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Gray-matter macrostructure in cognitively healthy older persons: Associations with age and cognition

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Abstract

A deeper understanding of brain macrostructure and its associations with cognition in persons who are considered cognitively healthy is critical to the early detection of persons at risk of developing dementia. Few studies have examined the associations of all three gray-matter macrostructural brain indices (volume, thickness, surface area) with age and cognition, in the same persons who are over the age of 65 and do not have cognitive impairment. We performed automated morphometric reconstruction of total gray matter, cortical gray matter, subcortical gray matter and 84 individual regions in 186 participants (60% over the age of 80) without cognitive impairment. Morphometric measures were scaled and expressed as difference per decade of age and an adjusted score was created to identify those regions in which there was greater atrophy per decade of age compared to cortical or subcortical brain averages. The results showed that there is substantial total volume loss and cortical thinning in cognitively healthy older persons. Thinning was more widespread than volume loss, but volume loss, particularly in temporoparietal and hippocampal regions, was more strongly associated with cognition.

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Keywords

Aging; cognition; MRI morphometry; volume; thickness; surface area

Introduction

It is well-established that macrostructural shrinkage of the brain occurs with older age in persons that are considered cognitively healthy, but substantial regional heterogeneity in atrophy is reported across studies (Fjell and Walhovd, 2010; Raz and Rodrigue, 2006). Likewise, it is well-established that older age impacts cognitive function (Hedden and Gabrieli, 2004; Salthouse 2010), even in persons who are considered cognitively healthy, but the association between macrostructural integrity and cognition in healthy aging, particularly on the level of regional associations and specific cognitive domains, remains unclear (Fjell and Walhovd, 2010; Salthouse, 2011).

It is important to be able to identify the macrostructural and cognitive alterations brought about by healthy aging in order to distinguish them from accelerated atrophy and concomitant cognitive patterns in persons who may be at increased risk of developing cognitive impairment and/or Alzheimer's disease (AD; Cummings et al. 2007; Sloane et al. 2002). However, as noted, there is currently a lack of clarity in the literature regarding the associations of brain morphometry, age and cognition in healthy aging. For example, the results of many studies argue for a frontostriatal pattern of age-related macrostructural loss that is often accompanied by executive memory dysfunction, while the results of just as many studies argue that the loss occurs primarily in a temporal or temporoparietal pattern and is often associated with episodic memory dysfunction. (These studies are comprehensively reviewed in the Discussion). This variability in results is due in part to sampling and measurement differences across studies. First, studies vary in the age ranges sampled from youth through old age. Many studies include a limited number of healthy participants over the age of 70, and atrophy may not be obvious until late adulthood (Scahill et al. 2003), particularly for some structures such as the hippocampus or regions of the frontal lobe (Allen et al. 2005; DeCarli et al. 2005; Raz 2004a). In some structures, such as the caudate, age-related increases in volume have been reported after age 50 (Good et al. 2001; Lemaitre et al. 2005; Zimmerman et al. 2006) and atrophy may actually diminish in late life (Walhovd et al. 2011). Second, studies differ in the inclusion of older persons who do not have dementia, but who are not cognitively-normal (Burgmans et al. 2009; Fjell, Walhovd et al. 2009). Thus, findings may be influenced by participants who already have mild cognitive impairment (MCI) due to Alzheimer's disease (Sperling et al. 2011). Third, studies differ in the inclusion of white-matter along with gray-matter in the macrostructural measurement. Reductions in both white- and gray-matter occur in healthy aging (Brickman et al. 2007), but may have differential effects on cognition (Head et al. 2008; Schmidt et al. 2005). Fourth, in studies of gray-matter macrostructure, most take primarily a whole-brain (Brickman et al. 2006; Fotenos, et al. 2008), lobar (Resnick et al. 2000, 2003, 2010), or regions-of-interest (Head et al. 2008; Kramer et al. 2007; Raz et al. 1998; Rusinek et al. 2003; Zimmerman et al. 2006) approach, and in the latter, often only a single region (e.g., hippocampus; Golomb et al. 1993; Hackert et al. 2002) is examined. Further, whole-brain

exploratory studies are inconsistent in adjusting regional age associations for the brain average, so it remains unclear which regions are differentially affected by age compared to the whole cortex or subcortex. This is important because regions that are affected more by age than the average of the whole brain may be candidate biomarker regions for incipient cognitive impairment. Fifth, most studies focus on a single morphometric index, although the three commonly used indices (volume, thickness and surface area) may be differentially sensitive to age (Barta and Dazzan 2003; Hutton et al. 2009; LeMaitre et al. 2012) and genetic influences (Panizzon et al. 2009). Three studies that we know of have reported data from all three morphometric measures in the same healthy older individuals (LeMaitre et al. 2012; Rettman et al. 2006; Salat et al. 2004), but in these studies there were few participants over the age of 60 and associations with cognition were not examined. Sixth, many macrostructural studies either do not measure cognition or measure just global cognition or cognition in a single domain (e.g., episodic memory; Golomb et al. 1993). Finally, studies vary in their method of statistical correction for multiple comparisons which influences the significance threshold of regional age differences and may account for the inconsistent regional patterns reported across studies.

In this study, a large sample of participants of the Rush Memory and Aging Project (MAP), a cohort study of aging and dementia, underwent macrostructural MR imaging. Because these participants were deeply-characterized clinically and cognitively, we were able to limit the sample to persons without dementia or MCI. We measured volume, thickness and surface area in whole-brain, cortex, subcortex (volume only), and 84 regions (74 cortical, 10 subcortical). In linear regression models, we first examined associations of brain gray-matter morphometry with age using scaled brain regions (to account for size differences) and scaled brain regions that were adjusted for the average brain morphometric measure (to identify regions that were affected by age more than the whole brain). We next examined, in separate models, the associations of global cognition and five cognitive domains (episodic memory, semantic memory, working memory, perceptual speed and visuospatial ability) with age. We then examined the association of brain gray-matter morphometry with cognition, controlling for age and examined whether gray-matter morphometry mediated associations between age and cognition. Finally, we examined the association between brain gray-matter morphometry and cognition in only those regions that were associated with age using the adjusted scaled score. All findings were subjected to two levels of correction for multiple comparisons, the commonly used False Discovery Rate (FDR), and the more stringent Bonferroni-Holm (BH), method. By using this two-tiered statistical approach, we were able to distinguish those regions that were more or less strongly affected by healthy aging.

Materials and Methods

Subjects

Participants were recruited from the Rush Memory and Aging Project, a cohort study of aging and dementia (Bennett, Schneider et al 2012). All participants gave informed consent. The study was approved by the Institutional Review Board of Rush University Medical Center and was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Of the first 245 scans post-processed, 244

passed quality control procedures, 6 persons were under age 65, 2 had dementia and 50 had MCI. The remaining 186 persons were without cognitive impairment proximate to scan date (mean time interval between clinical evaluation and scan = 2.2 months, SD = 1.9 months).

Clinical and Cognitive Evaluation

Each MAP participant underwent a structured, uniform evaluation that included a medical history, neurological examination, and cognitive function testing, which is fully described in Bennett, Schneider et al (2012). *Episodic memory* was measured using CERAD Word List Memory, Recall, and Recognition, immediate and delayed recall of the East Boston Story, and Story A from Logical Memory. *Semantic memory* was measured using a 20-item version of the Boston Naming Test, a 15-item version of Extended Range Vocabulary, a 20-item reading recognition test from the National Adult Reading Test, and Verbal Fluency which involves naming animals and fruits/vegetables in 1-minute epochs. *Working memory* was measured using Digit Span Forward, Digit Span Backward and Digit Ordering. *Perceptual speed* was measured with the oral version of the Symbol Digit Modalities Test, Stroop Test, and Number Comparison. *Visuospatial ability* was assessed with a 15-item version of Judgment of Line Orientation and a 17-item version of Standard Progressive Matrices. Summary measures of the five cognitive domains were formed, based in part on a principal-components factor analysis. Raw scores on each test were converted to z scores (mean of 0, standard deviation of 1 (based on all MAP participants at baseline) and then the average z score among tests in a given domain was computed. A global cognitive score was formed by averaging z scores of all tests.

MR Imaging

High-resolution T₁-weighted anatomical data were obtained on a 1.5 Tesla GE (General Electric, Waukesha, Wisconsin) MRI scanner, using a 3D magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence with the following parameters: TE=2.8ms, TR=6.3ms, preparation time=1000ms, flip angle 8, field of view 24cm × 24cm, 160 slices, 1mm slice thickness, 224×192 image matrix reconstructed to 256×256, 2 repetitions.

The MRI data from all participants were automatically segmented with Freesurfer (<http://surfer.nmr.mgh.harvard.edu>). All results were reviewed and manual intervention was used when necessary to increase the accuracy of labeling. The intracranial volume, whole brain volume, the volumes of 74 cortical and 10 subcortical gray matter structures (Destrieux et al. 2010), as well as the thickness and surface of the 74 cortical gray matter structures were obtained. Regions that the algorithm was unable to reliably segment due to the lack of sufficient image contrast were flagged. Fifty-one flags occurred across 38 scans. Most of these flags (76%) occurred within the insula. All brain measures from flagged regions were excluded from analyses.

Statistical Approach

Brain data were transferred to SAS (SAS Institute, Inc., 2012) for further data manipulation, linkage with demographic and neuropsychological data, and statistical analyses. Standard statistics were obtained for the demographic characteristics of the sample, the brain measures and the cognitive scores. All volumes were corrected for intracranial volume

(ICV) and expressed as tenths of a percent (0.1%) of ICV. Surface areas in mm^2 were normalized by ICV. Right and left sides were combined. Volume summary measures were calculated for total brain gray-matter, cortical gray-matter, subcortical gray-matter and 84 individual regions (74 cortical, 10 subcortical). Mean thickness was calculated by averaging thicknesses for the 74 cortical regions, omitting any regions flagged for a specific subject. Total cortical surface area was calculated by adding the surface areas of the 74 cortical regions, excluding 38 participants with flagged regions. We examined associations of age with the summary brain measures by regressing total gray-matter volume, cortical gray-matter volume, subcortical gray-matter volume, mean thickness and total surface area on age with terms to adjust for sex and education. To reduce leading zeros, the regression coefficients of the volumes are expressed in %ICV per decade of age; the coefficient of total surface area is cm^2 per tenths of percentage of ICV per decade of age; the coefficient of average thickness is mm/year.

To examine the association of age with individual regional volumes we followed a similar approach. In order to compare regions that have very different sizes, we scaled the volume of each region by dividing the value of a region by the mean volume of that region across all 186 participants. Thus, if a subject's volume for a specific region is exactly the same as the mean across participants, the scaled volume for that region and subject is 1; if a subject's volume for a specific region is 20% larger (smaller) than the mean across participants, the mean scaled volume for that region and subject is 1.2 (0.8). We then fit the models in which the scaled- regional volume was regressed on age with terms to correct for sex and education. To guide our conclusions and correct for multiple comparisons, we applied False Discovery Rate (FDR; Benjamini & Yekutieli 2001) corrections to the p-values for the coefficients of age. The FDR correction is frequently described via adjustment to the nominal significance level or the cut-off for the p-value. The k^{th} smallest unadjusted p-value (out of $M=74$ regions compared, in most of our examples) is compared with the $\alpha=0.05$ multiplied by (k/M) . Exactly the same hypotheses are rejected if instead a corrected p-value (p_{corr}) is defined as the k^{th} smallest p-value multiplied by (M/k) and then p_{corr} is compared with $\alpha=0.05$. We also include the more stringent Bonferroni-Holm (BH; Holm 1979) correction to help represent the strength of the evidence for each finding.

To establish whether the strengths of the associations of regional volumes with age differed compared to the cortical or subcortical brain average, we first calculated a mean scaled volume by averaging across the 74 cortical scaled volumes and the 10 subcortical scaled volumes separately for each subject, omitting volumes for any flagged regions. Thus, if a subject's volumes are all equal to the mean for the corresponding regions, the subject's mean scaled volume is 1; if all the volumes are 20% larger than the mean, the mean scaled volume is 1.2; if all the volumes are 20% less than the mean volume, then the mean scaled volume is 0.8. For each subject and each region, we then subtracted the subject's mean scaled volume from the scaled volume of the region to obtain an adjusted volume of the region. The adjusted volume for a specific region is negative if the scaled volume for that region (say 0.8) is smaller than the subject's mean scaled volume (say 1.1) and is positive if the scaled volume for that region (say 1.2) is larger than the subject's mean scaled volume (say 1.1). We then regressed the adjusted volume on age, with terms for sex and education, separately for each region. The fitted models were then used to identify regions with weaker

age associations (statistically significant positive coefficients) or with stronger age associations (statistically significant negative coefficients) than the average region. Statistical significance was again determined via FDR- and BH-adjusted p-values. We used the same approach for cortical thickness and surface area.

Before examining the associations of brain morphometry with cognition, we examined the association of age and cognition by regressing the cognitive summary score (global cognition, episodic memory, semantic memory, working memory, perceptual speed, or visuospatial ability) on age, with terms for sex and education. When the association of cognition with age was significant, in separate models for each summary brain measure (whole-brain, cortical, subcortical), we added that summary brain measure to our regression model. If there was a statistically significant association with the summary brain measure, we then performed two sets of regression analyses for the corresponding regional measures in order to examine regional associations with age and in order to compare these associations across regions. In both sets, the cognitive measure was the dependent variable. Our first set of regression models included terms for a scaled regional measure, as well as terms for age, sex and education. In the second set of regression models, the independent variables were the adjusted regional measure with additional terms to control for age, sex, education and the corresponding mean scaled summary brain measure. Adjusted regional measures were significant only if their association with cognition differed from that of the summary brain measures, that is, from that of the cortex or subcortex as a whole. Finally, in secondary analyses, we examined the association of brain morphometry and cognition in just those brain regions that were previously identified as showing a significant (FDR-corrected) difference per decade of age compared to the cortical or subcortical global average (i.e., the adjusted scores).

Results

Descriptives

Sample characteristics and cognitive scores are shown in Table 1. Of the 186 persons meeting eligibility criteria, 47 (25.3%) were male and 176 (95.1%) were non-Hispanic white. The mean age at the time of scan was 81.5 years, $SD = 6.7$, range 65 to 100. One hundred fifteen participants (62% of the sample) were aged 80 or older. Means for cognitive standard scores ranged from 0.315 to 0.605. All means were positive because this subsample without cognitive impairment typically performed better than the Rush Memory and Aging Project baseline sample. Although variation in cognitive performance in this subsample was smaller than the variation in the entire parent sample, the variation remained substantial.

Summary morphometric measurements in raw metric, %ICV and scaled units are shown in Table 2. Mean ICV was approximately 1565 cm^3 . Total gray matter volume was approximately 364 cm^3 with cortex and subcortex comprising 70% and 30% of this volume, respectively. Average thickness was approximately 2 mm. Surface area, based on 148 cases that were flag-free, averaged approximately 1667 cm^2 .

Brain morphometry and age

In this section, we examined the associations of summary brain regions with age followed by regional brain measures with age.

Summary brain measures with age—We first examined the associations of total gray-matter volume, cortical gray-matter volume and subcortical gray-matter volume with age. A substantial fraction of the cross-sectional variation of gray-matter volume was associated with age (uncorrected for sex and education; corrected percentages are given in Table 3), with the percentages of variation explained being 32.8% (total gray-matter volume), 30.1% (cortical gray-matter volume) and 22.3% (subcortical gray-matter volume). The estimated coefficients shown in Table 3 are all negative, which indicates that average age-specific gray-matter volume is lower among older persons. The coefficients show substantial age differences in gray-matter volumes: for example, persons who are on average 10 years older than a reference group will have an average total gray-matter volume that is 3.0 %ICV smaller. Because total gray-matter volume was on average 33.6 %ICV, these effects correspond to substantial differences in volume. Age was associated with average thickness, accounting for 24.7% of the variance. In contrast to volume and thickness, total surface area showed a weaker association with age (2.7% of explained variance).

Scaled regional brain measures with age—Regions are specified using the FreeSurfer [FS] label and number as described in Destrieux, Fischl, Dale and Halgren (2010). Most cortical and subcortical regions showed significant associations of volume with age using both correction methods, even after corrections for sex and education. All regional thicknesses had significant associations with age using both correction methods. In contrast to volume and thickness, the surface areas of most regions were *not* associated with age.

Adjusted regional brain measures with age—These regressions identified the regions that had stronger or weaker brain differences per decade of age compared to the cortical or subcortical average. Coefficients are given in Table 4. For cortical volume, 9 of 74 regions were found to have significant age differences compared to the cortical average. Those regions that had smaller adjusted volumes per decade of age (negative coefficients) using the BH method were the supramarginal gyrus [FS26] and the middle temporal gyrus [FS38], and the hippocampus. The FDR method added the superior frontal gyrus [FS16], planum temporale or temporal plane of the superior temporal gyrus [FS36], and the vertical ramus of the anterior segment of the lateral sulcus (or fissure) [FS40]. For cortical thickness, 7 regions passed using the BH method, and the FDR method produced an additional 10 regions. The regions that were thinner per decade of age compared to the cortical thickness average using the BH method were the angular gyrus [FS25], supramarginal gyrus [FS26], precentral gyrus [FS29], and middle temporal gyrus [FS38]. FDR added the transverse frontopolar gyri and sulci [FS5], posterior-dorsal part of the cingulate gyrus [FS9], superior frontal gyrus [FS16], postcentral gyrus [FS28], planum temporale or temporal plane of the superior temporal gyrus [FS36], and posterior ramus (or segment) of the lateral sulcus (or fissure) [FS41]. For cortical surface area, 5 regions passed using the BH method, and the FDR method added another 3 regions. Two regions had less surface area per decade of age

compared to the cortical surface area global average: the calcarine sulcus [FS44] passed using the BH method. The FDR method added the vertical ramus of the anterior segment of the lateral sulcus (or fissure) [FS40].

Those regions with larger adjusted volume, thickness or surface area per decade of age (positive coefficients) are also given in Table 4. Figures 1–6 graphically depict the age coefficients of the scaled and the adjusted scores for volume, thickness and surface area using the FDR multiple comparison correction.

Age, cognition and brain morphometry

In this section, we examined the associations of age with cognition, scaled brain morphometry with cognition, and then in mediation analyses, the influence of brain morphometry on the associations between age and global and domain-specific cognition. Finally, in secondary analyses, we examined the association of scaled brain morphometry and cognition in just those regions previously identified as having more atrophy than the cortical or subcortical average per decade of age (adjusted scores).

Associations of age and cognition—Associations were tested in linear regression models that controlled for sex and education (Table 5). In the core models, age, sex and education were significantly associated with cognitive performance, both global and domain-specific, and explained between 5% and 21% of the variation in cognitive performance. Older persons tended to have lower global cognitive scores (0.09 units lower per decade of age); the associations with perceptual speed (0.33 units lower per decade of age) and with semantic memory (0.11 units lower per decade of age) were the most statistically significant of the domain-specific associations with age. There were no associations of age with episodic memory, working memory or visuospatial ability.

Associations of brain and cognition—Associations were tested in linear regression models that controlled for age, sex and education. Associations between summary brain measures and cognition are given in Table 5. Summary measures showed significant and positive associations with global cognition, episodic memory and perceptual speed, but were not significantly associated with semantic memory, working memory, or visuospatial ability. Significant associations between the scaled regional morphometric measures and cognition are given in Table 6. The strongest (surviving BH correction) positive associations were between 1) global cognition and the volume of cerebellum-cortex, 2) episodic memory and the volumes of inferior occipital gyrus and sulcus [FS2], transverse frontopolar gyri and sulci [FS5], horizontal ramus of the anterior segment of the lateral sulcus (or fissure) [FS39], and hippocampus, and the surface areas of transverse frontopolar gyri and sulci and horizontal ramus of the anterior segment of the lateral sulcus or fissure, and 3) perceptual speed and volume of cerebellum-cortex. In models using the adjusted score and controlling for age, sex, education and the brain summary measure, positive associations occurred between 1) global cognition and orbital gyri [FS24] thickness, 2) episodic memory and subparietal sulcus [FS71] thickness, and 3) perceptual speed and orbital gyri thickness.

Mediation Analysis—Given that each summary brain measure (total, cortical and subcortical volume; average thickness; total surface area) was significantly associated with age, we were able to examine the influence of brain morphometry on the association between age and global and domain-specific cognition in mediation analyses. The associations were examined in a series of linear regression models in which each summary brain measure was added separately to the model (models shown in Table 5). The association between age and global cognition was no longer significant after adding any one of the volumetric summary measures and surface area. That is, each of these summary measures individually mediated the association of age with global cognition. Average thickness had no effect on the association. In the models with age and perceptual speed, all three volumetric measures attenuated the effect of age, but the association with age remained strongly significant. This indicates that total, cortical and subcortical gray-matter volumes each partially mediated the association of age with perceptual speed, but there were independent associations of perceptual speed with each volumetric measure even after controlling for age. In the models for semantic memory, the weak association with age was attenuated when morphometric summary measures were added. Mediation analyses were not conducted for the three cognitive domains for which age was not associated with performance in this group of participants without cognitive impairment: episodic memory, working memory and visuospatial ability. Indeed, variations in total (and in cortical) volume masked a weak association of age with episodic memory, because episodic memory was marginally significant when total or cortical volume was added into the model.

Secondary regional analysis—In this analysis, separately for each morphometric measure, we examined the associations between morphometric adjusted scores and cognitive scores for just those brain regions identified as showing reductions (negative coefficients) per decade of age compared to the cortical or subcortical global average based on the FDR-corrected adjusted scores. Global cognition was positively associated with volume of the middle temporal gyrus ($p_{\text{corr}} = 0.03$, BH) and the supramarginal gyrus ($p_{\text{corr}} = 0.045$, FDR). Episodic memory was associated with hippocampal volume ($p_{\text{corr}} = 0.001$, BH) and there was a trend for an association with superior frontal gyrus volume ($p_{\text{corr}} = 0.057$, FDR). Episodic memory was also associated with calcarine surface area ($p_{\text{corr}} = 0.01$, BH). There was a trend for working memory to be associated with hippocampal volume ($p_{\text{corr}} = 0.051$, BH).

Discussion

The results of this study, in which 60% of the sample was over the age of 80 and without dementia or MCI, suggest that a substantial degree of gray-matter volume loss and thinning occur in older persons who are considered cognitively healthy. Gray matter had significantly less volume and was thinner over the entire brain per decade of age, however, the association of surface area and age was weak. Volume is a composite measure of atrophy, computed from the product of thickness and surface area. Thickness and surface area have been shown to have distinct sources of genetic influence, measured on global, lobar and regional levels (Panizzon 2009), which argues for the examination of cortical thickness and surface area separate from volume in studies of aging. Regional thinning is typically more

widespread than volume reduction in older brains, and thus may be a more sensitive measure of the effect of age on the brain (Hutton 2009; Lemaitre 2012; Rettmann 2006). One possible explanation for this difference in sensitivity is that the effect of age on volume is attenuated by the surface area component that is not as strongly associated with age (Barta 2003; Lemaitre 2012, but see Dickerson 2007). The current findings support this explanation.

In this study, the most robust negative associations of volume and age occurred in supramarginal gyrus, middle temporal gyrus and hippocampus. For thickness, the most robust negative age associations occurred in supramarginal gyrus, middle temporal gyrus, angular gyrus, and precentral gyrus. Thus, thinning was more widespread than volume loss, as expected based on extant findings, but volume loss was most strongly associated with cognition, particularly in temporoparietal and hippocampal regions. The few regions that had less surface area per decade of age were located in the occipital and frontal lobes. The results of this study are discussed below within the context of the current literature.

Gray-matter global and regional volume and age

Whether measured cross-sectionally as age difference in volume per unit of time (such as decade; e.g., Brickman et al. 2007; Hutton et al. 2009; Jernigan et al. 2001; Lemaitre et al. 2005; Raz 1998; Resnick et al. 2000; Salat et al. 2004; Tisserand et al. 2000; Walhovd et al. 2005) or longitudinally as atrophic change over a continuous period (e.g., Driscoll et al. 2009; Fotenos et al. 2008; Resnick et al. 2003; Schill et al. 2003; Tisserand et al. 2004), it is largely accepted that whole-brain gray-matter volume is reduced with increasing age, and that this reduction is greater for cortex than subcortex (Jernigan et al. 2001; Zimmerman et al. 2006). We measured cross-sectional differences in volume per decade of age and found that, indeed, sex- and education-corrected coefficients with age were negative and accounted for about 40% of the variation in total gray-matter volume. Age accounted for over one-third of the variance in cortical gray-matter volume and over one-quarter of the variance in subcortical gray-matter volume.

There is substantially less consensus, however, regarding the effect of healthy aging on regional volumes within the cortex and subcortex, with a number of different patterns reported in the literature. A considerable number of studies suggest that frontal or frontostriatal cortical regions are most vulnerable to volume reductions in healthy aging, and that other regions, in particular those in the temporal lobe, including entorhinal cortex and hippocampus are less affected (Allen et al. 2005; Fjell, Amlie et al. 2010; Fjell, Westlye et al. 2009; Good et al. 2001; Lemaitre et al. 2010; Raz et al. 1997; Resnick et al. 2003; Salat et al. 2004; Van Petten 2004). This reported pattern runs contrary, however, to the significant regional medial-temporal volume losses reported in other studies of older persons considered cognitively normal (e.g., Du et al. 2006; Dickerson et al. 2009; Fjell, Westlye et al. 2010; Head et al. 2008; Mu et al. 1999; Raji et al. 2009; Raz et al. 2005; Tisserand et al. 2000; Tupler et al. 2007; Walhovd et al. 2011) and who may be at increased risk of cognitive impairment and dementia (Chetelat et al. 2003; den Heijer et al. 2006; Dickerson et al. 2011; Golomb et al. 1993; Jack et al. 1997; Kaye et al. 1997; Murphy et al. 2010; Rusinek et al. 2003). Other studies suggest that the volumes of secondary and tertiary

cortices are more affected by age than primary cortices (Allen et al. 2005; Jernigan et al. 2001; Lemaitre et al. 2012; Raz 1996, Raz et al. 1998; Tisserand et al. 2002), or that anterior regions are more affected by age than posterior regions (Raz et al. 1997; Head et al. 2005). These patterns are consistent with the “last in/first out” model of brain aging (Raz 2001) in which regions that are phylogenetically and ontogenetically older are predicted to be most robust against age-associated volume loss. Still other studies do not support any of these reported patterns, showing that age-related volume loss is widespread across the brain, and includes primary sensory and motor cortices (Driscoll et al. 2009; Good et al. 2001; Fjell, Walhovd et al. 2009; Hutton et al. 2009; Lemaitre et al. 2005; Raji et al. 2009; Resnick et al. 2003; Salat et al. 2004; Su et al. 2012; Tisserand et al. 2004; Walhovd et al. 2011), temporal cortex (Driscoll et al. 2009; Fjell, Amlie et al. 2010; Fjell, Walhovd et al. 2009; Hutton et al. 2009; Raji et al. 2009; Scallan et al. 2003; Tisserand et al. 2004), parietal cortex (Brickman et al. 2007; Fjell, Amlie et al. 2010; Fjell, Walhovd et al. 2009; Good et al. 2001; Lemaitre et al. 2005; Raji et al. 2009; Resnick et al. 2000, 2003; Smith et al. 2007; Tisserand et al. 2004), occipital cortex (Kalpouzos et al. 2009; Raji et al. 2009; Raz et al. 1998), subcortex (Driscoll et al. 2009; Hutton et al. 2009; Lemaitre et al. 2005; Su et al. 2012; Walhovd et al. 2005, 2011), and structures with ancient regions such as the cerebellum (Good et al. 2001; Su et al. 2012; Sullivan et al. 2000) and the thalamus (Brickman et al. 2007; Su et al. 2012; Sullivan et al. 2004; Van Der Werf et al. 2001; Walhovd et al. 2011). In the present study, the volumes of most regions were associated with age, indicating that volume reduction is, indeed, widespread across the brain in persons aged 65 and older. However, when using an adjusted score that controlled for average volume, a few of these regions had comparatively smaller volumes per decade of age. Using a stringent multiple-comparison correction (BH), smaller volumes per decade of age were found for supramarginal gyrus, middle temporal gyrus and hippocampus. When the multiple correction criteria were relaxed (FDR), superior frontal gyrus, superior temporal gyrus and the vertical ramus of the anterior segment of the lateral sulcus also had significantly smaller volumes per decade of age. These results do not offer support for the frontostriatal or the “last in/first out” models of healthy aging (the lateral sulcus is one of the earliest structures to develop ontogenetically [Jee et al. 1977]), but rather agree with studies that point to tempoparietal regions and hippocampus as being most vulnerable to volume loss in advanced aging. The participants in this study were exceptionally well-characterized clinically and it is unlikely that this pattern is accounted for by the inclusion of persons with mild cognitive impairment or mild dementia.

It is worth noting that the age coefficient for caudate volume was strongly positive in this study, indicating larger volume per decade of age. A number of studies suggest that the caudate volume is particularly vulnerable to aging (e.g., Raz et al. 2003), although some studies have reported age-related increases in caudate volume after age 50 (e.g., Lemaitre et al. 2005). Regional cortical and subcortical hypertrophy has been observed in older persons known to have Alzheimer’s disease pathology without cognitive impairment (Iacono et al. 2008; Riudavets et al. 2007) and caudate hypertrophy specifically has been reported in cognitively healthy persons at genetic risk for Alzheimer’s disease (Fortea et al. 2010; Lee et al. 2012). Thus, it is plausible that caudate hypertrophy is associated with increasing age and that it may be a biomarker for risk of cognitive impairment and Alzheimer’s disease, but

currently its biological basis remains unclear. Because the Rush Memory and Aging Study is a longitudinal, clinical-pathological study of aging and dementia that includes both biannual ante-mortem and post-mortem imaging, we will have the opportunity to interrogate the biological basis of caudate hypertrophy and examine associations with radiologic and cognitive measures in the future. The larger caudate volume may also be, at least partially, attributable to artifact in the automated labeling procedure (see Lemaitre et al. 2005 for a discussion). We observed this pattern of larger volume per decade of age in many of the insular subregions as well. The insular cortex is known to have ill-defined boundaries on MRI (Tisserand et al. 2004), and indeed, automated parcellation resulted in a large number of flags in this study. However, inaccurate labeling does not necessarily imply that volumes in these regions should be skewed toward larger size. It will be important to examine change in these regions in future longitudinal analyses.

Gray-matter global and regional thickness, surface area and age

The results of cortical thickness studies in the healthy aging literature look similar to the results of volume studies. That is, age differences and age changes in whole-brain average thickness are well-reported and there is regional heterogeneity reported across studies (Hutton et al. 2009; Lemaitre et al. 2012; Magnotta et al. 1999; Rettman et al. 2006; Salat et al. 2004; Thambisetty et al. 2010). Thinning is typically widespread, with studies varying in the strength of regional effects. Many studies find the strongest age effects on thickness in frontal regions (Fjell, Amlie et al. 2010; Fjell, Westlye et al. 2009; Ecker et al. 2009; Hutton et al. 2009; Resnick et al. 2003; Rettman et al. 2006; Salat et al. 2004; Thambisetty et al. 2010) followed by parietal (Ecker et al. 2009; Fjell, Amlie et al. 2010; Lemaitre et al. 2012; Resnick et al. 2003; Thambisetty et al. 2010) temporal (Fjell, Amlie et al. 2010; Fjell, Westlye et al. 2009; Hutton et al. 2009) and/or occipital (Ecker et al. 2009; Fjell, Westlye et al. 2009; Salat et al. 2004) regions. Some studies report a relative sparing of structures in the medial temporal lobe such as entorhinal and parahippocampal cortices (Fjell, Amlie et al. 2010; Lemaitre et al. 2010; Salat et al. 2004), but this is not a consistent finding. For example, medial temporal cortex has one of the strongest effect sizes of nine regions comprising an “Alzheimer-signature” thinning summary measure that has been shown to predict time to diagnosis of dementia in persons with normal cognition at baseline (Dickerson, Bakkour et al. 2009; Dickerson et al. 2011). A number of studies report thinning in primary sensory and motor regions (Ecker et al. 2009; Fjell, Westlye et al. 2009; Hutton et al. 2009; Lemaitre et al. 2005; Raji et al. 2009; Resnick et al. 2003; Salat et al. 2004; Thambisetty et al. 2010; Tisserand 2004). However, some do not (e.g., Lemaitre et al. 2012), and this may be related to the age of the sample. The results of the current study indicate that the entire cortex (as a summary measure and in every measured region) is thinner per decade of age over the age of 65, in line with extant findings. However, similar to the volumetric results, some regions stand out as being thinner per decade of age compared to the average cortical thickness. When stringently correcting for multiple comparisons, the regions that were thinnest were angular gyrus, supramarginal gyrus, precentral gyrus and middle temporal gyrus. Frontopolar, superior frontal, postcentral, posterior cingulate, superior temporal and posterior ramus of the lateral sulcus were added when the stringency of the correction method was relaxed. Again, these results do not support the frontal (anterior/posterior), last in/first out, or association cortex/primary cortex patterns reported for healthy

aging. Rather, they suggest that temporoparietal association cortex plus primary precentral motor cortex, are most vulnerable to thinning in old age, followed by a pattern of thinning that is more widespread than the pattern of volume reduction, and includes regions in the frontal, cingulate, and parietal (including primary postcentral) lobes.

The results of the few extant studies of age and surface area are somewhat different from what is reported for volume and thickness. Three studies that we know of have examined all three morphometric measures globally in healthy older persons (LeMaitre et al. 2012; Rettmann et al. 2006; Salat et al. 2004) and found significant age associations with each metric, surface area having the weakest association with age. The results of this study support these findings in that age accounted for a substantial amount of variance in total gray-matter volume (32.8%) and in average thickness (24.7%), but did not account for much of the variance in total surface area (2.7%). LeMaitre et al. (2010) found the greatest regional decrease in surface area to be in the frontal lobe (frontal pole, middle frontal gyrus, superior frontal gyrus), but these regions did not show significantly more reduction than the surface area average. Rettmann et al. (2006) measured surface area, sulcal depth and curvature and found a significant longitudinal decline in parietooccipital surface area and mean sulcal depth. Although Salat et al. (2004) reported the novel finding of age-associated thinning of calcarine cortex, they did not report reduced surface area in this same region. In this study we found that, when compared against the cortical average, calcarine cortex had less surface area per decade of age. Relaxing the multiple comparisons correction added the vertical ramus of the anterior segment of the lateral sulcus which subdivides the inferior frontal gyrus. Thus, our finding of less surface area in occipital and frontal regions, compared to the global cortical average, is consistent with the results of the few studies of surface area in healthy aging.

Age, gray-matter morphometry and cognition

As mentioned above, one important purpose of examining age associations with brain morphometry is to be able to characterize the influence healthy older age has on the brain and relate it to critical behavioral functions. One such function, cognition, is affected by advanced healthy aging, particularly within the domains of executive function (Buckner et al. 2004; Head et al. 2008; McPherson et al. 2002; Raz et al. 1998; Zimmerman et al. 2006), episodic memory (Buckner et al. 2004; Head et al. 2008; Prull et al. 2000) and perceptual speed (Finkel et al. 2007; Head et al. 2008; Salthouse 2000; Tisserand et al. 2000). In this study of persons aged 65 and older without dementia or MCI, we found that age was negatively associated with global cognitive function, and that the strongest domain-specific effects were in perceptual speed and semantic memory. These two cognitive domains included tasks that are known to challenge executive function (Symbol Digit Modalities Test, Stroop Test, Number Comparison and Verbal Fluency). Thus we found evidence of a link between age and executive function, but we did not find the expected association between age and episodic memory. Even though it is well-established that episodic memory function becomes more variable with increasing age (Christensen et al. 1999; Van Petten 2004; Wilson et al. 2002), we did not find a significant association likely due to a truncation of variance in performance on the episodic memory measures in this sample by the exclusion of persons carefully evaluated for the presence of mild dementia and MCI.

The literature concerning the associations of global and regional gray-matter macrostructure with global and domain-specific cognitive function in healthy aging is vast (and comprehensively reviewed in Fjell and Walhovd, 2010; Raz and Rodrigue 2006; Salthouse, 2011), but two patterns stand out. Many healthy aging studies have shown that compromised frontal or frontostriatal macrostructure is associated with diminished executive function (e.g., Schretlen et al. 2000; Raz et al. 1998; Zimmerman et al. 2006), and this is often accompanied by relatively preserved medial-temporal macrostructure and episodic memory function (e.g., Fjell, Westlye et al. 2009; Raz et al. 1998; Van Petten 2004). Our results did not support this pattern. Rather, when focusing on just those regions that were smaller or thinner per decade of age compared to the average, we found that temporoparietal volume was most strongly associated with global cognition and hippocampal volume was most strongly associated with episodic memory. We should caution, however, that because we did not find a significant association of age and episodic memory, this effect is likely strongly driven by the association of age and hippocampal volume. Episodic memory was also associated with calcarine cortex surface area. This is an intriguing result given that reactivation of sensory regions, including primary visual cortex, is known to occur during retrieval of previously processed episodic information (Harris et al. 2001; Wheeler et al. 2000), and it is possible that loss of brain integrity in this region may contribute to age-associated episodic memory loss.

Another interesting neurocognitive pattern points to the cortical thinning of a group of gray-matter regions that, as a summary measure, have been shown to be predictive of cognitive decline and AD dementia in cognitively-normal older adults. These regions are located across the cortex in the temporal (medial and inferior temporal, temporal pole), parietal (angular gyrus, supramarginal gyrus, superior parietal, precuneus), and frontal (middle and superior frontal) lobes. In a series of studies, three subgroups of cognitively-normal persons were identified: low/average/high on the summary thickness measure and high/middle/low on risk for preclinical AD. An inverse association of thickness with risk (e.g., low thickness/high risk) was reported. This AD-signature summary measure has been related to AD disease severity and amyloid positivity using PIB-PET (Dickerson 2009), risk of AD dementia (Dickerson 2011), and risk of cognitive decline and presence of abnormal CSF amyloid β levels (Dickerson 2012). This approach has potential for delivering an important brain biomarker for early identification of persons at risk for dementia, but current studies are limited by the small number of participants that fall into the highest risk group. When stringently corrected for multiple comparisons, we found thinning in just two of these “signature” regions (angular and supramarginal gyri) to be associated with age and global cognitive function in older persons with no overt cognitive impairment.

A central issue in this body of work relates to the pathway of effects between age, brain morphometry and cognition. A number of studies have reported that measures of brain atrophy (global or regional) either partially (e.g., Raz et al. 1998; Head et al. 2002, 2008) or fully (e.g., Kochunov et al. 2009) account for the association between age and cognition. In our mediation analyses, we found that each of the volumetric measures and surface area fully explained the association between age and global cognition. The association between age and perceptual speed, however, was only partially mediated by the volumetric measures. This is not an unexpected finding given the strong and well-established (e.g. Salthouse

2000) influence of age on cognitive speed. Still, the results of these mediation analyses must be interpreted with caution. It has been aptly pointed out that the associations between age, brain and cognition can occur across multiple pathways (Salthouse 2011) and that mediation analyses are best reserved for longitudinal investigation (Raz and Lindenberger 2011).

Strengths and Limitations

This study had important strengths. The large participant group was sampled from a community-dwelling population in which a comprehensive clinical evaluation allowed for careful exclusion of persons with mild cognitive impairment and dementia, and the average age of participants was over 80 years. Gray-matter was measured using three metrics and cognition was measured globally and in five domains. Two levels of correction for multiple comparisons were offered, one that is a more stringent test of regional associations (BH) compared to one that is commonly used in this literature (FDR). By controlling regional regressions for the brain average and using a stringent multiple-comparison correction, our approach contributed a sharper view of gray-matter morphometry and regional associations with age and cognition, which is critical for the development of morphometry as a biomarker of age-associated cognitive impairment. The study also had important limitations. It examined associations from which inferences were made but causation could not be established. It was cross-sectional and limited to examining age differences rather than age changes. Although the participants in this study were carefully characterized and had no overt cognitive impairment, the presence of Alzheimers disease pathology in the brains of some of these participants cannot be ruled out. Indeed, given the variance of cognitive function within the normal range, and that AD pathology is known to be present in a significant percentage of older persons without MCI or dementia (Bennett, Wilson et al 2012), it is likely that a percentage of this participant group did have the pathology. Finally, the study did not address associations between brain gray-matter morphometry and common medical conditions of aging. Studies are needed that examine associations between these three brain metrics, age and physical health. For example, a pattern of cortical thinning has recently been associated with high systemic inflammation in a small group of healthy older participants without cognitive impairment (Fleischman et al 2010). Other candidate physical health correlates relevant in this population include motor (particularly given that precentral thinning is a consistent finding across studies) and sensory impairments, metabolic syndrome, diabetes and cardiovascular and cerebrovascular diseases.

Conclusion

As evidenced by the literature review offered above, our understanding of the associations between gray-matter macrostructure, age and cognition is increasing, and the current study has added to that understanding by showing that the most robust pattern of brain atrophy in healthy aging comprises temporoparietal and precentral cortices and hippocampus, and that this is most strongly associated with global cognition and episodic memory. That said, there is still very much work to be done. What is critically needed are more longitudinal studies of healthy persons over the age of 65 that measure age-associated changes in brain morphometry and cognitive function in those brain regions that survive after controlling for cortical and subcortical averages and applying stringent multiple comparisons correction. In these target regions, age has its strongest influence on the brain and this association may

drive change in the integrity of certain cognitive functions. Information derived from this approach and applied within a longitudinal design may serve to identify those persons who are at greatest risk for acquiring a clinical diagnosis of mild cognitive impairment or dementia early in the course of the disease before progressive brain pathology has taken hold.

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Figure 1. Cortical and subcortical regions with a significant association (FDR-corrected) between the scaled volume and age are shown in color. The color bar shows the colors assigned to different values of the scaled volumes

Figure 2. Cortical and subcortical regions with a significant association (FDR-corrected) between the adjusted volume and age are shown in color. The color bar shows the colors assigned to different values of the adjusted volumes

Figure 3.

Cortical regions with a significant association (FDR-corrected) between the scaled thickness and age are shown in color. The color bar shows the colors assigned to different values of the adjusted thicknesses

Figure 4. Cortical regions with a significant association (FDR-corrected) between the adjusted thickness and age are shown in color. The color bar shows the colors assigned to different values of the adjusted thicknesses

Figure 5. Cortical regions with a significant association (FDR-corrected) between the scaled surface area and age are shown in color. The color bar shows the colors assigned to different values of the adjusted surface areas

Figure 6. Cortical regions with a significant association (FDR-corrected) between the adjusted surface area and age are shown in color. The color bar shows the colors assigned to different values of the adjusted surface areas

Table 1

Descriptive Statistics for Demographic and Cognitive Measures (n=186)

Measure	Mean	SD	Minimum	Maximum
Age at scan	81.526	6.674	65.374	100.290
Years education	15.403	3.137	8	28
# Male (%)	47 (25.3%)			
# Non-Hispanic White (%)	176 (95.1%)			
Global cognition	0.460	0.398	−0.643	1.467
Episodic Memory	0.605	0.480	−0.967	1.707
Semantic Memory	0.466	0.547	−1.509	3.070
Working Memory	0.348	0.655	−1.137	1.958
Perceptual Speed	0.315	0.654	−0.993	1.899
Visuospatial ability	0.405	0.602	−1.464	1.286

Table 2

Summary statistics for the morphometric measures

Morphometric Measure	Summary Statistics					
	Metric units		ICV-corrected Measures		Scaled Measures	
	Mean	SD	Mean	SD	Mean	SD
Total Gray Matter Volume	522.487 cm ³	52.130 cm ³	336.295	36.440	1.000	0.108
Total Cortical Gray Matter Volume	364.001 cm ³	41.816 cm ³	234.480	30.233	1.000	0.129
Total Subcortical Gray Matter Volume	158.485 cm ³	15.846 cm ³	101.815	9.028	1.000	0.089
Average Thickness	2.134 mm	0.196 mm	NA	NA	1.000	0.092
Total surface area (n=148)	1666.847 cm ²	184.319 cm ²	106.316 cm ⁻¹	7.195 cm ⁻¹	1.000	0.068
Intracranial Volume (ICV)	1564.690 cm ³	174.075 cm ³	1,000.00	0.000	NA	NA

The ICV-corrected volumes and total surface area are obtained by dividing the metric units by ICV units and multiplying by 1000, so that the resulting volume units are 10th of percentages of ICV. The scaled variables are obtained by dividing by the mean across participants, resulting in a variable with mean 1 and standard deviation (SD) equal to the coefficient of variation (expressed as a fraction not as a percentage). N=186, except for total surface area. NA=not applicable.

Table 3
Morphometric summary measures, associations with age, corrected for sex and education

Morphometric Measure	Associations with Age			
	Coefficients (for ICV-corrected)			R _{adj} ²
	Estimate	Std Err	p-value	
Total Gray Matter Volume, ICV-corrected	-3.023	0.311	<0.001	40.74%
Total Cortical Gray Matter Volume, ICV-corrected	-2.389	0.263	<0.001	38.44%
Total Subcortical Gray Matter Volume, ICV-corrected	-0.638	0.086	<0.001	25.88%
Average Thickness	-0.014	0.002	<0.001	35.54 %
Total surface area (n=148)	-0.203	0.088	0.023	3.57 %

The association of each morphometric measure with age is summarized by the coefficient of age from a regression of the ICV-corrected morphometric measure on age, with additional terms to correct for sex and education. The units for estimates and standard errors (SEs) for volumes are tenths of percentages of ICV per year. Thus the coefficients can also be interpreted as %ICV per decade of age. The coefficient of total surface area is cm² per tenths of percentage of ICV per year; the coefficient of average thickness is mm/year. The proportion of variation (R_{adj}²) in brain morphometry explained by age, sex and education is shown as a percentage.

Table 4

Significant regional associations with age

VOLUME		p-values			
FS Num	FS Label	Estimate	Std Err	UNC	FDR
16	Superior frontal gyrus	-2.878	0.883	0.002	0.102
26	Supramarginal gyrus	-4.521	1.258	0.000	0.029
36	Planum temporale or temporal plane of the superior temporal gyrus	-4.908	1.743	0.005	0.356
38	Middle temporal gyrus	-4.012	1.158	0.001	0.046
40	Vertical ramus of the anterior segment of the lateral sulcus (or fissure)	-6.442	2.248	0.005	0.312
SC	Hippocampus	-7.833	1.150	0.000	0.000
17	Long insular gyrus and central sulcus of the insula	5.611	1.546	0.000	0.027
48	Inferior segment of the circular sulcus of the insula	6.294	1.201	0.000	0.000
49	Superior segment of the circular sulcus of the insula	3.989	1.057	0.000	0.016
66	Pericallosal sulcus/sulcus of the corpus callosum	5.760	1.374	0.000	0.003
SC	Caudate	10.540	1.494	0.000	0.000
SC	Putamen	3.464	1.220	0.005	0.040

THICKNESS		p-values			
FS Num	FS Label	Estimate	Std Err	UNC	FDR
5	Transverse frontopolar gyri and sulci	-1.826	0.665	0.007	0.401
9	Posterior-dorsal part of the cingulate gyrus	-2.062	0.797	0.010	0.618
16	Superior frontal gyrus	-1.448	0.455	0.002	0.113
25	Angular gyrus	-2.208	0.592	0.000	0.018
26	Supramarginal gyrus	-2.228	0.568	0.000	0.009
28	Postcentral gyrus	-3.358	1.069	0.002	0.126
29	Precentral gyrus	-4.559	1.092	0.000	0.003
36	Planum temporale or temporal plane of the superior temporal gyrus	-2.823	0.844	0.001	0.067
38	Middle temporal gyrus	-3.100	0.643	0.000	0.000
41	Posterior ramus (or segment) of the lateral sulcus (or fissure)	-1.354	0.485	0.006	0.360
7	Middle-anterior part of the cingulate gyrus and sulcus	1.736	0.555	0.002	0.128

THICKNESS		Estimate	Std Err	p-values		
FS Num	FS Label			UNC	BH	FDR
11	Cuneus	2.687	0.723	0.000	0.018	0.003
22	Lingual gyrus/lingual part of the medial occipito-temporal gyrus	2.949	0.556	0.000	0.000	0.000
31	Straight gyrus/gyrus rectus	2.343	0.674	0.001	0.037	0.006
44	Calcarine sulcus	1.799	0.572	0.002	0.126	0.014
56	Intraparietal sulcus and transverse parietal sulci	1.248	0.488	0.011	0.658	0.049
66	Pericallosal sulcus (S of corpus callosum)	2.922	1.064	0.007	0.404	0.035

SURFACE AREA		Estimate	Std Err	p-values		
FS Num	FS Label			UNC	BH	FDR
40	Vertical ramus of the anterior segment of the lateral sulcus (or fissure)	-6.709	2.252	0.003	0.223	0.035
44	Calcarine sulcus	-5.838	1.583	0.000	0.021	0.006
3	Paracentral lobule and sulcus	3.304	1.158	0.005	0.324	0.045
17	Long insular gyrus and central sulcus of the insula	5.457	1.474	0.000	0.021	0.007
28	Postcentral gyrus	3.744	1.044	0.000	0.030	0.006
29	Precentral gyrus	4.458	1.045	0.000	0.002	0.002
37	Inferior temporal gyrus	4.220	1.306	0.001	0.101	0.018
48	Inferior segment of the circular aspect of the insula	3.601	0.872	0.000	0.004	0.002

Abbreviations: SC = Subcortical; UNC = uncorrected p-value; BH = Bonferroni-Holm corrected p-value; FDR = False Discovery Rate corrected p-value.

Table 5

Associations of age, cognition and summary morphometric measures

		Summary Morphometric Measure				
n=186	Decade of Age	Total Gray Matter	Total Cortical Gray	Total Subcortical Gray	Average Thickness	Total Surface Area (n=148)
Global Cognition						
Adj. R ²	21.19 %	24.12 %	23.64 %	22.82 %	21.46 %	22.83 %
Age						
Estimate	-0.092	-0.013	-0.024	-0.045	-0.063	-0.037
Std Err	0.039	0.047	0.046	0.044	0.045	0.043
p-value	0.020	0.779	0.606	0.310	0.168	0.400
Morphometric						
Estimate		0.003	0.003	0.007	0.212	0.009
Std Err		0.001	0.001	0.003	0.166	0.004
p-value		0.005	0.010	0.029	0.203	0.031
Episodic Memory						
Adj. R ²	15.57 %	19.17 %	19.22 %	16.29 %	15.74 %	20.04 %
Age						
Estimate	0.008	0.112	0.106	0.051	0.041	0.060
Std Err	0.049	0.059	0.058	0.056	0.057	0.054
p-value	0.872	0.059	0.069	0.364	0.467	0.267
Morphometric						
Estimate		0.003	0.004	0.007	0.242	0.013
Std Err		0.001	0.001	0.004	0.208	0.005
p-value		0.003	0.003	0.112	0.245	0.010
Semantic memory						
Adj. R ²	20.26 %	20.25 %	20.07%	20.51 %	19.88 %	21.27 %
Age						
Estimate	-0.108	-0.069	-0.080	-0.070	-0.095	-0.045
Std Err	0.054	0.067	0.065	0.062	0.063	0.061

		Summary Morphometric Measure				
n-186	Decade of Age	Total Gray Matter	Total Cortical Gray	Total Subcortical Gray	Average Thickness	Total Surface Area (n=148)
p-value	0.048	0.303	0.223	0.255	0.132	0.459
Morphometric						
Estimate		0.001	0.001	0.006	0.091	0.001
Std Err		0.001	0.002	0.005	0.231	0.006
p-value		0.323	0.448	0.210	0.694	0.849
Working Memory						
Adj. R ²	4.75%	4.23%	4.23 %	4.23 %	4.46 %	4.92 %
Age						
Estimate	-0.004	-0.002	-0.002	-0.005	-0.031	0.078
Std Err	0.071	0.088	0.086	0.081	0.082	0.080
p-value	0.955	0.978	0.984	0.949	0.704	0.330
Morphometric						
Estimate		0.000	0.000	-0.000	-0.199	0.009
Std Err		0.002	0.002	0.006	0.301	0.007
p-value		0.974	0.962	0.976	0.511	0.223
Perceptual Speed						
Adj. R ²	14.93%	17.71 %	16.83 %	17.82 %	15.77 %	12.12 %
Age						
Estimate	-0.325	-0.196	-0.223	-0.221	-0.260	-0.254
Std Err	0.067	0.082	0.080	0.076	0.077	0.075
p-value	<0.001	0.018	0.006	0.00	0.001	0.001
Morphometric						
Estimate		0.004	0.004	0.016	0.474	0.010
Std Err		0.002	0.002	0.006	0.284	0.007
p-value		0.009	0.025	0.008	0.097	0.150
Visuospatial ability						
Adj. R ²	19.37 %	19.41 %	19.24%	19.60 %	19.31%	18.49 %
Age						

n=186	Decade of Age	Summary Morphometric Measure				
		Total Gray Matter	Total Cortical Gray	Total Subcortical Gray	Average Thickness	Total Surface Area (n=148)
Estimate	-0.096	-0.051	-0.062	-0.054	-0.064	-0.113
Std Err	0.060	0.074	0.072	0.069	0.070	0.066
p-value	0.110	0.492	0.389	0.437	0.361	0.088
Estimate		0.002	0.001	0.007	0.237	0.001
Std Err		0.001	0.002	0.005	0.255	0.006
p-value		0.300	0.405	0.220	0.354	0.876

The units for estimates and standard errors (SEs) for volumes are tenths of percentages of ICV per year.

Table 6

Significant Associations of regional scaled morphometric measures and cognition, corrected for age, sex and education.

FS Num	FS Label	Estimate	Std Err	UNC	BH	FDR
GLOBAL COGNITION (scaled subcortical volumes)						
SC	Caudate	-0.594	0.183	0.001	0.014	0.014
SC	Cerebellum cortex	0.760	0.261	0.004	0.037	0.020
EPISODIC MEMORY (scaled subcortical volumes)						
SC	Caudate	-0.687	0.230	0.003	0.029	0.016
SC	Hippocampus	0.750	0.228	0.001	0.012	0.012
EPISODIC MEMORY (scaled cortical volumes)						
1	Fronto-marginal gyrus (of Wernicke) and sulcus	0.643	0.196	0.001	0.086	0.018
2	Inferior occipital gyrus and sulcus	0.668	0.169	0.000	0.008	0.003
5	Transverse frontopolar gyri and sulci	0.681	0.167	0.000	0.005	0.005
6	Anterior part of the cingulate gyrus and sulcus	0.823	0.249	0.001	0.080	0.021
8	Middle-posterior part of the cingulate gyrus and sulcus	0.679	0.232	0.004	0.261	0.041
9	Posterior-dorsal part of the cingulate gyrus	0.508	0.192	0.009	0.541	0.044
13	Orbital part of the inferior frontal gyrus	0.388	0.144	0.008	0.484	0.044
17	Long insular gyrus and central sulcus of insula	0.515	0.193	0.009	0.519	0.045
18	Short insular gyri	0.584	0.212	0.007	0.419	0.044
31	Straight gyrus, Gyrus rectus	0.700	0.219	0.002	0.113	0.020
39	Horizontal ramus of the anterior segment of the lateral sulcus (or fissure)	0.615	0.152	0.000	0.006	0.003
43	Temporal pole	0.559	0.206	0.007	0.455	0.045
44	Calcarine sulcus	0.506	0.182	0.006	0.395	0.045
49	Superior segment of the circular sulcus of the insula	0.704	0.244	0.004	0.293	0.040
63	Medial orbital sulcus (olfactory sulcus)	0.623	0.224	0.006	0.388	0.048
EPISODIC MEMORY (scaled surface area)						
5	Transverse frontopolar gyri and sulci	0.750	0.214	0.001	0.043	0.022
39	Horizontal ramus of the anterior segment of the lateral sulcus (or fissure)	0.830	0.187	0.000	0.001	0.001
PERCEPTUAL SPEED (scaled subcortical volumes)						

FS Num	FS Label	Estimate	Std Err	P-values		
				UNC	BH	FDR
SC	Cerebellum Cortex	1.455	0.471	0.002	0.023	0.023
SC	Ventral DC	1.213	0.442	0.007	0.060	0.033

Abbreviations: SC = Subcortical; UNC = uncorrected p-value; BH = Bonferroni-Holm corrected p-value; FDR = False Discovery Rate corrected p-value.