

Thinning of the Cerebral Cortex in Aging

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The thickness of the cerebral cortex was measured in 106 nondemented participants ranging in age from 18 to 93 years. For each participant, multiple acquisitions of structural T₁-weighted magnetic resonance imaging (MRI) scans were averaged to yield high-resolution, high-contrast data sets. Cortical thickness was estimated as the distance between the gray/white boundary and the outer cortical surface, resulting in a continuous estimate across the cortical mantle. Global thinning was apparent by middle age. Men and women showed a similar degree of global thinning, and did not differ in mean thickness in the younger or older groups. Age-associated differences were widespread but demonstrated a patchwork of regional atrophy and sparing. Examination of subsets of the data from independent samples produced highly similar age-associated patterns of atrophy, suggesting that the specific anatomic patterns within the maps were reliable. Certain results, including prominent atrophy of prefrontal cortex and relative sparing of temporal and parahippocampal cortex, converged with previous findings. Other results were unexpected, such as the finding of prominent atrophy in frontal cortex near primary motor cortex and calcarine cortex near primary visual cortex. These findings demonstrate that cortical thinning occurs by middle age and spans widespread cortical regions that include primary as well as association cortex.

Keywords: aging, atrophy, calcarine cortex, cortical thickness, dementia, executive function, magnetic resonance imaging, MRI, prefrontal cortex

Introduction

Age-related changes in brain morphology are apparent in both postmortem histological and *in vivo* magnetic resonance imaging (MRI) studies (for reviews, see Kemper, 1994; Raz, 2000). The majority of post-mortem studies report age-related alteration of global morphometric properties including decline in total brain weight, cortical thinning and gyral atrophy that is particularly accelerated during the sixth and seventh decades (Kemper, 1994). Questions remain as to how early such changes begin and whether specific cortical regions are preferentially vulnerable to the morphologic changes associated with aging. In the present study, age-associated cortical atrophy was mapped as the thinning of cortex across the entire cortical mantle, allowing visualization of regional cortical atrophy patterns.

Previous neuronal counting studies have suggested that degenerative changes are accelerated in specific areas of the cortex, including frontal pole and premotor cortex (Kemper, 1994). Comparisons across species led to speculation that age-related cortical changes follow a gradient, with greatest and

earliest changes occurring in association areas and lesser changes occurring later in primary sensory regions (Flood and Coleman, 1988). Although early studies postulated this atrophy to be due to neurodegeneration, several recent studies suggest that neuron number is relatively preserved in the healthy aging brain of both humans and nonhuman primates (Morrison and Hof, 1997; Peters *et al.*, 1998), although alterations in neuronal morphology are evident.

Contemporary *in vivo* neuroimaging studies have confirmed that there are alterations in global brain morphologic properties (Jernigan *et al.*, 1991, 2001; Pfefferbaum *et al.*, 1994; Blatter *et al.*, 1995; Raz *et al.*, 1997; Good *et al.*, 2001; Sowell *et al.*, 2003). These studies additionally support the view that morphological alterations may be accelerated in particular areas of the cortex – described by Raz (2000) as a ‘patchwork pattern of differential declines and relative preservation’. Preferential vulnerability of prefrontal cortex, in particular, has been demonstrated across studies, prefrontal change being greater than changes in other regions (Jernigan *et al.*, 1991; Raz *et al.*, 1997; Sowell *et al.*, 2003). Although this preferential vulnerability has been statistically demonstrated in certain studies (e.g. Raz *et al.*, 1997), the majority of MRI studies of brain aging have not directly compared regional effects to describe patterns of regional selectivity.

The specific patterns of regional change place important constraints on what may underlie cortical atrophy and how atrophy may relate to the complex constellation of cognitive changes associated with aging. One idea, originally proposed in the context of developmental myelination, is that age-associated changes are characteristic of association cortex as opposed to primary cortex (reviewed by Kemper, 1994). Consistent with this possibility, Raz (2000) recently reported a strong relation between order of developmental myelination and degree of age-associated volumetric atrophy, with regions developing late showing the strongest age-related atrophy. Maps of cortical atrophy, as produced in the present study, provide a test of this idea, in so far as it applies to cortical atrophy patterns. More broadly construed, maps of age-associated cortical thinning provide constraints on hypotheses concerning regionally specific processes related to atrophy.

In the present study, we measured the thickness of the cerebral cortex from MR images (Dale and Sereno, 1993; Dale *et al.*, 1999; Fischl *et al.*, 1999a, 2001; Fischl and Dale, 2000), using a technique that has been validated via histological (Rosas *et al.*, 2002) as well as manual measurements (Kuperberg *et al.*, 2003), to examine the regional patterns of age-associated cortical thinning. As a secondary question, we explored the

lower age limit at which reliable effects are demonstrable. All older participants were clinically characterized to minimize the contribution of potential common medical comorbidities that could confound the interpretation of the data. We found that accelerated cortical thinning followed a pattern of progression across various brain regions that span association to primary sensory and motor areas. Tests of the reliability of this pattern yielded highly reproducible spatial patterns between independent participant samples and manual measurements confirmed the novel finding of thinning in primary sensory cortex.

Materials and Methods

High-resolution structural MR scans were obtained from a total of 106 participants in three basic age-ranges: younger (YP; $n = 31$; mean age = 22.8, 18–31; 13 men/18 women); middle-aged (MP; $n = 17$; mean age = 48.6, 41–57; 7 men/10 women); and older participants (OP; $n = 58$; mean age = 76.6, 60–93; 16 men/42 women). All OP were recruited through the Washington University Alzheimer's Disease Center (ADRC) and were screened for a variety of health factors as described previously (Berg *et al.*, 1998). OP were non-demented, with a clinical dementia rating of 0; (Morris, 1993). YP and MP were recruited from the Washington University community. Participants from all groups were excluded if they had a history of neurologic, psychiatric, or medical illness that could contribute to dementia or a serious medical condition that could confound the interpretation of the results. Participants consented to participation in accordance with guidelines of the Washington University Human Studies Committee.

Two to four high-resolution MP-RAGE scans were motion corrected and averaged per participant (four volumes were averaged for all except five participants; Siemens 1.5 T Vision System, resolution $1 \times 1 \times 1.25$ mm, $T_R = 9.7$ ms, $T_E = 4$ ms, $FA = 10^\circ$, $T_1 = 20$ ms, $T_D = 200$ ms) to create a single image volume with high contrast-to-noise. These acquisition parameters were empirically optimized to increase gray/white and gray/cerebrospinal fluid contrast. Cortical thickness measurements were obtained by reconstructing representations of the gray/white matter boundary (Dale and Sereno, 1993; Dale *et al.*, 1999) and the cortical surface and then calculating the distance between those surfaces at each point across the cortical mantle. This method uses both intensity and continuity information from the entire three-dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, as shown in Figure 1a–c (Fischl and Dale, 2000). The maps are created using spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups (Fischl and Dale, 2000).

Thickness measures were mapped on the 'inflated' surface of each participant's reconstructed brain (Dale and Sereno, 1993; Fischl *et al.*, 1999a). This procedure allows visualization of data across the entire cortical surface (i.e. both the gyri and sulci) without interference from cortical folding (Fig. 1d–f). Maps were smoothed using a circularly symmetric Gaussian kernel across the surface with a standard deviation of 22 mm and averaged across participants using a non-rigid high-dimensional spherical averaging method to align cortical folding patterns (Fischl *et al.*, 1999a). This procedure provides accurate matching of morphologically homologous cortical locations among participants on the basis of each individual's anatomy while minimizing metric distortion, resulting in a mean measure of cortical thickness for each group at each point on the reconstructed surface. Statistical comparisons of global data and surface maps were generated by computing a general linear model of the effects of age on thickness at each vertex with gender as a grouping factor to control for potential gender effects.

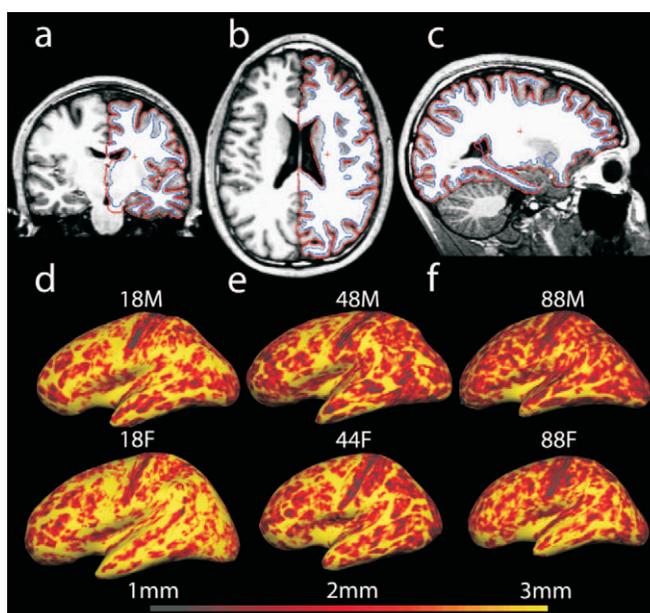


Figure 1. Cortical reconstruction technique. Top panel: example of MR image segmentation in the coronal, axial and sagittal planes (a–c). The segmentation procedure uses both intensity and continuity information from the three-dimensional high-resolution, high signal-to-noise MR image volume to produce accurate representations of the gray matter/white matter boundary (blue line) and the outer surface of the cortex (red line). The red cross-hair represents the same volumetric point in each slice of the three cardinal axes. Thickness measures were obtained by calculating the distance between the two surfaces across the entire volume in each hemisphere. Bottom panel: example of cortical thickness maps in the left hemisphere of six individual participants on the inflated surface of the cortex (age and gender is given for each). The color scale at the bottom represents the thickness (in millimeters). Age-associated thinning is apparent in these individual participants as the surface maps show a greater portion of cortex below the midpoint of the color scale (red) with increasing age.

Results

Global Measures

Mean global thickness measures for each group are presented in Table 1. Mean thickness measures across the surface of the cortex followed previously described histological patterns in each group. For example, gyral regions were thicker than sulcal regions and the anterior bank of the central sulcus was thicker than posterior bank as previously described in MR and post-mortem studies (Meyer *et al.*, 1996; Fischl and Dale, 2000).

Global thickness and volume measurements were examined by ANCOVA, with age and gender as independent variables. Volume measures were examined as percentage of total intracranial volume to correct for premorbid head size. This analysis revealed a significant effect of age on thickness and volume in the left and right hemispheres: $F(1,102) = 21.78$ and 19.88 , respectively, both $P < 0.0001$ for thickness, and $F(1,102) = 97.87$ and 125.67 , respectively, both $P < 0.0001$ for volume (Fig. 2a,c). Both measures declined with increasing age. There was a trend toward an effect of gender on thickness in the left and right hemispheres, $P = 0.05$ and $P = 0.06$, respectively, with men having thicker cortex. There were no significant effects of gender on volume when this measure was corrected for total intracranial volume. There were no significant age \times gender interactions in thickness or volume. Qualitatively, decline in

Table 1
Mean global thickness measures

Group	Left thickness	Right thickness
YP (men)	2.26 ± 0.020 (2.12–2.35)	2.24 ± 0.019 (2.07–2.32)
YP (women)	2.26 ± 0.023 (2.10–2.49)	2.22 ± 0.021 (2.05–2.48)
YP (total; <i>n</i> = 31)	2.26 ± 0.015 (2.10–2.49)	2.23 ± 0.015 (2.05–2.48)
MP (men)	2.26* ± 0.024 (2.20–2.38)	2.22 ± 0.021 (2.13–2.31)
MP (women)	2.17 ± 0.027 (2.05–2.30)	2.15 ± 0.025 (2.03–2.26)
MP (total; <i>n</i> = 17)	2.21 ± 0.021 (2.05–2.38)	2.18** ± 0.019 (2.03–2.31)
OP (men)	2.17 ± 0.021 (2.03–2.28)	2.14 ± 0.016 (2.03–2.25)
OP (women)	2.16 ± 0.012 (1.99–2.34)	2.13 ± 0.011 (2.01–2.31)
OP (total; <i>n</i> = 58)	2.16*** ± 0.010 (1.99–2.34)	2.14*** ± 0.009 (2.01–2.31)

Measures are presented as mean, standard error of the mean and range. *** $P \leq 0.001$ compared to YP (total), unpaired comparison; ** $P < 0.05$ compared to YP (total), unpaired comparison; * $P < 0.05$ compared to MP (women).

thickness was ~ 0.016 mm per decade across the sampled age range.

Gender differences in thickness and volume were explored separately within each of the three age groups by unpaired *t*-tests. These analyses revealed an effect of gender on thickness in the left hemisphere of the MP group only $t(15) = -2.22$, $P < 0.05$, and a trend in the right hemisphere ($P = 0.08$), with men having thicker cortex than women. This tentative finding of sex differences limited to the MP group could suggest that cortical thinning is influenced by sex hormones, as women are likely to undergo menopause during this period and thus experience a decline in hormone levels. Men generally had greater total cortical volume than women in both hemispheres, but no sex differences existed when values were corrected for total intracranial volume (Fig. 2*b,d*).

In order to test whether change occurred early in the lifespan, an ANCOVA was performed with age and gender as independent variables while limiting the age span to participants ≤ 57 years (the YP and MP groups). This analysis revealed a significant effect of age on thickness in the left and right hemispheres: $F(1,44) = 4.69$ and 6.45 , respectively, both $P < 0.05$. Global thickness declined with increasing age. There were no effects of gender or age \times gender interactions for thickness in this age range. There was a significant effect of age on volume in the left and right: $F(1,44) = 9.83$ and 15.58 , respectively, both $P < 0.01$. Global cortical volume declined with increasing age. There were no significant effects of gender or age \times gender interactions for volume in the left and right hemispheres. Interestingly, there was a significant age effect on thickness in the left and right hemispheres when limiting the sample to participants ≤ 31 years (only YP): $F(1,27)$

$= 8.06$ and 8.02 , respectively, both $P = 0.01$. Thus, cortical thinning was present as early as middle age and was apparent in these data by the third decade of life.

Most previous neuroimaging studies have calculated total volumes, which can be factored into thickness and surface area. Thus, to further characterize the components of the morphological alterations contributing to total cortical change, we next examined age-related decline in the surface area of the cortex by ANCOVA with age and gender as independent variables. There was a decline in total cortical surface area with increasing age in the left and right hemispheres: $F(1,102) = 34.25$ and 36.22 , respectively, both $P < 0.0001$ (Fig. 2*e*). There was an effect of gender on surface area in the left and right hemispheres $F(1,102) = 41.27$ and 41.60 , respectively, both $P < 0.0001$. There were no age \times gender interactions for surface area. When men and women were compared within each group by unpaired *t*-test, there was a gender difference in surface area in all groups with men having greater surface area than women in the left and right hemispheres in all groups examined $t(29) = -2.05$ and -2.01 , respectively in YP, both $P = 0.05$, $t(15) = -6.73$ and -6.59 respectively in MP, both $P < 0.001$, and $t(56) = -3.54$ and -3.58 , respectively in OP, both $P < 0.001$ (Fig. 2*f*). Thus, age-related reductions in both thickness and surface area likely contribute to the age-related reductions in global volume reported in prior studies. In contrast, it remains possible that developmental differences in cortical surface area largely account for gender differences in global brain volumes.

Regional Measures and Maps of Cortical Thinning

Age-related thinning was widespread and spanned a number of cortical regions when thickness was regressed on age controlling for gender (Fig. 3). Significant thinning was found in primary sensory (occipital lobe/calcarine), primary somatosensory and motor (pre/post central gyrus and central sulcus) and association cortices (inferior lateral prefrontal cortex), with greatest statistical significance in inferior prefrontal, precentral and supramarginal regions (Fig. 3). Thinning was qualitatively variable across the cortex and was regionally variable within the major lobes (Fig. 4*a-d*). Regions within the temporal lobe were relatively spared from significant thinning compared to other areas of the brain. Thickening of the cortex was also observed with increasing age, although very little thickening achieved statistical significance. These regions were mainly localized to the anterior cingulate and medial orbitofrontal/subcallosal cortex.

The majority of the cortical mantle showed thinning rates of at least 0.01 mm/decade. The greatest rate (>0.07 mm/decade) was found in primary motor cortex. The greatest magnitude of regional thinning was found in inferior prefrontal, precentral, and supramarginal regions (Fig. 5). We next tested whether the qualitative regional rates of thinning seen in the presented maps were statistically discernable. To do this, we created unbiased regions of interest (ROIs) in each of the cortical lobes (frontal, parietal, occipital, and temporal). These ROIs were defined in a subset of participants defined by splitting the present data set into two independent samples by ranking all of the participants by age (sorted by sex) and placing every other participant in each group to calculate group maps. Regions showing maximal and minimal thinning on the effect size maps in the first half of participants were then mapped to an independent sample of participants (the other half of the partici-

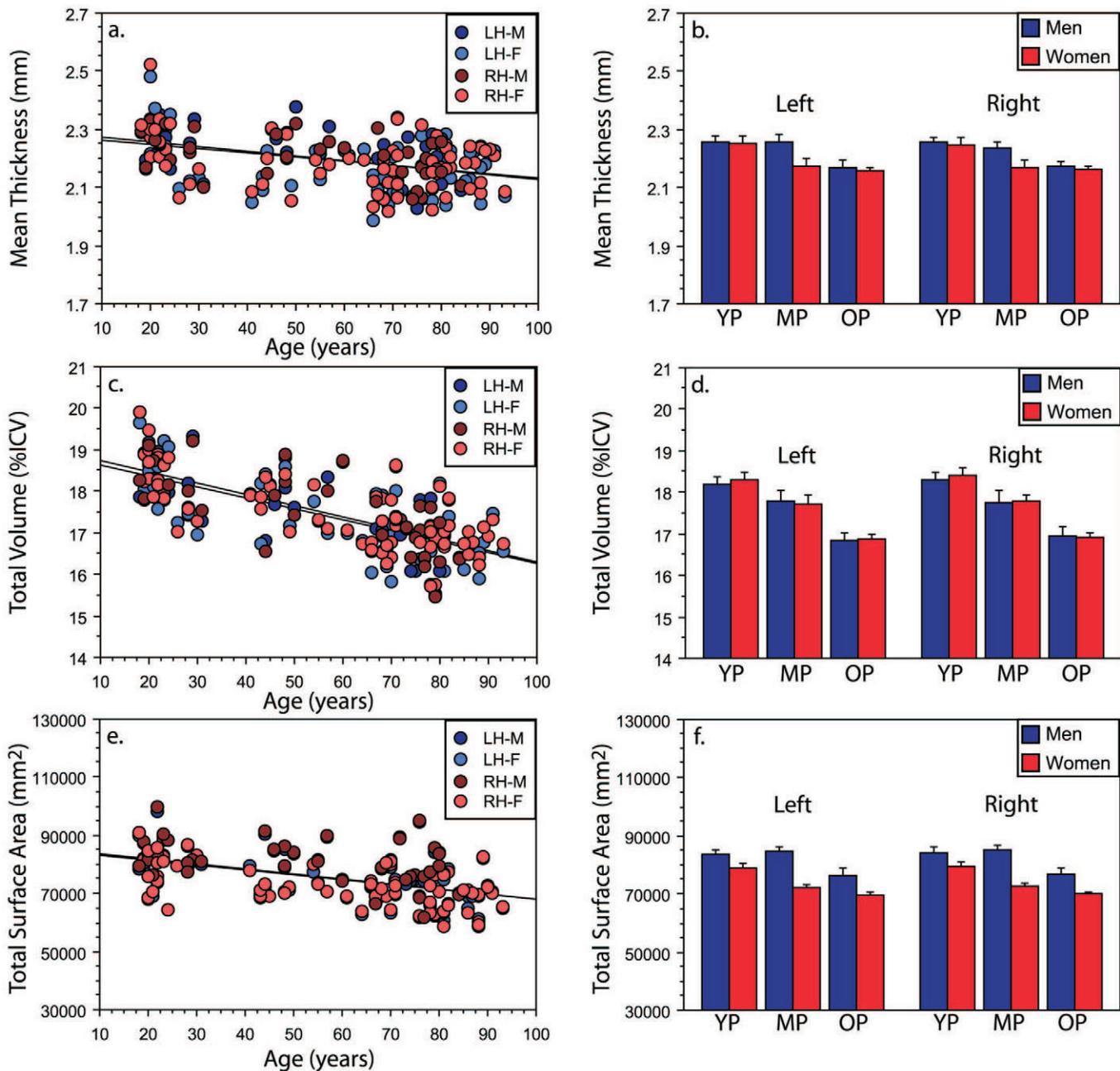


Figure 2. Effects of aging on total mean cortical thickness (a,b), total cortical volume (percentage of intracranial volume; c,d) and total cortical surface area (e-f). Scatter plots of mean cortical thickness (a), total cortical volume (percentage of intracranial volume; c) and total cortical surface area (e) in each hemisphere regressed by age, separated by sex and cortical hemisphere (lh, left hemisphere; rh, right hemisphere). Age significantly correlates with all three measures. Mean cortical thickness (b), total cortical volume (percentage of total intracranial volume; d) and total cortical surface area (f) in young participants (YP), middle-aged participants (MP) and older participants (OP) separated by gender. Minimal gender differences were apparent in measures of cortical thickness within each group. In contrast, gender differences in total cortical surface area were apparent within each group. Bars represent mean and standard error of the mean.

pants). In this way, the regional delineations were not biased by thinning rates in the participants examined because they were created from an independent sample of participants.

These regional analyses demonstrated that the effects observed in the statistical maps were reliable across populations (Fig. 6). We applied Steiger's Z^* statistic which determines the significance of slope differences while accounting for the correlation between the nonoverlapping variables as described in Steiger (1980) and employed in Raz *et al.* (1997)

to determine whether slopes differed within and across lobes. First, rates of thinning were compared for the regions of maximal and minimal thinning within each lobe. Within lobe comparisons limited to gyral regions in the frontal, parietal and temporal lobes were next examined. The third analysis compared regions of maximal thinning in the frontal, parietal and occipital lobes to the gyral region of minimal thinning in the temporal lobe. These analyses demonstrated that rates of thinning are variable within and across cortical lobes with

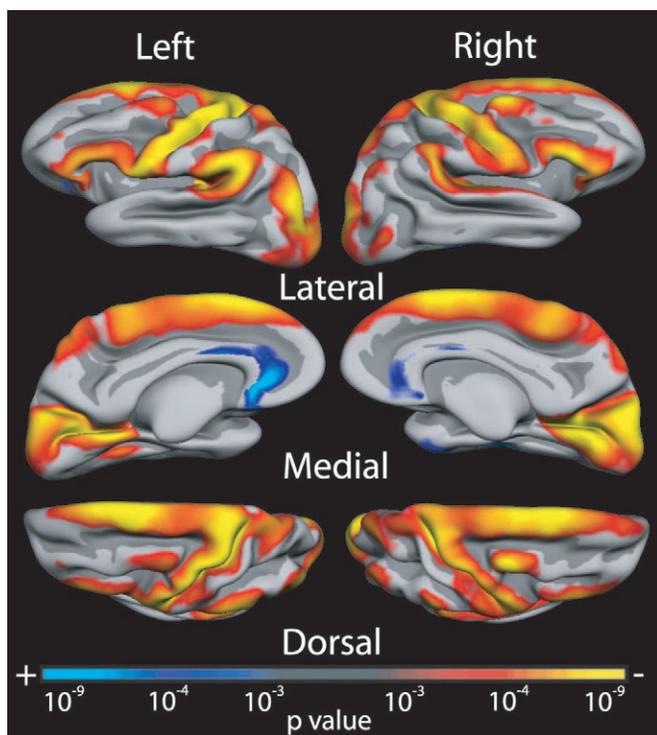


Figure 3. Age-associated map of cortical thinning. Surface maps of cortical thinning in aging were generated by assessing the influence of age on thickness (using the general linear model) at each vertex across the entire cortical mantle. Maps are presented on the semi-inflated cortical surface of an average brain with dark gray regions representing sulci and light gray regions representing gyri. Non-neocortical regions and regions that are not part of the cortical mantle (such as the corpus callosum and thalamus) have been excluded from the analysis. The colorscale at the bottom represents the significance of the thickness change with yellow indicating regions of most significant thinning.

greater thinning occurring in motor, supramarginal and inferior frontal cortex relative to temporal cortex as well as other regions (Table 2).

Manual measurements were performed to validate the negative finding of preservation in temporal cortex and the novel finding of thinning in calcarine cortex. To do this, regions were mapped from the effect maps to the volume of 12 of the youngest and 12 of the oldest participants (matched for gender) and by obtaining 10 manual measurements within each participant of cortical thickness (10 samples of the distance from the gray/white border to the gray/CSF border for each participant). The mean of these 10 measurements was then taken as the regional thickness for each participant. This procedure confirmed the negative finding showing preservation of temporal cortex and the novel finding of thinning in calcarine cortex (Fig. 7).

Discussion

Age-associated change in brain structure has been explored previously using a variety of methods, including post-mortem measurement of brain volume, microscopic examination of neuronal loss and morphological change and *in vivo* measurement of regional brain volume (for reviews, see Kemper, 1994; Raz, 2000). In the present study, age-associated cortical change was examined using a recently developed computational approach that estimates the thickness of cortex (Fischl and

Table 2

Comparisons of regional rates of thinning within and across cortical lobes

	Frontal	Parietal	Temporal	Occipital
Within lobe	-4.53* (2v1)	-2.60* (4v3)	-2.15* (6v5)	0.23 (8v7)
Within lobe gyri	-0.43 (2v9)	-2.34* (4v11)	-1.05 (6v12)	NA
Temporal lobe	-3.74* (2v12)	-2.65* (4v12)	NA	-3.44* (8v12)

Measures are presented as Steiger's Z^* statistic. * $P \leq 0.01$, one-tailed test comparing region of maximal thinning to region of minimal thinning within each lobe (top row), within gyral regions of each lobe (middle row) and compared to middle temporal gyrus (bottom row). The specific regions of comparison are noted to the right of the Z^* value in parentheses, with reference to Figure 6.

Dale, 2000); for related approaches, see Miller *et al.* (2000), Chung *et al.* (2003) and Sowell *et al.* (2003). Changes in cortical thickness are important to the study of aging because they provide a local measure of alterations in gray-matter morphology that can be made continuously across the cortical surface. In applying these methods to a large ($n = 106$), clinically well-characterized non-demented sample of older adults, a high-resolution description of age-associated cortical changes was produced. Global thinning was prominent and these changes were clear by middle age.

Regionally, certain results, including prominent thinning of prefrontal cortex (Raz *et al.*, 1997; Jernigan *et al.*, 2001; Sowell *et al.*, 2003) and relative sparing of temporal cortex (DeCarli *et al.*, 1994) and parahippocampal cortex (Raz *et al.*, 1997), converged with previous findings from volumetric neuroimaging studies. However, other results were unexpected, in particular, the finding of prominent thinning in diverse regions of cortex including frontal cortex near the primary motor and premotor areas and calcarine cortex near striate cortex. Thus, the present results do not support theories of cortical aging proposing that atrophy progresses from association to primary sensory/motor cortex. Neither do the data support theories suggesting that cortical atrophy progresses in reverse order to maturational development. Rather, the present results suggest that atrophy is widespread across the cortex and may begin early in adulthood. These issues are discussed below along with potential caveats associated with the methods.

Patterns of Thinning and Relation to Theories of Cognitive Aging

The central result of this paper is the regional pattern of age-associated cortical thinning. By measuring change in cortical thickness along the continuous cortical surface, areas of accelerated thinning and relative sparing were visualized. Figure 3 presents a description of the results in terms of those changes reaching a threshold level of statistical significance. Figure 5 presents a visualization of cortical change in terms of the absolute magnitude of age-associated thinning (in mm/decade). We do not see a clear relationship with previously established patterns of morphology or function in these maps. For example, thinning was found in regions with both large and small thickness measurements, suggesting that atrophy is not simply related to the initial thickness. Thinning was not obviously lateralized, even in regions with lateralized function such as the ventral lateral prefrontal cortex, although some subtle lateralized patterns are tentatively suggested by the data and prominent atrophy is noted in several regions that are classically considered language areas. Finally, cortical thinning did not appear to follow patterns based on the variance of the

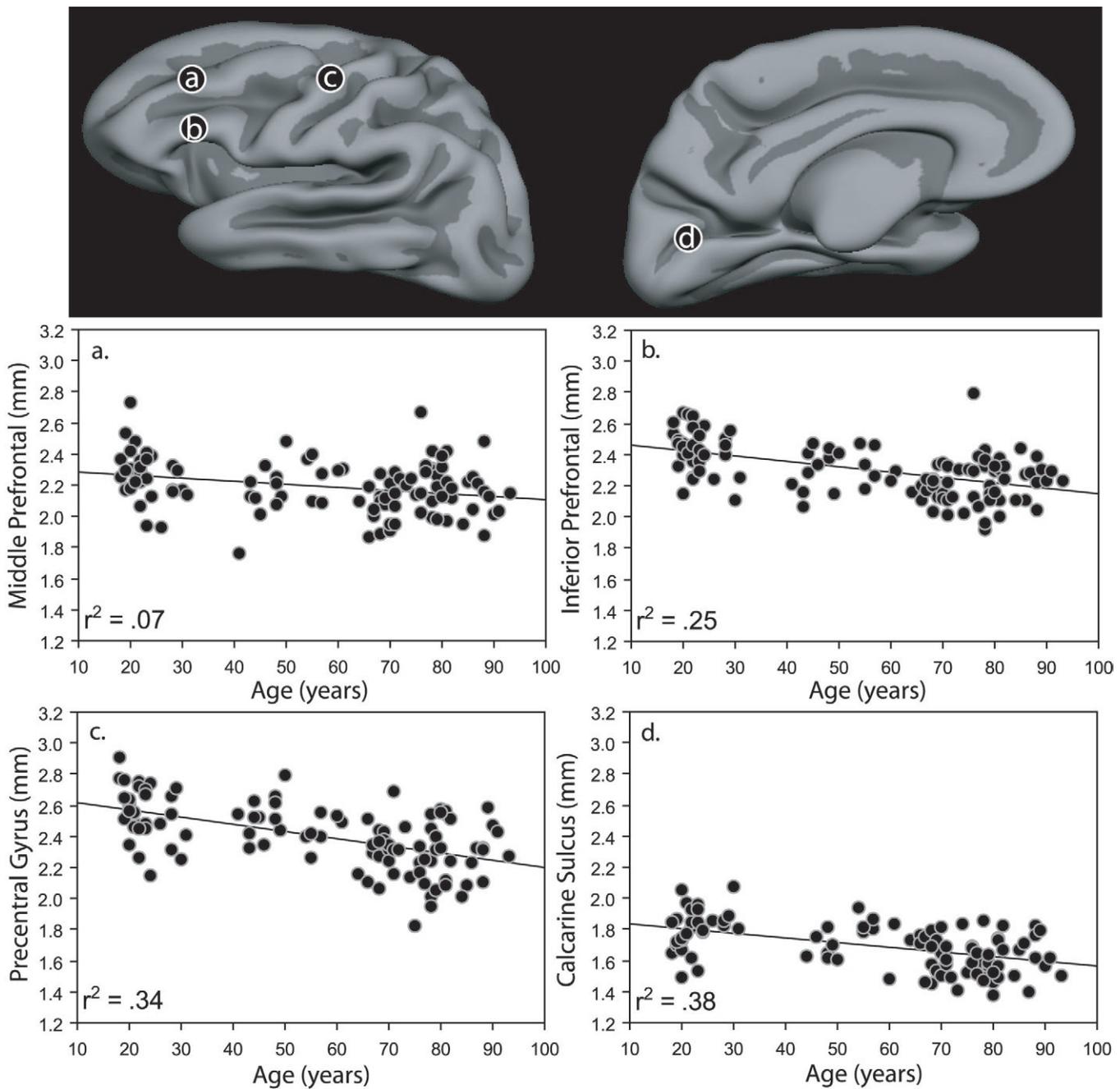


Figure 4. Age-associated regional cortical thinning. Top panel: lateral (left) and medial (right) views of the semi-inflated cortical surface of an average brain with dark gray regions representing sulci and light gray regions representing gyri. Bottom panel: scatterplots of regional thickness regressed by age as denoted by the regional demarcations of the top panel. Thinning was variable across the cortex. Significant thinning was found in various regions including portions of inferior prefrontal (b) precentral (c) and calcarine cortex (d).

measure. Regions of the cortex with both high (ventrolateral prefrontal cortex) and low (central sulcus, primary visual cortex) morphological variability in group data showed significant thinning – see Fischl and Dale (2000) for a description of group variance in thickness and curvature across the cortical surface. The direct statistical comparison of unbiased regional measures is an important aspect of brain mapping studies as discussed in recent reviews (Jernigan *et al.*, 2003). Our independent sample analyses demonstrated that the variability in rates of cortical thinning was reliable across samples and that rates statistically differed across regions. Thus, the data suggest

a heterochronous nature of morphological alterations that is anatomically widespread and agrees with the suggestion that ‘the aging brain exhibits a patchwork pattern of differential declines and relative preservation’ (Raz, 2000). These regional patterns do not exclude a bias to thinning (atrophy) based on some pattern (or combination of patterns) of gene expression, protein synthesis, neurochemical or other physiology property (Morrison, 2000). In this regard, the maps of regional thinning presented here may be useful toward guiding histological or molecular imaging studies attempting to elucidate such mechanisms.

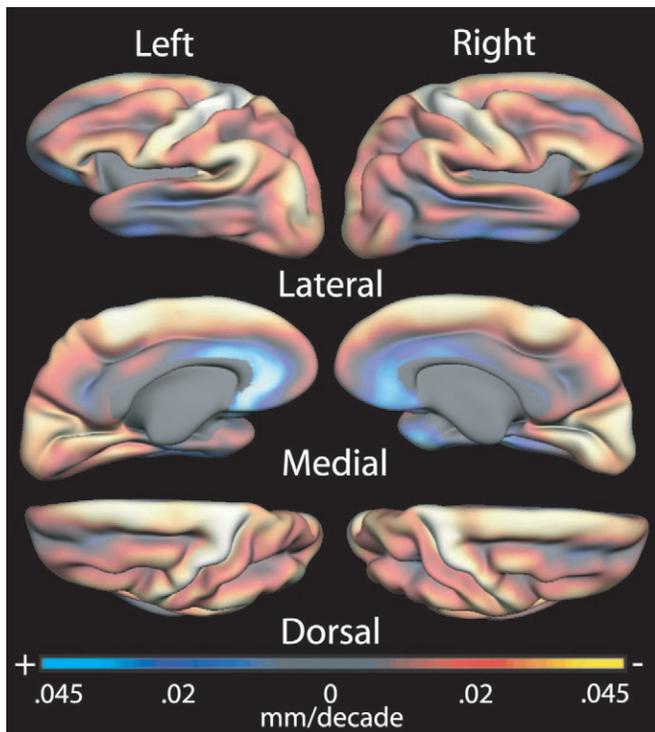


Figure 5. Age-associated map of cortical thinning in mm/per decade. Absolute thinning per decade is presented on the inflated cortical surface of an average brain. The colorscale at the bottom represents the absolute size of the thickness change (in mm/per decade) with red and yellow indicating regions of greatest thinning.

Prominent cortical thinning was noted within occipital cortex, in or near primary visual cortex, as well as within the precentral gyrus. While prior studies using imaging measures have noted significant (or trends towards significant) age-associated change in occipital cortex, most volumetric studies have emphasized the relatively smaller change in occipital in contrast to prefrontal cortex (e.g. Raz *et al.*, 1997). The present study found prominent and proportionate changes between regions within prefrontal and occipital cortex (see Fig. 5). This finding has important theoretical implications.

One hypothesis regarding structural change in aging is that regions of cortex that are late to develop are earliest to atrophy. Support for this theory has come from correlation of relative atrophy rates from volumetric studies to estimated developmental course. For example, Raz (2000) plotted the effect of age for 11 cortical regions against their rank order within Flechsig's myelination precedence (a metric of developmental myelination of intracortical fibers). Results suggested a strong relation between the two with those regions developing late showing the strongest aging effects. The present observation of prominent cortical thinning in or near primary visual cortex and motor cortex is inconsistent with this theory and argues against a 'last in, first out' model of aging, in so far as cortical (as opposed to subcortical or white-matter) aging effects are concerned. Evidence for a 'last in, first out' development and degradation of myelin, such as discussed by Kemper (1994), may still exist. In this regard, an interesting future research direction will be to link changes in white-matter to cortical atrophy. While the two may be associated, cortical

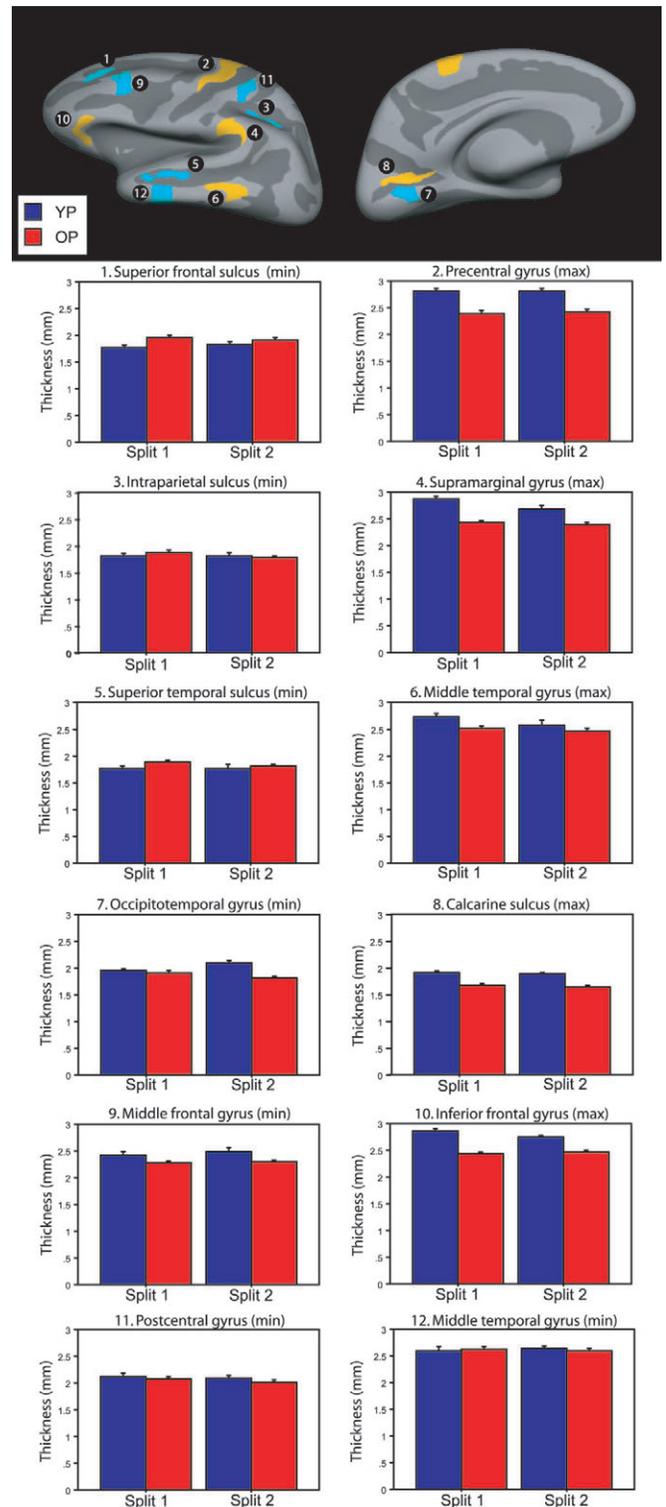


Figure 6. Reliability of regional measures of cortical thinning. Regional measures of cortical thickness are presented for two independent samples of participants comprising age-matched splits of the total sample (Split 1 versus Split 2). Regions were defined in areas of maximal and minimal thinning across each cortical lobe in the first sample and then mapped to the second sample of participants for an unbiased, independent measure of regional cortical thickness (top panel). Regional patterns of maximal and minimal thinning were similar across the two samples suggesting reliability in the measured pattern (bottom panel). Data are presented as the mean and standard error of the mean in the YP (blue bars) and OP groups (red bars) in each of the numbered regions chosen as showing minimal (min) or maximal (max) thinning.

atrophy and white-matter change may also reflect distinct underlying processes.

Consistent with many volumetric studies, marked thinning was noted in prefrontal cortex. Prefrontal cortex has received much attention in the field of cognitive aging as it has been noted that older adults can perform poorly on tasks that require executive functions presumed to rely on prefrontal cortex, among other structures (Moscovitch and Winocur, 1995; West, 1996; for a critical review, see Greenwood, 2000). Thus, it is possible that early age-related alterations in this region could contribute to age-related declines in executive processing tasks such as working memory tasks (Salat *et al.*, 2002a). The present data are consistent with this possibility.

One final point is that, while the present study does not specify the underlying mechanisms of cortical thinning, current literature based on histology suggests that such changes are unlikely to originate from neuronal death, as careful post-mortem studies have found relatively comparable

neuronal counts between older and younger subjects (for reviews, see Dani, 1997; Morrison and Hof, 1997), a finding that is supported by work with nonhuman primates (Peters *et al.*, 1998). Rather, cellular shrinkage and reduction in dendritic arborization are more likely to account for cortical thinning (Morrison and Hof, 1997).

Methodological Considerations and Caveats

The present methods rely on a recently developed computational approach to measure the thickness of the cerebral cortex (Fischl and Dale, 2000). To make these measurements, estimates of the gray/white boundary and pial surface are constructed based on segmentation of the white matter and subsequent deformation outward to find the outer cortical surface (Dale and Sereno, 1993; Dale *et al.*, 1999; Fischl *et al.*, 1999a,b, 2001; Fischl and Dale, 2000). This measurement, and other related kinds of measurement (e.g. Sowell *et al.*, 2003), are therefore highly sensitive to the contrast of the images and can potentially produce unreliable results from one sample to the next. From a data acquisition standpoint, we minimized such concerns by acquiring and averaging two to four (most often, four) structural images per participant. None the less, direct replication of the results would be the ideal test of reliability. Figure 6 demonstrates the reliability of the method using an ROI approach and Figure 7 demonstrates that the measures are manually replicable. As another measure of reliability, we examined whole surface maps in the two independent samples described for the ROI analyses for Figure 6, by ranking all of the participants by age (sorted by sex) and placing every other participant in each group to calculate group maps. Figure 8 shows the results. The specific patterns of age-associated cortical thinning are strikingly similar between the two independent samples and also highly similar to the map produced from the full sample of participants. These results support the consistency of the findings in independent samples.

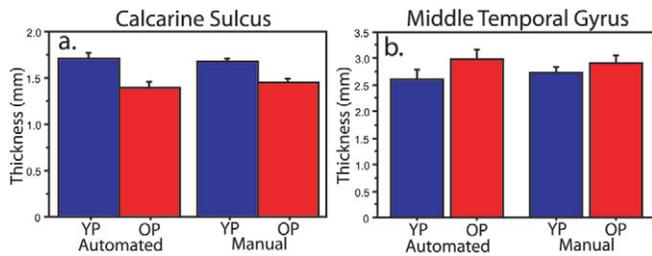


Figure 7. Manual measures of cortical thickness. A region of the middle temporal gyrus and a region of the calcarine sulcus were defined from the effect maps and mapped to the volume of 12 of the youngest and 12 of the oldest participants (matched for gender). Ten manual measurements of cortical thickness were obtained in these regions for each participant (the distance from the gray/white border to the gray/CSF border). The mean of these 10 measurements was then taken as the regional thickness for each participant. This procedure confirmed our negative finding showing preservation of temporal cortex and our novel finding of thinning in calcarine cortex.

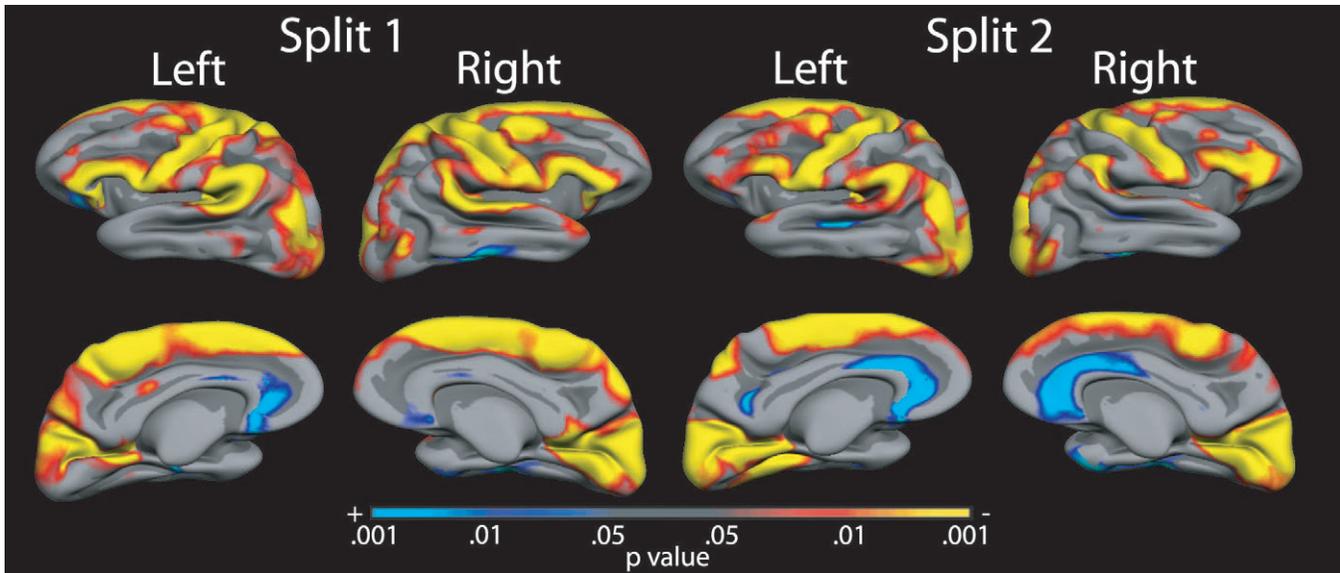


Figure 8. Reliability of cortical thinning maps. Using the same procedures as Figure 3, statistical maps of cortical thinning are presented for two independent samples of participants comprising age-matched splits of the total sample (Split 1 versus Split 2). While some differences between samples can be detected, the overall patterns of statistically significant cortical thinning are remarkably conserved between the independent samples and these maps are similar to the map produced by the total sample of participants (Figure 3) suggesting reliability in the measured pattern.

Two caveats should be considered in this context. First, although the methods employed were performed on high quality data and have been validated using histological methods in one study (Rosas *et al.*, 2002) and manual measurements in this and another study (Kuperberg *et al.*, 2003), it is possible that changes in MR tissue parameters and/or other unforeseen methodological variables, that associate with age, could influence these measures (Ogg and Steen, 1998; Jernigan *et al.*, 2001). Most notably, age-related changes in signal on T_1 -weighted MR images could contaminate image segmentation methods (Jernigan *et al.*, 2001; Davatzikos and Resnick, 2002) and recent studies have demonstrated that such change could influence the placement of the gray matter/white matter border (Davatzikos and Resnick, 2002) and could potentially alter the regional sensitivity of the methods. The current study attempted to reduce such confounds by motion correcting and averaging multiple high-resolution MR volumes for each participant to create a single volume with high signal-to-noise. Importantly, the reduced signal in brain white matter with increasing age would be expected to result in apparent cortical 'thickening' with age. Although we did find such thickening, this occurred partially in regions of common MRI signal loss and artifact, which somewhat overlap to regions of signal intensity changes reported in prior studies (Davatzikos and Resnick, 2002). Similar increases in structural measures in medial frontal regions, particularly in later decades of the agespan, have been hinted at in prior studies (e.g. Raz *et al.*, 1997; Salat *et al.*, 2002a; Sowell *et al.*, 2003), yet the etiology of such increases is unclear. Thus, it is possible that changes in tissue parameters and other imaging artifacts such as 'bias fields' contribute to the present findings and we are currently examining the distribution of age-related signal changes within the brain (Salat *et al.*, 2002b). The second limitation is that the data presented are cross-sectional. Cross-sectional data could be influenced by potential cohort effects and an important future goal will be to use these procedures to examine longitudinal change.

Conclusions

Description of cortical thinning provides a potentially important means to visualize local and global atrophy. Our initial exploration of cortical thinning in non-demented aging suggests prominent atrophy in some expected regions, such as prefrontal cortex. Results also suggest surprisingly widespread cortical change that includes primary motor and visual areas. These specific patterns of cortical thinning are reliable across independent subsets of the data. Further research that extends estimates to aging in dementia may provide valuable insights into distinct forms of change associated with non-demented aging as contrast to aging associated with Alzheimer disease.

Notes

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References

- Berg L, McKeel DW Jr, Miller JP, Storandt M, Rubin EH, Morris JC, Batty J, Coats M, Norton J, Goate AM, Price JL, Gearing M, Mirra SS, Saunders AM (1998) Clinicopathologic studies in cognitively healthy aging and Alzheimer's disease: relation of histologic markers to dementia severity, age, sex, and apolipoprotein E genotype. *Arch Neurol* 55:326-335.
- Blatter DD, Bigler ED, Gale SD, Johnson SC, Anderson CV, Burnett BM, Parker N, Kurth S, Horn SD (1995) Quantitative volumetric analysis of brain MR: normative database spanning 5 decades of life. *Am J Neuroradiol* 16:241-251.
- Chung MK, Worsley KJ, Robbins S, Paus T, Taylor J, Giedd JN, Rapoport JL, Evans AC (2003) Deformation-based surface morphometry applied to gray matter deformation. *Neuroimage* 18:198-213.
- Dale AM, Sereno MI (1993) Improved localization of cortical activity by combining EEG and MEG with MRI cortical surface reconstruction: a linear approach. *J Cogn Neurosci* 5:162-176.
- Dale AM, Fischl B, Sereno MI (1999) Cortical surface-based analysis. I. Segmentation and surface reconstruction. *Neuroimage* 9:179-194.
- Dani S (1997) Histological markers of neuronal aging and their meaning. In: *Principals of neural aging* (Dani SU, AH, Walter GF, eds), pp. 263-278. Amsterdam: Elsevier Science.
- Davatzikos C, Resnick SM (2002) Degenerative age changes in white matter connectivity visualized *in vivo* using magnetic resonance imaging. *Cereb Cortex* 12:767-771.
- DeCarli C, Murphy DG, Gillette JA, Haxby JV, Teichberg D, Schapiro MB, Horwitz B (1994) Lack of age-related differences in temporal lobe volume of very healthy adults. *Am J Neuroradiol* 15:689-696.
- Fischl B, Dale AM (2000) Measuring the thickness of the human cerebral cortex from magnetic resonance images. *Proc Natl Acad Sci USA* 97:11050-11055.
- Fischl B, Sereno MI, Dale AM (1999a) Cortical surface-based analysis. II: inflation, flattening, and a surface-based coordinate system. *Neuroimage* 9:195-207.
- Fischl B, Sereno MI, Tootell RB, Dale AM (1999b) High-resolution intersubject averaging and a coordinate system for the cortical surface. *Hum Brain Mapp* 8:272-284.
- Fischl B, Liu A, Dale AM (2001) Automated manifold surgery: constructing geometrically accurate and topologically correct models of the human cerebral cortex. *IEEE Trans Med Imaging* 20:70-80.
- Flood DG, Coleman PD (1988) Neuron numbers and size in the aging brain: comparison of human, monkey, and rodent data. *Neurobiol Aging* 9:453-463.
- Good CD, Johnsrude IS, Ashburner J, Henson RN, Friston KJ, Frackowiak RS (2001) A voxel-based morphometric study of ageing in 465 normal adult human brains. *Neuroimage* 14:21-36.
- Greenwood PM (2000) The frontal aging hypothesis evaluated. *J Int Neuropsychol Soc* 6:705-726.
- Jernigan TL, Archibald SL, Berhow MT, Sowell ER, Foster DS, Hesselink JR (1991) Cerebral structure on MRI, Part I: localization of age-related changes. *Biol Psychiatry* 29:55-67.
- Jernigan TL, Archibald SL, Fennema-Notestine C, Gamst AC, Stout JC, Bonner J, Hesselink JR (2001) Effects of age on tissues and regions of the cerebrum and cerebellum. *Neurobiol Aging* 22:581-594.
- Jernigan TL, Gamst AC, Fennema-Notestine C, Ostergaard AL (2003) More 'mapping' in brain mapping: statistical comparison of effects. *Hum Brain Mapp* 19:90-95.
- Kemper TL (1994) Neuroanatomical and neuropathological changes during aging and in dementia. In: *Clinical neurology of aging*, 2nd edn (Albert ML, Knoepfel EJE, eds), pp. 3-67. New York: Oxford University Press.
- Kuperberg GR, Broome MR, McGuire PK, David AS, Eddy M, Ozawa F, Goff D, West WC, Williams SC, van der Kouwe AJ, Salat DH, Dale AM, Fischl B (2003) Regionally localized thinning of the cerebral cortex in schizophrenia. *Arch Gen Psychiatry* 60:878-888.

- Meyer JR, Roychowdhury S, Russell EJ, Callahan C, Gitelman D, Mesulam MM (1996) Location of the central sulcus via cortical thickness of the precentral and postcentral gyri on MR. *Am J Neuroradiol* 17:1699-1706.
- Miller MI, Massie AB, Ratnanather JT, Botteron KN, Csernansky JG (2000) Bayesian construction of geometrically based cortical thickness metrics. *Neuroimage* 12:676-687.
- Morris JC (1993) The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* 43:2412-2414.
- Morrison JH (2000) Age-related shifts in neural circuit characteristics and their impact on age-related cognitive impairments. In: *The aging mind* (Stern PC, Carstensen LL, eds), pp. 83-113. Washington, DC: National Academies Press.
- Morrison JH, Hof PR (1997) Life and death of neurons in the aging brain. *Science* 278:412-419.
- Moscovitch M, Winocur G (1995) Frontal lobes, memory, and aging. In: *Structure and functions of the human prefrontal cortex* (Grafman J, Holyoak KJ, Boller F, eds), pp. 119-150. New York: New York Academy of Sciences.
- Ogg RJ, Steen RG (1998) Age-related changes in brain T1 are correlated with iron concentration. *Magn Reson Med* 40:749-753.
- Peters A, Morrison JH, Rosene DL, Hyman BT (1998) Feature article: are neurons lost from the primate cerebral cortex during normal aging? *Cereb Cortex* 8:295-300.
- Pfefferbaum A, Mathalon DH, Sullivan EV, Rawles JM, Zipursky RB, Lim KO (1994) A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood. *Arch Neurol* 51:874-887.
- Raz N (2000) Aging of the brain and its impact on cognitive performance: integration of structural and functional findings. In: *Handbook of aging and cognition - II* (Craik FIM, Salthouse TA, eds), pp. 1-90. Hillsdale, NJ: Erlbaum.
- Raz N, Gunning FM, Head D, Dupuis JH, McQuain J, Briggs SD, Loken WJ, Thornton AE, Acker JD (1997) Selective aging of the human cerebral cortex observed *in vivo*: differential vulnerability of the prefrontal gray matter. *Cereb Cortex* 7:268-282.
- Rosas HD, Liu AK, Hersch S, Glessner M, Ferrante RJ, Salat DH, van der Kouwe A, Jenkins BG, Dale AM, Fischl B (2002) Regional and progressive thinning of the cortical ribbon in Huntington's disease. *Neurology* 58:695-701.
- Salat DH, Kaye JA, Janowsky JS (2002a) Greater orbital prefrontal volume selectively predicts worse working memory performance in older adults. *Cereb Cortex* 12:494-505.
- Salat DH, Fischl B, van der Kouwe AJW, Clarke RJ, Segonne F, Corkin S, Dale AM (2002b) Age-related changes in T1 relaxation times across the surface of the cortex. In: *8th International Conference on Functional Mapping of the Human Brain*. Sendai, Japan: Neuroimage.
- Sowell ER, Peterson BS, Thompson PM, Welcome SE, Henkenius AL, Toga AW (2003) Mapping cortical change across the human life span. *Nat Neurosci* 6:27-32.
- Steiger JH (1980) Tests for comparing elements of a correlation matrix. *Psychol Bull* 87:245-251.
- West RL (1996) An application of prefrontal cortex function theory to cognitive aging. *Psychol Bull* 120:272-292.