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The Structure of the Cerebral Cortex Across Adult Life: Age-Related Patterns of Surface Area, Thickness, and Gyrification

Larson J. Hogstrom, Lars T. Westlye, Kristine B. Walhovd and Anders M. Fjell

Center for the Study of Human Cognition, Department of Psychology, University of Oslo, Oslo 0317, Norway

Address correspondence to Larson J. Hogstrom, Center for the Study of Human Cognition, Department of Psychology, University of Oslo, P.O. Box 1094, Blindern, Oslo 0317, Norway. Email: l.t.westlye@psykologi.uio.no (L.T. Westlye).

Older adults exhibit global reductions in cortical surface area, but little is known about the regional patterns of reductions or how these relate to other measures of brain structure. This knowledge is critical to understanding the dynamic relationship between different macrostructural properties of the cortex throughout adult life. Here, cortical arealization, local gyrification index (LGI), and cortical thickness were measured vertex wise across the brain surface in 322 healthy adults (20–85 years), with the aims of 1) characterizing age patterns of the three separate cortical measures and 2) testing the age-independent relationships among cortical surface area, gyrification, and thickness. Surface area showed strong age-related decreases, particularly pronounced in dorsomedial prefrontal, lateral temporal, and fusiform cortices, independently of total white matter volume. LGI decreased with age independently of regional surface area, with strongest effects laterally, extending from the angular gyrus in all directions. As expected, regional surface area and LGI were positively related. However, both measures correlated negatively with thickness, indicating increasing local arealization and gyrification with decreasing cortical thickness. We suggest that this pattern of regional "cortical stretching" reflects the well-established phylogenetic principle of maximizing surface area and gyrification rather than increase thickness to facilitate brain connectivity and functional development.

Keywords: aging, cortical thickness, gray matter, magnetic resonance imaging morphometry, neurodevelopment

Introduction

The advent of surface-based modeling has offered new possibilities to study the effects of aging on brain structure by allowing measurement of the two distinct morphometric variables that define cortical volume: Surface area and cortical thickness. Although both thickness and area are highly heritable (Rogers et al. 2007; Kremen et al. 2010; Eyler et al. 2011), recent studies have suggested that the two are genetically independent (Panizzon et al. 2009) and differentially affected by the timing of prenatal perturbations (White et al. 2010). The unique regional variations of each measure along the cortical surface, as well as their genetic independence, have prompted authors to evaluate cortical thickness and surface area as separate morphometric features of neurodevelopment, aging, and disease (Im et al. 2008; Dickerson et al. 2009; Ostby et al. 2009; Panizzon et al. 2009; Lemaitre et al. 2010; Winkler et al. 2010; Eyler et al. 2011).

Cortical folding, or the degree of gyrification, is an additional facet of cortical structure that is intrinsically related to area. Individual and regional differences in gyrification and arealization of the cerebral cortex partly arise from processes reflecting the fundamental principles of cortical development and organization, including forces driving the extensive wiring of cortico-cortical connections along the brain surface (Van Essen 1997). After dramatic increases in cortical gyrification occurring during fetal development, gross folding patterns are thought to stabilize after the brain reaches approximately half of its final volume (Armstrong et al. 1995). Dynamic morphometric alterations along the cortical surface, however, continue throughout the lifespan. These changes likely reflect interactions between early neurodevelopmental processes including pruning, lifelong experience-related reshaping, and neurodegenerative processes during the course of aging. Interestingly, computational modeling studies have suggested that increased gyrification and areal expansion might be more efficient means to facilitate brain connectivity and functional development than increasing the thickness of the cortex (Ruppin et al. 1993; Murre and Sturdy 1995), and that pruning during early phases of neurodevelopment may be a prerequisite for optimal gyrification and associated areal increase (White et al. 2010). As such, regional increases in surface area during the ontogeny may be driven or facilitated by plastic processes inducing cortical thinning, suggesting regional negative correlations between area and thickness originating from early childhood. Although speculative, these processes provide a mechanistic account of the proposed relationship between the two measures of brain morphometry and further suggest that the association between thickness and area contains biologically meaningful information that complement the details carried by the two indices alone.

Both phylogenetically and ontogentically, important principles governing cortical arealization and thickness have been distinguished: The radial unit hypothesis identifies the cortical column as a fundamental unit of cortical organization. In ontogeny, neurons that are born close to each other in the ventricular zone migrate along a common pathway to form cortical columns (Rakic 1988). While the final number of ontogenetic columns largely determines cortical surface area, cortical thickness is closely linked to the number of cells within a column (Rakic 1995). Ontogenetic and phylogenetic increases in cortical volume are largely driven by increasing gyrification and associated surface area expansion rather than increased cortical thickness (Rakic 2009; White et al. 2010). Models of cortical structure based on transgenic manipulation have begun to pinpoint the cellular and molecular factors most influential in surface arealization (Chenn and Walsh 2002). In humans, surface area expansion and reduction have been observed in development and aging, respectively (Pakkenberg and Gundersen 1997; Ostby et al. 2009; Lemaitre et al. 2010). In older adults, volume loss appears more closely related to surface area than cortical thickness (Im et al. 2008; Dickerson et al. 2009; Winkler et al. 2010). Dickerson et al. (2009) found

that in the middle temporal lobe, the area of entorhinal and posterior parahippocampal surfaces, underwent age-related reductions after adjusting for head size. Such regional decreases parallel a global reduction in surface area in adults (Lemaitre et al. 2010), likely mirroring reductions in total brain volume (Walhovd et al. 2011).

To date, the regional changes in cortical surface area that occur during the course of the adult lifespan are poorly defined. Recent methodological advancements now allow for an improved analysis and visualization of regional surface area variations. By recording the local distortions needed to fit a subject's brain to a standardized atlas, a point-by-point map of areal expansion or reduction can be created (Dale et al. 1999; Fischl and Dale 2000; Joyner et al. 2009; Rimol et al. 2010). Such per-vertex methods show promise because, as seen from genetic studies of surface arealization, area variations are highly regional and results do not always follow traditional anatomical divisions (Chen et al. 2011, 2012). Although continuous per-vertex methods afford high spatial resolution, they have not yet been applied to study the changes in cortical surface area and gyrification that occur during the adult life span.

Age-related changes in cortical thickness are well-established (Salat et al. 2004; Sowell et al. 2004; Fjell et al. 2009; Hutton et al. 2009; Westlye et al. 2010a; McGinnis et al. 2011), but few studies have addressed the dynamic relationship between cortical thickness and surface area. Hill et al. (2010) noted qualitatively that in postnatal development, regions with high-expanding surface area, including the dorsolateral prefrontal cortex, and dorsal parietal cortex, tend to reach peak cortical thickness after low-expanding regions, such as the visual cortex. Examining a series of predefined surface regions in adults. Winkler et al. (2010) reported weak or no correlations between surface area and thickness, but noted that the relationship between the two measures is likely to be dynamic across the cortical mantle. Quantitative assessments relating thickness and area throughout the brain on a point-by-point basis are currently lacking. Existing evidence suggests that both metrics undergo age-related decrease. This phenomenon in older adults appears to also affect gyrification complexity by widening of sulci and narrowing of gyral crowns (Magnotta et al. 1999). However, because of their distinct morphometric footprint, it is unclear how surface arealization relates to the thickness or gyrification of gray matter along the cortical mantle.

Understanding the dynamic relationships between surface area, gyrification, and cortical thickness in a lifespan perspective will give insight into traits that appear to be genetically independent. These efforts will also help contextualize the driving factors underlying basic cortical organization and age-related differences in cortical morphometry. In the present study, we created the surface-based models of surface area, gyrification, and cortical thickness using T_1-weighted magnetic resonance imaging datasets from 322 healthy adults aged 20–85 years. We 1) characterized the age-related differences in area, gyrification, and cortical thickness across the cortical mantle, and 2) tested the relationship between the three measures at each vertex. We hypothesized negative correlations between all measures and age. Further, we predicted a positive relationship between area and gyrification and expected both measures to correlate negatively with cortical thickness.

Materials and Methods

Subjects

The sample consisted of 322 healthy adults ranging in age from 20 to 85 years (mean age 51.3 years, standard deviation, SD = 17.3 years, 43% female). All subjects were right-handed, native Norwegian speakers. The study was approved by the Regional Ethical Committee of South Norway (REK-Sør) and all participants gave written informed consent. Subjects with a history of injury or disease known to affect the function of the central nervous system (CNS) such as neurological or psychiatric illness, serious head injury, or stroke were excluded from the study. Additional exclusion criteria included the use of medicines know to affect the CNS and self-reported worries concerning their memory abilities. All included participants scored <16 on the Beck Depression Inventory (Beck and Steer 1987) and participants over the age of 40 scored >25 on the mini-mental state examination (Folstein et al. 1975; Bravo and Hebert 1997). The mean full-scale intelligence quotient as assessed with the Wechsler Abbreviated Scale of Intelligence (Wechsler 1999) was 114.9 (SD = 9.1). All datasets were examined by a neuroradiologist and were deemed free of significant injury or disease. For subsequent analysis participants were binned into three separate age groups: Young, middle, and older adults. The young group consisted of adults age 20–39 years ($n = 92$, mean age 28.5 years, SD = 6.1 years), the middle group was age 40–59 years ($n = 114$, mean age 51.9 years, SD = 5.2 years), and the old group was age 60–85 years ($n = 116$, mean age 69.1 years, SD = 6.6 years).

Image Acquisition

Imaging was performed at the Oslo University Hospital Rikshospitalet using a 1.5-T Siemens Avanto scanner (Siemens Medical Solutions) and a 12-channel head coil. The sequences used for surface-based analysis were two 3D T_1-weighted Magnetization Prepared Rapid Gradient Echo with the following imaging parameters: repetition time/echo time/time to inversion/flip angle = 2400 ms/3.61 ms/1000 ms/8°, matrix 192 × 192, field of view = 240. Each scan lasted 7 min 42 s and consisted of 160 sagital slices with a voxel size of 1.20 × 1.25 × 1.25 mm. During postprocessing, the two runs were averaged to increase signal-to-noise ratio.

Image Analysis

Automated cortical surface reconstructions of T_1-weighted images were carried out using FreeSurfer (http://surfer.nmr.mgh.harvard.edu/). Detailed descriptions of the surface-based methods are given elsewhere (Dale et al. 1999; Fischl et al. 1999, 2001; Fischl and Dale 2000). Briefly, processing steps include motion correction, removal of non-brain tissue, automated Talairach transformation, and intensity correction. Intensity and continuity information from the 3D volume are used in segmentation and deformation procedures to reconstruct a gray/white matter boundary throughout the brain (Dale et al. 1999). Cortical surfaces then undergo inflation, registration to a spherical atlas, and identification of gyral and sulcal regions (Desikan et al. 2006). Reconstructed data sets were visually inspected for accuracy, and segmentation errors were corrected. Surface area maps of the gray matter–white matter (GM–WM) boundary were computed for each subject by calculating the area of every triangle in a cortical surface tessellation. The surface area at each vertex in native space was calculated as the average of the triangles that surround it. This value was then compared with the area of the analogous points in registered space to give an estimate of surface area expansion or contraction continuously along the cortical surface (Fischl et al. 1999; Joyner et al. 2009; Rimol et al. 2010). The value of this measure at each vertex is referred to subsequently as the "surface area factor". In anatomical regions of interest, the raw surface area values for each subject were calculated as the sum of the triangular area tessellations. For each subject, cortical thickness maps were obtained by calculating the distance between the gray and white matter surface at each vertex. Before statistical analyses, cortical thickness, gyrification, and surface area maps were smoothed with a full-width of half maximum Gaussian kernel of 30 mm. The effects of smoothing with smaller kernels (10 and 20 mm) can be seen in Supplementary Figure 1.

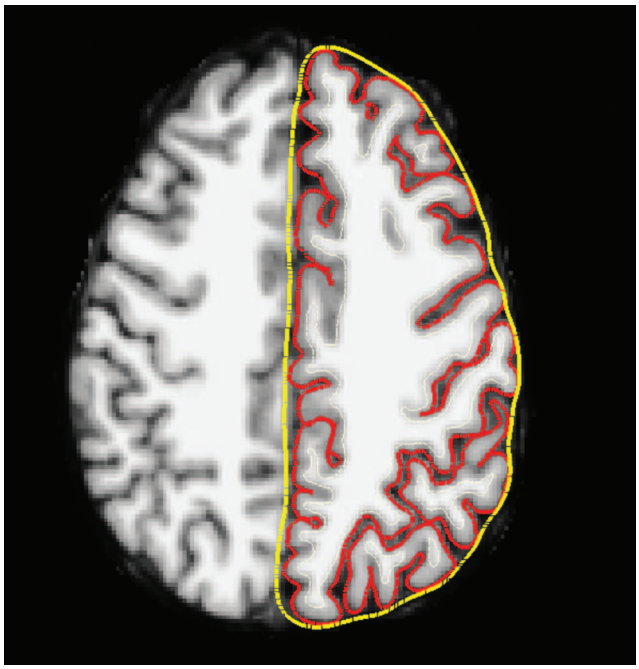

Figure 1. Cortical reconstruction surfaces used to calculate LGI for the hemisphere of 1 subject. The pial surface is depicted in red, while the outer surface is represented in yellow. The LGI measure was calculated continuously as the surface area ratio between buried cortex compared with the visible cortex on the outer surface.

Analyses in the present study were performed with the larger kernel to illustrate the broader, more consistent age patterns that occur along the cortical surface.

The estimation of total WM volume was done as part of the volume-based processing in FreeSurfer, including full-brain tissue segmentation of ventricular compartments, gray and white matter, and various subcortical structures (Fischl et al. 2002). Per-vertex LGI was calculated using a package distributed with FreeSurfer (Schaer et al. 2008, 2012). In brief, an outer surface was first created based on visible cortex on the very outside of the brain. Multiple overlapping, circular regions of interest were then defined on the outer surface. A matching algorithm paired the outer surface ROI with the corresponding cortical surface defined during FreeSurfer's normal processing. The LGI measure was calculated continuously as the surface area ratio between buried cortex compared with the visible cortex on the outer surface (Fig. 1). For each subject the surface area, average cortical thickness, and average LGI were calculated for the frontal, occipital, temporal, and parietal lobe. Metrics were extracted using FreeSurfer's built-in lobe surface maps.

Statistical Analysis

Data from the larger sample and subgroups were analyzed with a series of general linear models (GLMs). Across the whole group, we first tested for an interaction between gender, age, and age^2. After no interaction was found, we co-varied for the effects of sex in all subsequent analyses, but did not perform separate analyses based on sex. We then proceeded to test the effects of age and age^2 in separate analyses on cortical surface area and thickness in all participants. These GLMs were repeated while covarying for participants' total WM volume. Further, we tested the relationship between thickness and area by entering the surface area map of each subject as a per-vertex regressor of interest to their cortical thickness map, covarying for age. Per-vertex regression models were also used to test the thickness-gyrification and surface area-gyrification relationship. This was repeated for each subgroup covarying for age. All of the surface GLMs were corrected for multiple comparisons using a false discovery rate (FDR) of 0.05 (Genovese et al. 2002). As a post hoc test, the relationship among each cortical measure was visualized for each cortical lobe. For each measure, the variability associated with age was removed and values were plotted as *z*-transformed residuals.

Results

Age-Related Changes in Cortical Surface Area and Thickness

Figure 2*A* shows the results from the GLM testing for associations between surface area and age while covarying for sex. The significant relationships between age and surface area were found throughout almost all regions, the only exception being part of the lateral precentral gyri. Areas with the strongest effects of age included the temporal lobes, the dorsomedial prefrontal cortex (DMPFC) and lateral orbitofrontal cortices, and the fusiform and parahippocampal gyri. Figure 2*D* shows plots of the raw surface area values with age. We observed a linear relationship between total WM volume and the total surface area of the cortex (Supplementary Fig. 2). Supplementary Figure 3*A* shows the regional effects of age on surface area when including total WM volume as a covariate. The results show that the age-related changes in surface area to some extent are explained by total WM volume, but strong age effects on surface area remain, including frontotemporal areas, for example, the medial and lateral prefrontal cortices, lateral and medial parts of the temporal lobes, as well in as parts of the occipital lobes. We also observed a significant vertex-wise correlation between surface area and total white matter volume throughout the brain, with strongest weights in fronto-temporal regions (Supplementary Fig. 4).

The results from the GLM testing for associations between cortical thickness and age while covarying for sex are shown in Figure 2B. Age effects were strongest in precentral gyrus, medial parts of superior frontal gyrus, DMPFC, and rostral middle frontal cortex. Supplementary Figure 3*B* shows the effects of age on thickness while covarying for total WM volume. The effects were generally not influenced by including total WM volume in the model. We found no significant quadratic effects of age on surface area, indicating largely linear effects of age. We did, however, identify some weaker but significant negative quadratic effects of age on thickness in bilateral insula and cingulate gyrus (reduced estimated thinning with age), and positive quadratic effects of age in the right lateral occipital lobe (increased estimated thinning with age; Supplementary Fig. 5).

Figure 2*C* shows significant relationships between age and local gyrification index (LGI) on nearly the entire surface of the brain. Age-related changes in gyrification were strongest in the postcentral, supramarginal, and inferior parietal lobes. The quadratic effects of age on gyrification were found strongest in the frontal lobe (Supplementary Fig. 6). The non-linear gyrification patterns suggest that the frontal lobe undergoes less change in gyrification in the later decades of life. Results from the age-gyrification model changed little when covarying for total WM volume. The results of the age-gyrification model were more attenuated when including subjects' total cortical surface area as a regressor (Supplementary Fig. 7), but significant effects were still seen across most of the surface. To better visualize the influence of age across structural metrics, the *P*-values from each age GLM were converted

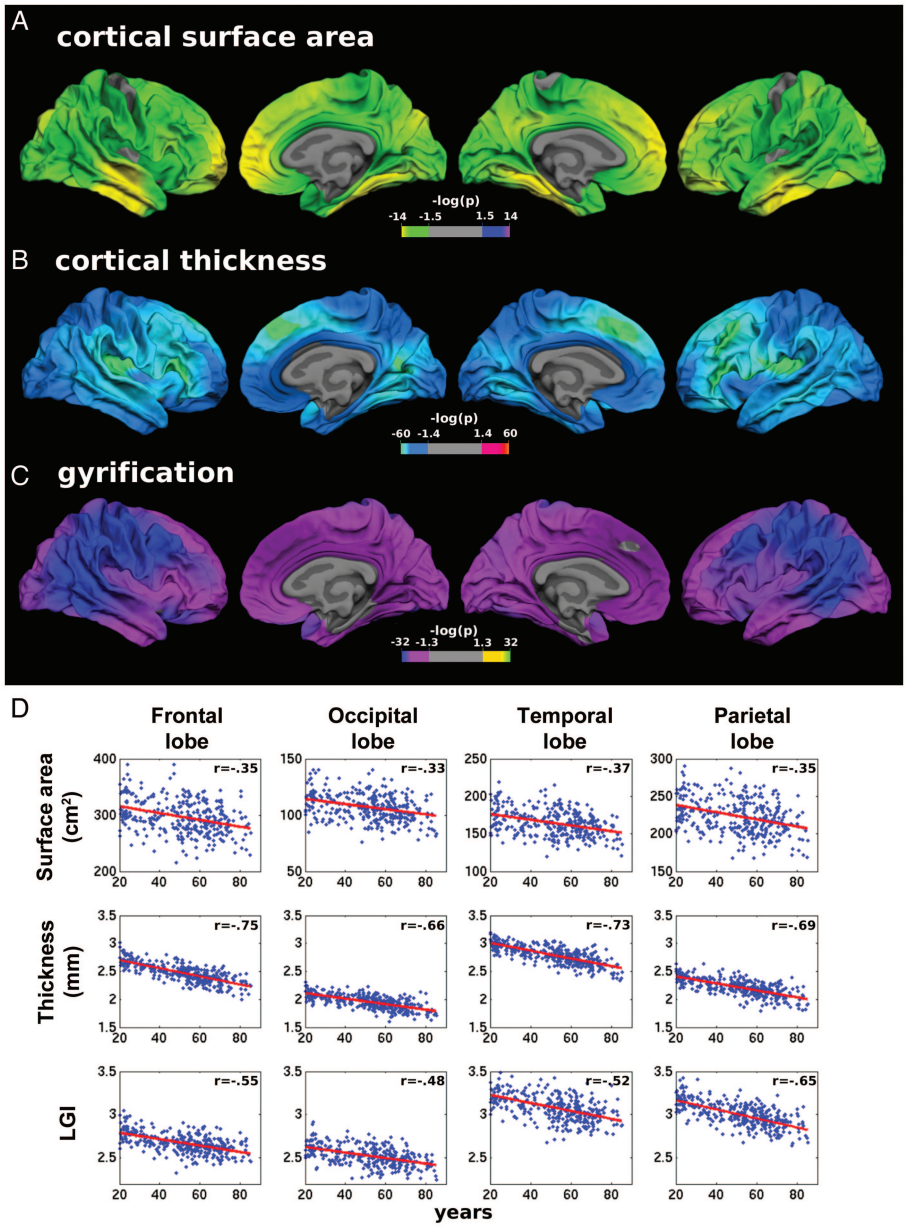

Figure 2. Probability maps for age-related cortical structure patterns. (*A*) Effects of age on cortical surface area covarying for gender. (*B*) Effects of age on cortical thickness covarying for gender. (*C*) Effects of age on local gyrification covarying gender. Surface area, thickness, and gyrification maps are displayed at their unique FDR thresholds and overlayed on the WM surface template. (*D*) Raw values of each measure plotted with age in 4 brain lobes.

to Pearson's correlations and displayed at the same threshold in Figure 3.

Association Between Cortical Surface Area, LGI, and Thickness

The results from the per-vertex regression model of cortical thickness and surface area while covarying for age are shown in Figure 4*A*. Significant negative correlations were observed in areas including the DMPFC, superior frontal, inferior temporal, and lingual gyri, bilaterally. Cortical thickness and gyrification were also negatively related in a per-vertex GLM model covarying for age (Fig. 4*B*). Cortical surface area and gyrification were positively related in a per-vertex GLM model covarying for age (Fig. 4*C*). The two metrics were most strongly related in precuneus, insula, and superior frontal gyrus. Figure 4*D* shows plots of the relationship between surface area and cortical thickness in 4 brain lobes. The linear effect of age was removed and values are plotted as *z*-transformed residuals.

Since age has a profound influence of all the measures examined, we also tested the relationship between cortical thickness and surface area in three separate age bins; young adults (age 20–39 years, $n = 92$), middle adults (age 40–59 years, $n = 114$), and older adults (age 60–85 years, $n = 116$; Fig. 5*A*). Age and gender were included as covariates. For each age group, significant negative relationships between thickness and surface area were found in similar brain regions, including orbitofrontal cortex, posterior cingulate, superior frontal gyrus, and parts of the temporal lobe,

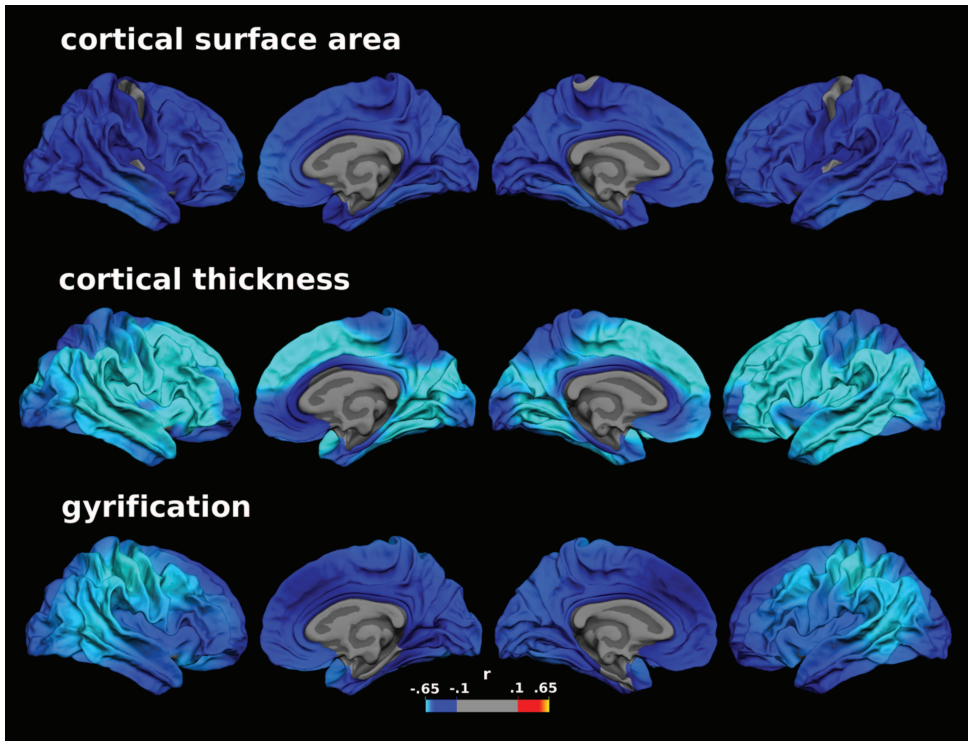

Figure 3. Pearson's correlation maps for age-related cortical structure patterns. The GLMs are the same as those in Figure 2. (*A*) Effects of age on cortical surface area covarying for gender. (*B*) Effects of age on cortical thickness covarying for gender. (*C*) Effects of age on local gyrification covarying gender.

bilaterally. To compare effect sizes across groups, for each group, significant vertices from the whole surface GLM were analyzed together in a post hoc correlation of mean thickness and mean surface area factor. Figure 5*B–D* shows scatter plots and the linear fits between surface area and cortical thickness in the significant areas for the three groups, respectively. Young adults showed a negative relationship between the two in these regions ($r = -0.23$, $P < 0.005$). Similar patterns were found for the middle-aged ($r = -0.32$, $P < 0.001$), and older ($r = -0.33$ $P < 0.001$) subgroups. Using a Fisher r to z transform, we found no significant difference in the thickness-area relationship within significant vertices between the three groups, indicating high stability of the associations across the adult lifespan. We also tested for differences in the thickness-area relationship in three anatomical ROIs, where main effects were found for the three subgroups: superior frontal lobe, cingulate, and inferior temporal gyri. The APARC atlas in FreeSurfer was used to extract the surface area and mean thickness values for each ROI. After removing the variance associated with age, no significant differences in the area-thickness relationship between groups were found.

Figure 6 shows the results from the age-bin analysis testing for associations between cortical thickness and LGI in the three age cohorts. Highly similar patterns of negative age-independent relationships were observed in all three age bins, including in the frontal lobe and inferior temporal gyrus.

Discussion

In the present study, we have characterized the effects of age on cortical surface area, gyrification, and thickness in a large sample of healthy adults. We also tested the relationships among these morphometric measures across the brain surface. The first major finding was the regional patterning of areal reduction with increasing age beyond what can be explained by global WM volume loss. The regions showing the strongest age-related surface area reduction were the orbitofrontal cortex, temporal lobe, and DMPFC. Next, we have documented regional negative correlations between cortical thickness and surface arealization that were shown to be stable across the adult lifespan. The strongest relationships between the two measures were found in the medial prefrontal cortices and the precuneus, bilaterally, indicating decreasing thickness with increasing arealization in these regions. The LGI measure was also negatively related to cortical thickness and positively related to arealization. These results provide novel insight into the macrostructural organization of the adult cerebral cortex.

The Spatial Pattern of Age-Related Cortical Area Decrease

Using sets of anatomically pre-defined surface regions, previous research has revealed age-related changes in cortical surface area, with little variation in age-sensitivity across regions (Lemaitre et al. 2010). By using a vertex-wise analysis that is sensitive to local variations in arealization, we found significant negative correlations between age and regional surface area throughout the brain. These patterns were somewhat attenuated, but for most regions remained significant, when covarying for total WM volume, indicating surface area reductions beyond what can be explained by WM volume loss. The strongest age-related differences in surface area when adjusting for total WM volume were found in the temporal lobe, DMPFC, lateral orbitofrontal cortex, and fusiform

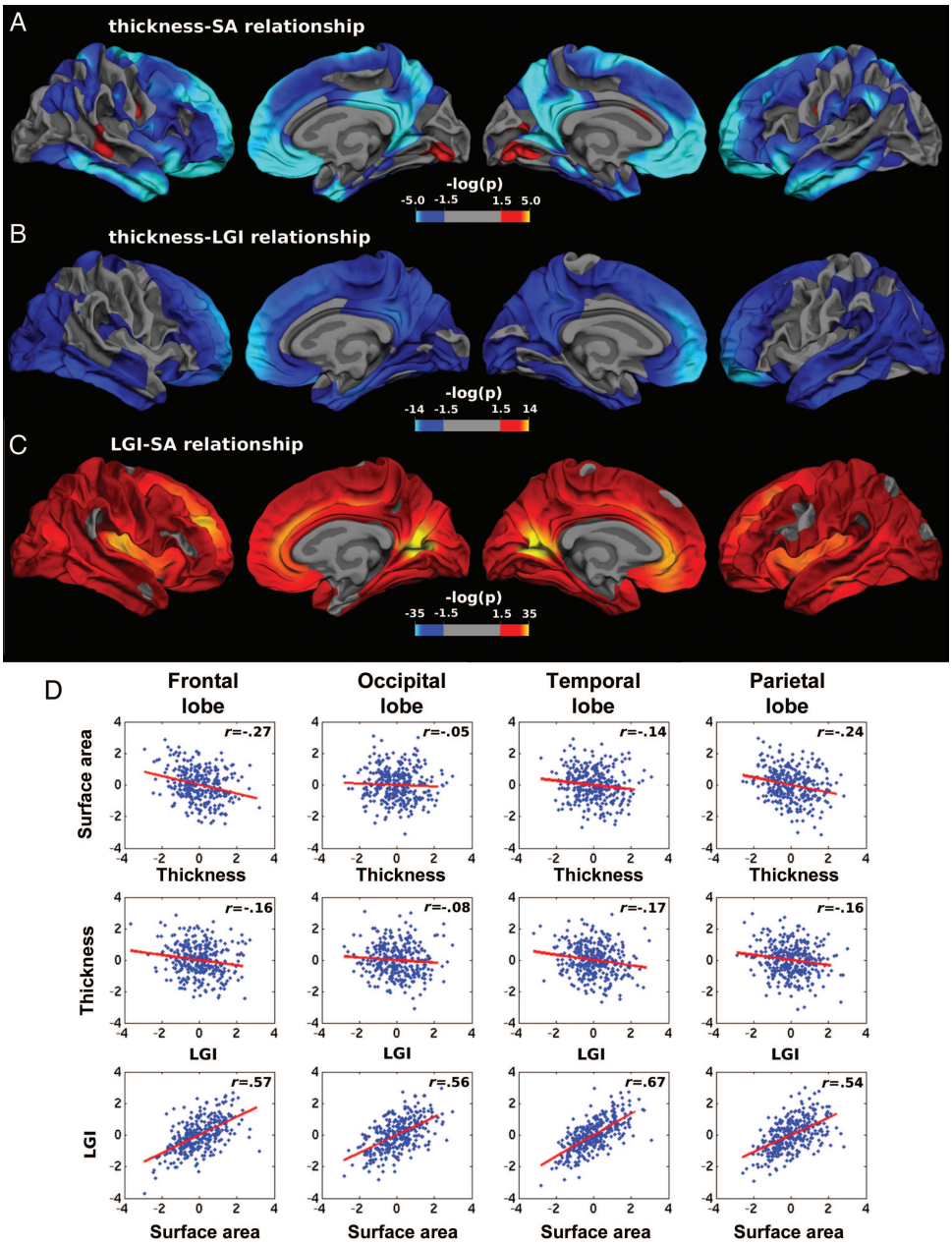

Figure 4. Per-vertex relationships among the three morphometric measures tested. (*A*) Associations between cortical thickness and surface area—covarying for age and gender. (*B*) Associations between cortical thickness and gyrification—covarying for age and gender. (*C*) Associations between cortical surface area and gyrification—covarying for age and gender. (*D*) Scatter plots of the per-vertex relationships among the 3 morphometric measures in 4 brain lobes. The variability associated with age is removed and values are plotted as *z*-transformed residuals.

gyrus. These relationships were found to be independent of individual differences in cortical thickness.

Regional differences in surface area expansion have been observed during development and are suggested to be driven by cellular events such as synaptogenesis, gliogenesis, and intracortical myelination (Hill et al. 2010). The extent to which analogous cellular changes are driving surface area reduction in adulthood is unclear. The loss of dendritic size and complexity, for example, is known to occur with age (Feldman and Dowd 1975). This disruption may differentially affect brain regions with highly branched and spinous dendrites such as the temporal lobe and prefrontal cortex (Jacobs et al. 1997; Elston 2000; Elston et al. 2001). Jacobs et al. (2001) noted increased dendritic complexity in frontal regions of high integration including Brodmann area 10. In the present study, the relative arealization of this region was especially age-sensitive. However, we also observed age-related surface area changes in occipital regions known to have lower dendritic complexity.

It has been suggested that intracortical myelination plays a role in the stretching of the cortical surface along the tangential axis (Seldon 2005). In line with this, we found that when covarying for subjects' total WM volume, the strength of the age-related surface area changes decreased. This finding lends support to a model positing that subcortical and intracortical myelin growth stretches the cortex tangentially along the

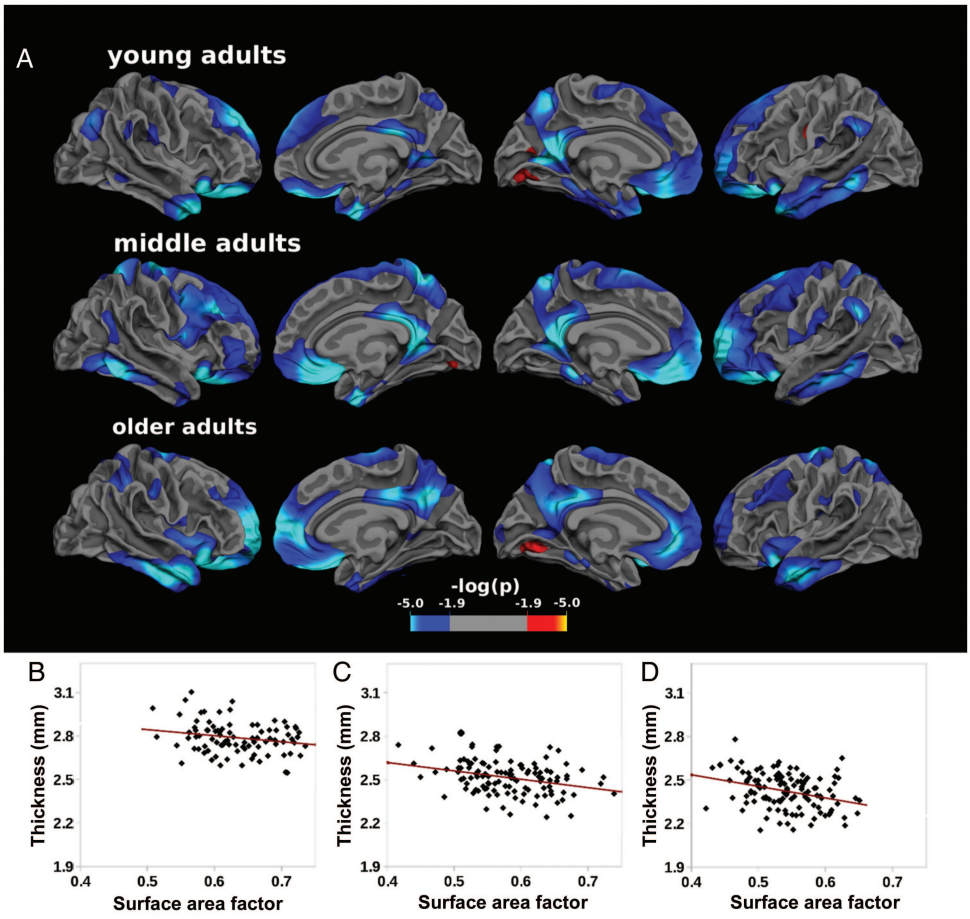

Figure 5. (*A*) Results from general linear models testing for linear relationship between cortical surface area and thickness in young (top row), middle-aged (middle row), and older (bottom row) adults—covarying for gender and age. Scatter plot and linear fit line of surface area and thickness averaged across significant vertices for young (*B*), middle-aged (*C*), and older adults (C).

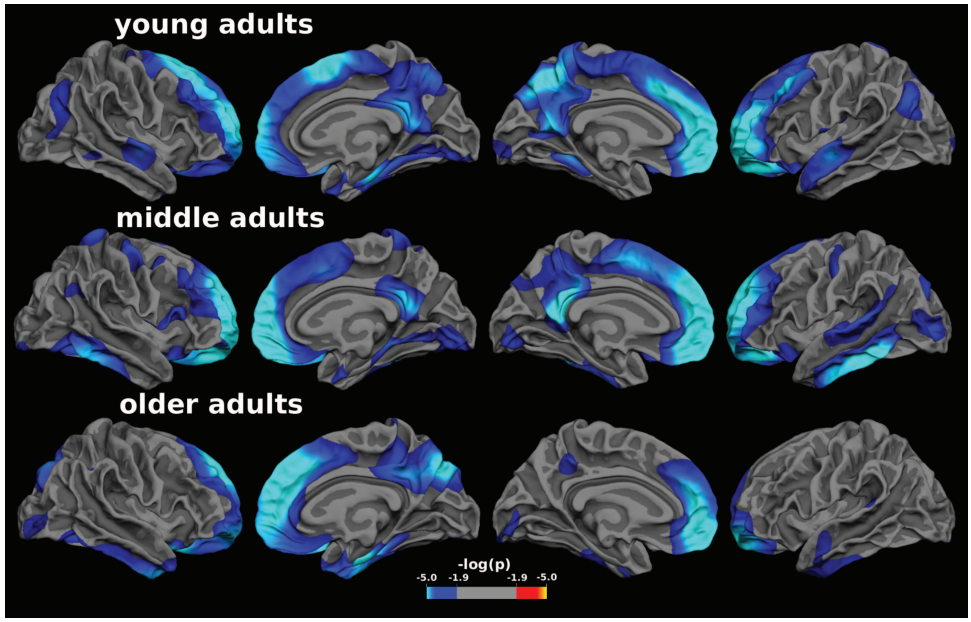

Figure 6. Results from general linear models testing for linear relationship between local gyrification index and cortical thickness in young (top row), middle-aged (middle row), and older (bottom row) adults—covarying for gender and age.

surface (Seldon 2005). This stretching, along with, for example, experience-related pruning and strengthening of specific connections, is hypothesized to disentangle neighboring neuronal columns and enable the relevant parts of the cortex to better differentiate afferent signal patterns and increase functional specialization (Seldon 2007). This model provides one possible mechanistic and functional account of the present findings of a negative correlation between cortical thickness and surface arealization.

Because age effects on cortical surface area were shown to be sensitive to WM volume, a reasonable hypothesis is that decreases in WM tissue components including demyelination occurring in older individuals (Svennerholm et al. 1997; Davis et al. 2009; Peters and Kemper 2011) affect surface area at the gray–white tissue boundary. This is partly supported by previous research showing moderate correlations between diffusion tensor imaging (DTI)-derived indices of WM microstructure and regionally corresponding cortical thickness (Fjell et al. 2008; Avants et al. 2010). However, the linear relationship between age and surface area across the adult life span observed in the present study differs markedly from the previously documented non-linear trajectory of white matter volume and DTI-derived microstructure (Westlye et al. 2010a, b; Walhovd et al. 2011). Thus, linear and relatively modest decreases in cortical surface area seem to co-occur with accelerating changes in white matter volume and microstructure from the seventh and eighth decade of life (Westlye et al. 2010a,b). It is likely that some of the WM volume loss is accounted for by expansion of the ventricular compartments, and therefore to a lesser degree affect the outer surface of the brain. Methodological issues preclude vertex-wise WM volume calculations within the same framework as the cortical GM measures used in the present study, and we do not yet know to what degree regional differences in WM volume map onto differences in surface arealization.

In accordance with previous research, we observed a significant relationship between age and cortical gyrification (Magnotta et al. 1999). The linear age-related decreases in LGI along most of the brain surface are consistent with previous research (Schaer et al. 2009; Palaniyappan et al. 2011). We also observed non-linear age patterns in LGI that indicate that the frontal lobe undergoes less change in gyrification in the later decades of life. Age-related decreases in gyrification were strongest in the parietal lobe. These findings complement research describing age-related changes in the folding of the cortex, such as the flattening and opening of the sulci (Kochunov et al. 2005). LGI is likely influenced by other factors including narrowing of the gyral crowns (Magnotta et al. 1999), but we suspect that opening of the sulci is a driving factor in decreasing LGI as increases in sulcal span have been reported to reach as high as 0.9 mm per decade in some brain regions (Kochunov et al. 2008). This reduced gyrification in aging appears to parallel reductions in surface area.

Relationships Between Surface Area, Gyrification, and Cortical Thickness

The second aim of the present study was to quantify the relationships among surface area, gyrification, and cortical thickness. We found a negative, age-independent relationship between cortical thickness and surface area. This was strongest in orbitofrontal cortex posterior cingulate, parts of superior frontal gyrus, and precuneus and was also found moderately in other areas, including inferior temporal gyrus (ITG), DMPFC, and middle frontal gryus. We examined further the relationship between thickness and surface area in the three separate age bins; young, middle-aged, and older adults. Results across the three age groups were highly similar and confirmed the whole sample model. For all three groups, cortical thickness showed a negative relationship with surface area in superior frontal lobe, cingulate, and inferior temporal gyri. Although both surface area and thickness change continuously with age, our results suggest that the relationship between these two measures of cortical structure is relatively stable throughout healthy adulthood. The observed negative relationship suggests that within these regions of the brain, individuals with the largest surface area tend to have a thinner cortex. Local gyrification also showed a negative relationship with thickness, but was positively related to surface area. Based on thickness, surface area, and volume measurements in a longitudinal adult sample, Rettmann et al. (2006) conclude that "cortical stretching" (decreased thickness with increased surface area) is unlikely to be a mechanism of adult aging. Indeed, our observations show stable negative associations between thickness and area across the adult lifespan. We believe that this pattern reflects neurodevelopmental processes arising before adulthood and may be due to the early growth of white matter stretching the adjacent gray matter tissue.

Mouse models have demonstrated that the interplay between thickness and area begins during neurogenesis in fetal life (Chenn and Walsh 2002). The division of radial unit progenerators seem most influential in determining cortical surface area (Rakic 2009) with intermediate progenitor cells making an important contribution to cortical thickness (Pontious et al. 2008). Other factors hypothesized to influence thickness and area such as mechanical tension (Van Essen 1997) and changes in neurophil (DeFelipe et al. 2002) may be especially relevant as these descriptions incorporate the pattern of connections and the spatial influence of adjacent brain structures. Regardless of the underlying cellular mechanism, the genetic factors influencing cortical surface area have been found to be largely independent from the factors controlling cortical thickness (Panizzon et al. 2009) and have partially been attributed to select genetic polymorphisms (Joyner et al. 2009; Rimol et al. 2010). Recent studies have also demonstrated that genetic variability exerts strong influence on regional surface arealization (Chen et al. 2011).

As the present, analyses are based on cross-sectional data. The conclusions should be confirmed by longitudinal examinations and could also be extended to include childhood development and possible different neurological conditions.

Conclusion

This study demonstrates hitherto unknown characteristics of regional cortical arealization. First, age-related decrease in surface area was found independent of total WM volume loss and was especially strong in the temporal lobes, DMPFC, lateral orbitofrontal cortices, and the fusiform gyrus. Although individual variation in cortical gyrification was strongly related to regional surface area, the age-related patterns of gyrification differed from those of surface area and cortical

thickness. Secondly, our observations provide evidence for an inverse relationship between area and thickness in orbitofrontal cortex, posterior cingulate, and ITG across the adult life span. For these regions, results indicate increased surface area and gyrification with thinner cortices. Importantly, since this pattern was observed in all age cohorts, it is unlikely to be a result of aging processes but rather established earlier through the course of neurodevelopmental processes. In sum, the present results indicate that different measures of cortical macrostructure provide complementary information, and that future studies could benefit from studying several cortical properties simultaneously.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/

Notes

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