: TR/TE/TI/Flip angle = 5 s, 353 ms, 1.8 s, 180° . This sequence uses a nonselective inversion recovery pulse that removes CSF pulsation artifacts that are commonly seen in 2D FLAIR studies [Bakshi et al., 2000]. The inversion recovery pulse also attenuates signal from tissues with long T1 such as CSF in ventricular and sulcal spaces, thus simplifying identification of HWM regions.

Image processing

T1-weighted images

Processing of T1-weighted images for measuring indices of cortical health was performed in the following steps: removal of non-brain tissue, registration to the Talairach frame, RF inhomogeneity correction, brain tissue partial volume segmentation, and sulcal extraction and verification.

Removal of non-brain tissue. The non-brain tissues such as skin, muscle, fat etc. were removed using an automated skull stripping procedure, BET [Brain Extraction Tool; Smith, 2002], which is provided as an add-on for the MEDx (Sensor Systems) image analysis package (see Fig. 1A). The extracted brain images were cropped at the level of cerebellum.

Registration to Talairach frame. All brain images were globally, spatially normalized to the Talairach coordinate sys-

Figure 1.

T1-weighted image processing pipeline consists of skull stripping (A); spatial normalization, RF homogeneity correction and tissue segmentation (B); extraction of GM and WM surfaces (C,D); extraction of sulcal folds (E), and automated labeling of sulci (F).

tem to remove gross differences in brain size and orientation. Automated, nine-parameter (3 rotations, 3 scales, and 3 translations) FSL FLIRT global spatial normalization software [Smith et al., 2004] was used to register all images into the Talairach reference frame. The midline and AC-PC alignments were manually verified by two experienced neuroanatomists. All images were resliced at isotropic 800

μm resolution using a 3D, 15-voxel-wide sinc interpolation kernel (Fig. 1B).

RF inhomogeneity correction. All images were RF inhomogeneity corrected using the FAST method distributed with FSL package [Zhang et al., 2001]. RF inhomogeneity artifact manifests itself as a low-frequency variation in MRI

Figure 2.

Measurement of indices of cortical health: average sulcal span and average gyral GM thickness. Average sulcal span was defined as an average 3D distance between opposing gyral banks along the normal projections to the medial sulcal mesh. New tracings,

normal to the exterior GM mesh, were started at the intersections between normal projections to the sulcal mesh. The average gyral GM thickness was defined as an average 3D distance from the outer GM mesh to the inner cortical WM mesh.

image intensity, which confounds intensity-based image analyses unless corrected (Fig. 1B). Default FAST parameters were used.

Brain tissue partial volume segmentation. The partial volume, anatomical segmentation method FAST, distributed with the FSL package [Zhang et al., 2001], was used to segment MRI images into WM, GM, and CSF (Fig. 1B). A partial volume classifier approach provides a solution to partial voxel averaging which arises when there is more than one tissue-type (e.g., WM and GM) present within a single voxel. In such a case, the effective T1 relaxation time and voxel intensity will be a superposition (weighted average) of signals from each of the tissues present within the voxel. As the output, the FAST algorithm produces a 3D map of partial volume coefficients for each tissue type: CSF, GM, and WM. Partial volume coefficients vary in value from 0, indicating absence of a tissue class within a voxel to 1.0, indicating that a tissue class completely fills the voxel.

Extraction and identification of cortical and sulcal surfaces. Segmented images were imported into the BV (BrainVisa) database and processed through BV sulcal extraction and identification pipelines as described in [Kochunov et al., 2005]. The BrainVisa image processing pipeline extracts hemispheric spherical meshes from segmented GM and WM images (Fig. 1C,D). The medial surface of the cortical in-folds are obtained using a homotopic erosion technique [Mangin et al., 1995] and a “crevasse detector” is used to reconstruct sulcal structures as the medial surfaces from the two opposing gyral banks that span from the most internal point of sulcal fold to the convex hull of the cortex [Mangin et al., 1995, 2004] (Fig. 1E).

The BrainVisa sulcal identification pipeline incorporates a congregation of 500 artificial neural network-based pattern classifiers. Each classifier is tuned to identify a particular feature of the sulcal patterns. These neural networks work collaboratively to identify 56 sulcal structures for each hemisphere. The neural networks were trained on a database of twenty six expertly classified images, resulting in a classification accuracy ranging from 95% for primary and secondary fissures to around 70% for the highly variable tertiary sulcal structures [Rivière et al., 2002].

A skilled neuroanatomist reviewed results of automated sulcal identification and in an infrequent event (~5%), where a sulcus was assigned an incorrect label, it was manually relabeled while overlaid on cortical surface (Fig. 1F). The main task of manual processing was removal of anastomotic sulci (AS) associated with the sulci used in this project. AS are small, accessory sulci, usually <5 mm in length, originating, usually at a right angle, from the stem of the main sulcus and considered to be random folds [Ono et al., 1990]. AS were excluded from this analysis since a span measurement performed at the intersections between the main sulcus and an AS, especially along the direction of the AS, would lead to exaggerated values.

TABLE 1. Sulcal structures used in calculation of average sulcal span and average gyral GM thickness and their lobar association

Lobe	Structure
Frontal	Superior frontal sulcus Inferior frontal sulcus
Parietal	Pre-central sulcus Postcentral sulcus Intraparietal fissure
Temporal	Superior temporal sulcus
Limbic	Cingulate sulcus
Occipital Lobe	Lateral occipital, transverse occipital and lunate sulci Calcarine fissure
Inter-lobar	Central sulcus Parietoccipital fissure Collateral sulci

Selection of sulcal structures. Fourteen primary and secondary fissures were selected for this analysis (Table I). The selected structures had very high intersubject incidence rate (~100%) and were present in all subjects. Tertiary structures, such as the middle temporal and intermediate frontal sulci, and any AS, were not used in this analysis because tertiary structures are often absent (incidence rate of ~30–70%) and the AS are random folds that do not occur consistently across subjects [Ono et al., 1990]. Special attention was given to the cingulate sulcus. The cingulate sulcus is interrupted in about half of the population (55%) and is often divided into anterior and posterior cingulate sulci [Ono et al., 1990]. To establish intersubject consistency, the measurements for anterior and posterior portions of cingulate sulcus were combined.

Measurements of sulcal span and gyral GM thickness. A sulcal-span measurement method described in [Kochunov et al., 2005] was modified to simultaneously measure the span of the sulcal space and the thickness of GM ribbon on each of the gyral banks. Subvoxel resolution meshes for individual sulcal structures and exterior and interior GM meshes were used to perform measurements of the average sulcal span and gyral GM thickness.

The average sulcal span for an individual sulcal structure was defined as the average span of the sulcal space along the normal projections to the medial sulcal mesh (Fig. 2). High-resolution medial sulcal meshes for each sulcus were created by the BV sulcal extraction pipeline and labeled by automated/manual labeling. Geometrically, a medial sulcal mesh traverses the sulcal space in the middle of the sulcal “span” dimension, parallel to the gyral GM borders and spans the entire sulcal “depth” dimension (Fig. 2). To calculate sulcal span for individual sulci (Fig. 2A), we first identified the sulcal for this structure, as follows: The medial sulcal mesh for each sulcus was used to seed a 3D region growing algorithm to mask CSF volume associated with this sulcal structure. To prevent region-

growing from “spilling over” into intersecting sulci, points that were further than 10 mm away from the sulcal skeleton were rejected. The convex hull of the cortical GM ribbon was then used to isolate sulcal space from subarachnoid CSF. The Euclidean distance between two points residing on gyral GM mesh on either side of the sulcal surface, was taken as the sulcal span (Fig. 2). These points correspond to voxels with a partial volume of CSF at 50%; this is different from our previous method where projection tracing was stopped at the level of 10% CSF.

At the point of intersection between a normal projection to the sulcal mesh and the exterior GM mesh, a new tracing was started to measure the thickness of the GM ribbon. To measure GM thickness, a normal projection to the exterior GM mesh was traced until it intersected with the interior GM mesh that describes the GM/WM interface (see Fig. 2). The point of intersection between the normal projection and the interior GM mesh corresponds to voxels with partial WM/GM values of ~50%.

Sulcal span measurements were averaged along the entire sulcal surface, resulting in ~5,000 measurements per individual structure. Special attention was paid to the AS which are small, accessory sulci, originating, usually at a right angle, from the stem of the main sulcus and considered to be random folds [Ono et al., 1990]. As noted earlier, the AS were excluded from this analysis since the sulcal span GM thickness measurements performed near the intersections between the main sulcus and an AS, especially along the direction of the AS, would show an exaggerated value. Span measurements were not performed at sulcal points located within a 4 mm distance from an intersection between an AS and/or other sulci.

T2-image processing

T2-weighted FLAIR images were processed to prepare them to measure the total volume of HWM volume. The processing included the following steps: removal of non-brain tissue, registration to the T1-weighted images/Talairach frame, RF inhomogeneity correction, and manual delineation of hyperintense lesions by two neuroanatomists.

Removal of non-brain tissue. As in the T1-weighted image processing steps, the non-brain tissues were removed from T2-weighted images, such as skin, muscle, fat, etc., using the automated skull stripping procedure, BET [Smith, 2002]. Similar, to T1-weighted image processing, the extracted brain images were cropped at the level of cerebellum.

Registration to T1-weighted images/Talairach frame. Each subject's T2-weighted image was spatially registered to their own T1-weighted images that were already transformed to the Talairach coordinate system. Automated, nine-parameter (3 rotations, 3 scales, and 3 translations) FSL FLIRT global spatial normalization software [Smith et al., 2004] was used to register all images into the Talairach reference frame. Correlation ratio was used as the cost function and

a 3D, 15-voxel-wide sinc kernel was used as the interpolation function.

RF inhomogeneity correction. As for the T1-weighted images, all T2-weighted images were RF inhomogeneity corrected using a method FAST distributed with the FSL package [Zhang et al., 2001].

Manual delineation of FLAIR lesions. T2-hyperintense WM lesions were manually identified and labeled by two experienced neuroanatomists. Deskulled, RF-corrected and spatially normalized FLAIR images were loaded into MNI Display software (<http://www.bic.mni.mcgill.ca/software/Display>). Two neuroanatomists, blind to each subject's demographic information, independently identified WM lesions and “painted” them in 3D for each subject. For each subject a total HWM volume was calculated as an average from both observers. The average interobserver difference in HWM volumes was $5.3 \pm 2.5\%$ and interobserver correlation was highly significant ($r = 0.96$, $P < 0.01$).

Statistical analyses of age-related trends among degeneration markers

Age-related trends for cerebral health indices were estimated using linear regression analysis. This analysis was used to calculate the slope, intercept, and correlation coefficient that best represented the linear age-related change in average sulcal span, average gyral GM thickness, and HWM volume, as well as relationships among them. Partial correlation and multiple regression analyses were used to examine interrelationships among the cerebral health indices while controlling for subjects' age. Statistical significance for individual tests that were not part of an omnibus analysis was set at $P < 0.01$ (as opposed to $P < 0.05$) using two-tailed tests. The more conservative P -value was selected using a method described in Sankoh et al. [1997]. This method controls type I error rates for multiple tests of correlated measures (e.g., the cerebral health measures) and insures an overall α level of 0.05.

RESULTS

Age-related trends for indices of cerebral health

The results of the linear regression analysis for age-related trends for cerebral health indices are summarized in Figure 3 (solid lines). Average gyral GM thickness had a slightly stronger correlation with age ($r = -0.52$, $P < 0.01$) than did average sulcal span ($R = 0.50$, $P < 0.01$). The linear trends indicated that average sulcal span increase at the rate of 0.3 mm/decade (Fig. 4, top) and GM thickness decreased at a rate of 0.07 mm/decade, (Fig. 4, middle). HWM volume, showed a less robust relationship with age ($r = 0.19$, $P = 0.30$; Fig. 4, bottom) than did the other two cerebral health indices. HWM volume increased with age at a rate of $0.32 \text{ cm}^3/\text{decade}$.

Figure 3.

Linear (r) and age-corrected partial (pr) correlation coefficients are illustrated among age and three indices of cerebral health. *Indicates statistically significant correlations ($P < 0.01$).

Age-corrected relationships for indices of cerebral health

Partial correlation analysis was used to examine interrelationships among cortical and subcortical cerebral health indices while controlling for subjects' age (Fig. 3, dotted lines). The two indices of cortical health, average sulcal span and average GM thickness (see Fig. 5), were highly correlated ($r = 0.67$, $P < 0.01$). However, they only margin-

ally related to each other (using the conservative alpha of 0.01) when age was controlled ($pr = -0.43$, $P = 0.02$). Linear regression analysis of sulcal span on GM thickness indicated an approximately one-to-two relationship between the two indices of cortical health (slope = -2.08 ± 3.03 mm; intercept = 7.17 ± 6.64 mm): for every 1-mm reduction in GM thickness there was an approximately 2-mm dilation of sulcal structures. Whereas sulcal span was significantly related to the total HWM volume ($r = 0.49$, $P < 0.01$; Fig. 6), even when age was controlled ($pr = 0.48$, $P < 0.01$). The correlation between GM thickness and HWM volume approached statistical significance ($r = -0.34$, $P = 0.08$; Fig. 7); however, it was not significant when age was controlled for ($pr = -0.18$, $P = 0.34$).

Next, simultaneous multiple regression was used to examine whether average gyral GM thickness and total HWM volume predicted significant and unique variance in average sulcal span while accounting for subjects' age. Simultaneous regression provides an overall test of significance for all predictors in a regression model. It also provides significance tests for each predictor's beta coefficient and semipartial correlation. A beta coefficient describes the change in a criterion (sulcal span) corresponding to a unit change in a predictor (GM thickness or HWM volume). A semipartial correlation (sr) describes the amount of unique variance in a criterion accounted for by a predictor when all other predictors in the model are controlled.

Figure 4.

Cerebral health indices vs. age: average sulcal span (top), GM thickness (middle), and HWM volume (bottom).

Figure 5.

Age-corrected relationship between sulcal span and HWM volume. The solid line corresponds to the initial (0–1 cm³) increase in HWM volumes and dotted line the later (1 cm³ and up) increase in HWM volumes.

The simultaneous multiple regression performed here treated average GM thickness, total HWM volume, and subjects' age as predictors and average sulcal span as the criterion. The analysis was used to examine whether changes in sulcal span covaried primarily with GM thickness or HWM volume, while controlling for age. The overall (omnibus) regression model was significant when all predictors were considered simultaneously ($F[3,27] = 9.49$, $P < 0.001$, $R^2 = 0.51$). Sulcal widening was significantly related to decreases in GM thickness ($b = -1.29$, $t = -2.51$, $P = 0.03$, $sr = -0.30$) and to increases in HWM volume ($b = 0.13$, $t = 2.59$, $P = 0.02$, $sr = 0.35$). However, sulcal widening was not related to subjects' age when the indices of cerebral health (GM thickness and HWM volume) were considered ($b = 0.01$, $t = 1.59$, $P = 0.12$, $sr = 0.21$).

Figure 6.

Age-corrected relationship between cortical health indices: average sulcal span is plotted vs. average GM thickness.

DISCUSSION

Global age-related trends and age-corrected interrelationships were examined for three indices of cerebral health. The resulting data are especially interesting in that they examine the association between structural indices in the age range where subjects are developing first signs of cerebral aging.

Aging trends for individual indices were consistent with previously published work. Cortical GM thickness and sulcal spans showed statistically significant correlations with subject's age ($P < 0.01$). The average cortical GM thickness reduced at the rate of 0.07 mm/decade and had the highest correlation $r = -0.52$ with age. This finding is consistent with a previous report by Magnotta et al. [1999] who studied reduction of cortical GM thickness in a cross-sectional study of 148 healthy subjects age 18–82. They reported an average reduction rate of 0.06 mm/decade ($r = -0.50$). HWM regions were observed in all of the subjects with a mean volume of 0.82 ± 0.13 cm³ (expressed as mean $\pm$ standard error). Incidence rate (100%) and average HWM volume are consistent with findings of the largest HWM study to date—the Rotterdam Scan Study with over 1,000 normal subjects. That study reported an incidence rate of 92% and average HWM volume of 0.975 ± 0.28 cm³ for subjects in the age range we examined (60–80 years).

Novel and important finding were seen in the analysis of the interrelationship among indices of cerebral health. When corrected for age, the average sulcal span was only significantly correlated ($pr = 0.48$; $P < 0.01$) with the HWM volume and marginally correlated with the GM thickness ($pr = -0.42$, $P = 0.02$). Simultaneous regression analysis further confirmed that the sulcal widening could be associated with the increase in HWM volume ($t = 2.59$) and the reduction of GM thickness ($t = -2.51$). It appears that the age-corrected relationship between sulcal span and HWM is bimodal (see Fig. 5). The initial (0–1 cm³)

Figure 7.

Age-corrected relationship between GM thickness and HWM volume.

increase of HWM volume corresponded to an increase in sulcal span at the rate of 0.5 mm/cm³. The later (1 cm³ and up) increase in HWM volume corresponded to a marginal increase in sulcal span at the rate 0.1 mm/cm³ (see Fig. 5). Decrease in cortical GM thickness appears to produce a “double” increase in sulcal span (see Fig. 5). This two-to-one relationship between GM thickness and sulcal span corresponds with our previous finding of a global two-to-one relationship between sulcal span and sulcal depth [Kochunov et al., 2005]. This is possibly due to the cortical mantle being present on both banks of the sulcus. Age-related decline in gyral GM thickness (0.07 mm/decade) explains only about 40% of the age-related rate of sulcal dilation (0.3 mm/decade), when taking the rate for both gyral banks into consideration (e.g., 2×0.07 mm/decade).

Limitations

A potential limitation of this work is the fact that studies are cross-sectional and not serial, longitudinal examinations. Previous research have shown that cross-sectional measurements cannot fully represent the trajectory of age-related change [Kraemer et al., 2000; Royall et al., 2005] obtained from serial examination of longitudinally studied cohorts. However, our result should guide future studies in the selection of neuroimaging indices for studies in aging populations.

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