



Age Differences in Prefrontal Surface Area and Thickness in Middle Aged to Older Adults

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Age is associated with reductions in surface area and cortical thickness, particularly in prefrontal regions. There is also evidence of greater thickness in some regions at older ages. Non-linear age effects in some studies suggest that age may continue to impact brain structure in later decades of life, but relatively few studies have examined the impact of age on brain structure within middle-aged to older adults. We investigated age differences in prefrontal surface area and cortical thickness in healthy adults between the ages of 51 and 81 years. Participants received a structural 3-Tesla magnetic resonance imaging scan. Based on *a priori* hypotheses, primary analyses focused on surface area and cortical thickness in the dorsolateral prefrontal cortex, anterior cingulate cortex, and orbitofrontal cortex. We also performed exploratory vertex-wise analyses of surface area and cortical thickness across the entire cortex. We found that older age was associated with smaller surface area in the dorsolateral prefrontal and orbitofrontal cortices but greater cortical thickness in the dorsolateral prefrontal and anterior cingulate cortices. Vertex-wise analyses revealed smaller surface area in primarily frontal regions at older ages, but no age effects were found for cortical thickness. Results suggest age is associated with reduced surface area but greater cortical thickness in prefrontal regions during later decades of life, and highlight the differential effects age has on regional surface area and cortical thickness.

Keywords: adult age differences, cortical thinning, volumetrics, aging, MRI

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INTRODUCTION

Advancing age is associated with structural brain changes, even in the absence of dementia or other pathological conditions (Raz et al., 2007a). The frontal and temporal lobes are most affected, with many studies showing disproportionate changes in regions within the prefrontal cortex (Small et al., 2000; Liu et al., 2003; Resnick et al., 2003; Raz et al., 2004, 2010; Raz and Rodrigue, 2006; Driscoll et al., 2009; Fjell et al., 2009b; Spreng et al., 2010), including the anterior cingulate (ACC), dorsolateral prefrontal (DLPFC) and orbitofrontal (OFC) cortices. Much of our understanding of age differences and age changes in brain structure comes from volumetric studies, which typically show reductions in regional volumes with age, although increased volumes have also been reported (Salat et al., 2002).

Gray matter volume is a composite measure that is derived from both surface area and cortical thickness, separate measures that may be differentially affected by the aging process (Fleischman et al., 2010; Marsland et al., 2015), due, at least in part, to their differential relationship with genetic and environmental factors (Jefferson et al., 2007; Panizzon et al., 2009; Krishnadas et al., 2013). Individual differences in brain volumes may be more closely related to surface area rather than cortical thickness (Reuter et al., 2010; Winkler et al., 2010; Solana et al., 2012), while cortical thickness is thought to be more closely related to features of the cortex such as the organization of cortical layers and the size, number, and density of cell bodies in the neurons, as well as synaptic connections (Kabani et al., 2001; Du et al., 2007). Supporting the contention that surface area and cortical thickness are independent measures of brain structure are findings that the two measures are negatively correlated in older adults (Hogstrom et al., 2013; Fjell et al., 2014; Storsve et al., 2014).

Both cross-sectional and longitudinal studies have provided evidence for decreased surface area and cortical thinning at older ages (Salat et al., 2004; Preul et al., 2006; Fjell et al., 2009b; Ostby et al., 2009; Thambisetty et al., 2010; Lemaitre et al., 2012; Long et al., 2012; Solana et al., 2012; Hogstrom et al., 2013; van Velsen et al., 2013), with many showing disproportionate reductions in the prefrontal cortex (Salat et al., 2004; Thambisetty et al., 2010; Lemaitre et al., 2012). Older age is consistently associated with decreases in surface area, but the literature regarding age and cortical thickness is mixed, with some showing age-related decreases and others showing age-related increases. For example, in healthy adults age 18–91 years from the Alzheimer's Disease Neuroimaging Initiative sample, most regions were found to be associated with cortical thinning at older ages, but a nonlinear effect of age was found for the rostral and caudal ACC, such that cortical thickness was greater after age 60 (Fjell et al., 2014). Increased thickness at older ages was postulated to be related to neuroplastic adaptation to increased environmental demands, given the ACC's role in the allocation of attentional resources, or to a cross-sectional artifact since longitudinal increases in thickness were not observed in the ACC (Fjell et al., 2014). However, results from the Baltimore Longitudinal Study of Aging provide evidence of longitudinal increases in cortical thickness in multiple frontal, temporal, and parietal regions (Thambisetty et al., 2010) despite an overall pattern of decreased cortical thickness with age in most regions. Another study reported selective increases in cortical thickness in older adults who performed well on fluid intelligence measures (Fjell et al., 2006), suggesting that sample differences in cognitive abilities may contribute to the different findings across studies. The mechanisms underlying age-related increases in cortical thickness are unclear, but increases in low-grade inflammation with age may contribute, as inflammatory markers have been associated with cortical thickening (Sörös, 2010; Krishnadas et al., 2013).

Despite the accumulation of knowledge regarding age-related structural changes, differences in results across previous studies highlight the need for additional research to clarify the nature

and timing of these changes. As the population continues to age, it is particularly important to complement studies that compare young and older adults with examinations of age differences within middle-age to older adults. Such studies will help elucidate the potentially progressive brain changes that occur in later decades of life. Longitudinal studies in middle-age to older adults, as well as cross-sectional lifespan studies, show non-linear structural brain changes (Sowell et al., 2003; Allen et al., 2005; Du et al., 2007; Curiati et al., 2009; Driscoll et al., 2009; Fjell et al., 2009b, 2014; Raz et al., 2010; Thambisetty et al., 2010; Schuff et al., 2012; Ziegler et al., 2012; Pfefferbaum et al., 2013; Taki et al., 2013), suggesting age differences may be apparent within middle aged to older samples, rather than only being evident when comparing young and older adults. Examining age differences in both surface area and cortical thickness within the same sample is also important given evidence that age may differentially impact these measures of brain structure.

The current study was designed to address this issue. Based on research suggesting that the prefrontal cortex is particularly vulnerable to age effects, we were primarily interested in the impact of age on prefrontal surface area and cortical thickness in healthy middle-aged to older adults, specifically within the DLPFC, ACC and OFC. We also performed an exploratory vertex-wise analysis, in which surface area and thickness are mapped onto each vertex of the cortical surface. This procedure provides an examination of the entire cortical surface rather than being limited to predefined regions of interest (ROIs). Thus, we addressed a gap in the literature by distinguishing between the two constituent components of brain volume and by examining age effects starting in midlife, an age for which less data are available in the literature. We predicted that older age would be associated with reductions in both surface area and cortical thickness in the DLPFC, ACC, and OFC.

MATERIALS AND METHODS

Participants

Forty-six healthy, community-dwelling adults ranging in age from 51 to 81 years ($mean = 68.54 \pm 7.43$; 67.39% female) participated in this study. The current study involved secondary analysis of data from healthy control participants in a larger investigation that focused on age differences in depression-related changes in brain structure and function. The larger study included functional magnetic resonance imaging (fMRI), thus, participants were required to be right-handed, speak English as their first language, and have at least 10 years of education (range = 10–20 years; $mean = 15.05 \pm 2.48$). Potential participants were excluded if they scored less than 30 on the Telephone Interview for Cognitive Status (TICS; Brandt et al., 1988), the traditional cutoff for possible dementia, or if they met criteria for major psychiatric disorder based on administration of the Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version (First et al., 2001). Additional exclusionary criteria based on self-report included severe or acute medical illness, history of neurological conditions

(e.g., stroke, head injury, epilepsy), learning disorders, and MRI contraindications. The study protocol was approved by the University of Florida's Institutional Review Board, and all participants provided both written and verbal informed consent in accordance with the Declaration of Helsinki.

MRI Data Acquisition

Scanning took place at the University of Florida's McKnight Brain Institute in a 3-Tesla Phillips (Amsterdam, Netherlands) scanner. A standard 8-channel head radio-frequency coil was used to collect a high-resolution, T_1 -weighted turbo field echo structural MRI scan. Scanning parameters were as follows: TR = 28.1 ms, TE = 2.7 ms, FOV = 240 mm × 240 mm (AP) × 170 mm (RL), matrix = 240 × 240, 170 slices acquired in a sagittal orientation, flip angle = 8°, 1 mm cubic resolution (isotropic).

Regional Surface Area and Cortical Thickness Measurement

Freesurfer version 5.3 was used to extract surface area and cortical thickness. This image processing suite provides automated parcellation of both cortical and subcortical brain structures. Details of the procedure are documented elsewhere (Fischl et al., 2002) and are freely available for download (<http://surfer.nmr.mgh.harvard.edu/>). In brief, processing included motion correction and averaging of T_1 weighted images (Reuter et al., 2010), skull stripping using a hybrid watershed/surface deformation procedure (Ségonne et al., 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (Fischl et al., 2002, 2004a), intensity inhomogeneity correction (Sled et al., 1998), gray/white matter boundary tessellation, topology correction (Fischl et al., 2001; Ségonne et al., 2007), and surface deformation following intensity gradients to ensure optimal gray/white and gray/cerebrospinal fluid boarder (Dale and Sereno, 1993; Sled et al., 1998; Dale et al., 1999; Fischl and Dale, 2000; Fischl et al., 2004a; Ségonne et al., 2004, 2007). Cortical regions were parcellated into specific regions with respect to sulcal and gyral structures (Fischl et al., 2004b; Desikan et al., 2006), with manual inspection for errors in the automatic program by one of two trained raters.

Surface area was calculated along the white matter surface boundary. This surface was then tessellated and the value for each ROI represented the sum of the area of all of the triangles that compose each cortical parcellation. Interclass correlation coefficients (ICCs) were calculated for manual adjustments in surface area using a two-way mixed effects model. ICC between raters was high (≥ 0.876), likely reflecting the minimal manual adjustments needed following the automatic processing.

Both intensity and continuity information in segmentation and deformation procedures were used to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale, 2000). Automated cortical thickness measures have been validated against histological analysis (Rosas et al., 2002) and manual

measurements (Kuperberg et al., 2003; Salat et al., 2004). ICC for manual adjustments in cortical thickness segmentation was also high (≥ 0.882).

Based on *a priori* hypotheses, primary analyses focused on surface area and cortical thickness in ROIs in the DLPFC (sum of the inferior and middle frontal gyri), ACC (sum of the rostral and caudal ACC), and OFC (sum of the medial and lateral OFC). For cortical thickness, the weighted means (regional thickness divided by regional volume) were summed to create the ROIs. Additionally, exploratory analyses used a vertex-wise approach. For each subject, a thickness measurement was mapped on each vertex of the cortical surface, allowing an examination of surface area and cortical thickness across the brain. Images were smoothed using a Gaussian kernel with a full-width-half-maximum of 10 mm.

Statistical Analyses

Bivariate correlations between surface area and cortical thickness in each ROI were calculated using Pearson correlations. To address our primary hypotheses, regression analyses were performed using SAS version 9.4 (Cary, NC, USA) with a continuous measure of age as the independent variable, and with either surface area or thickness in each ROI as the dependent variable. Analyses were performed separately by hemisphere given evidence of asymmetries in age-related brain changes (Raz et al., 1997). Analysis of surface area included a covariate for estimated total intracranial volume, and analysis of cortical thickness included a covariate for mean cortical thickness. Initially, each model also controlled for sex and education, but these variables were removed since they were not significant in any of the models. The type I error used for statistical significance was $\alpha \leq 0.05$ for all analyses. For the exploratory vertex-wise analyses, separate general linear models were conducted in Freesurfer with age predicting either surface area or cortical thickness at each vertex. A false discovery rate (FDR) threshold of ≤ 0.05 was used to account for type I error.

RESULTS

Surface area and cortical thickness were significantly negatively correlated in the left DLPFC ($r = -0.329$, $p = 0.026$), bilateral ACC (left $r = -0.350$, $p = 0.017$; right $r = -0.354$, $p = 0.016$), and bilateral OFC (left $r = -0.406$, $p = 0.005$; right $r = -0.368$, $p = 0.012$). Results of the regression analyses on primary ROIs are summarized in **Table 1** and **Figure 1**. After controlling for total intracranial volume, older age was associated with decreased surface area in the bilateral DLPFC (left $B = -47.313$, $p = 0.021$, $R^2 = 0.310$; right $B = -57.161$, $p = 0.005$, $R^2 = 0.356$) and bilateral OFC (left $B = -15.452$, $p = 0.021$, $R^2 = 0.322$; right $B = -17.398$, $p = 0.021$, $R^2 = 0.331$), but not with surface area in the ACC. In contrast, cortical thickness analyses revealed greater cortical thickness at older ages in the right DLPFC ($B = 0.002$, $p = 0.021$, $R^2 = 0.768$) and bilateral ACC (left $B = 0.007$, $p = 0.021$, $R^2 = 0.269$; right $B = 0.009$, $p = 0.011$, $R^2 = 0.407$) after controlling for mean thickness, while age was not associated with cortical thickness in the OFC.

TABLE 1 | Age effects on surface area and cortical thickness in the ROI analysis, adjusted for total intracranial volume (surface area) and thickness (cortical thickness).

Region	Surface area (mm ²)		Cortical thickness (mm)	
	B	SE (df)	B	SE (df)
Dorsolateral prefrontal cortex				
Left	-47.313*	19.668 (43)	0.002	0.001 (43)
Right	-57.161**	19.073 (43)	0.002*	0.001 (43)
Anterior cingulate cortex				
Left	3.023	11.314 (43)	0.007*	0.004 (43)
Right	1.554	15.036 (43)	0.009*	0.003 (43)
Orbitofrontal cortex				
Left	-15.451*	6.579 (43)	-0.002	0.002 (43)
Right	-17.398*	6.954 (43)	-0.001	0.002 (43)

Note: ROI, regional of interest; B, beta weight; SE, standard error; df, degrees of freedom; * $p < 0.05$, ** $p < 0.01$.

The vertex-wise analysis revealed significantly smaller surface area at older ages in primarily frontal regions, including bilateral superior frontal, left rostral middle frontal, and right lateral orbitofrontal regions. There were no significant associations between age and cortical thickness in the vertex-wise analysis. Significant effects for the surface area analysis are summarized in **Table 2** and **Figure 2**.

DISCUSSION

We examined age differences in prefrontal surface area and cortical thickness in a middle-aged to older adult sample.

As expected, age differences were observed for each of our ROIs; however, the nature of the differences varied, as older age was associated with smaller surface area in the DLPFC and OFC, but higher cortical thickness in the DLPFC and ACC.

The finding of reduced surface area in the DLPFC and OFC at older ages is consistent with previous cross-sectional and longitudinal research documenting age-related structural changes within these regions (Raz et al., 2010; Lemaitre et al., 2012; Hogstrom et al., 2013; Persson et al., 2014). The majority of past studies have compared young and older adults, but some studies have examined age differences in later decades

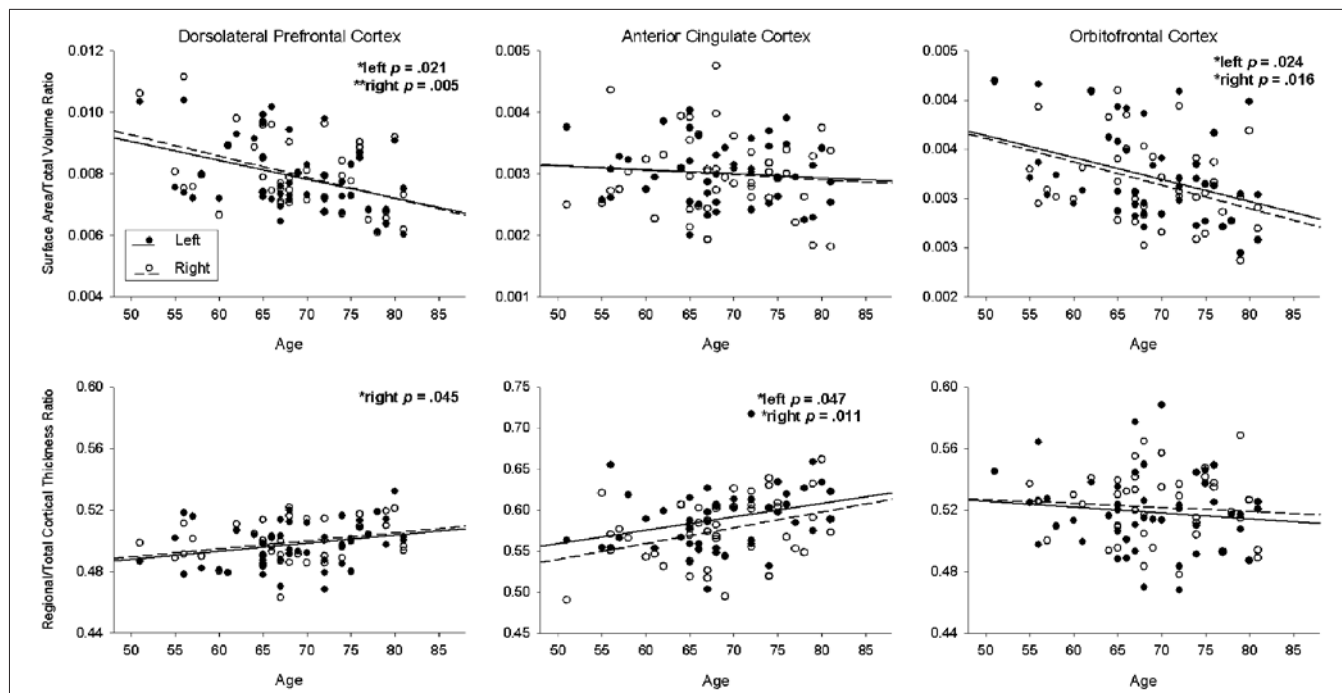


FIGURE 1 | Association of age with surface area (upper row; ratio of regional surface area to total volume) and cortical thickness (lower row; ratio of regional thickness to mean thickness) for each region of interest. The solid line and black circles represent the left hemisphere; the dotted line and white circles represent the right hemisphere.

TABLE 2 | Brain regions showing a significant age effect on surface area in the vertex-wise analysis.

Region	Side	Coordinate			Cluster size (mm ²)	p
		x	y	z		
Cuneus	R	18.8	-65.3	12.4	624.48	0.00001
Inferior temporal	L	-45.1	-26.7	-23.3	487.44	0.00003
Superior frontal	R	7.4	-6.1	56.4	374.79	0.00007
	R	11.0	54.0	11.0	241.28	0.00013
	R	13.1	39.5	21.8	29.47	0.00049
	L	-9.0	18.3	44.7	284.72	0.00001
	L	-9.1	41.3	25.6	74.85	0.00012
	L	-38.5	41.2	3.9	85.21	0.00009
Rostral middle frontal	L	-38.5	41.2	3.9	85.21	0.00009
Lingual	R	8.8	-61.0	2.2	76.71	0.00014
Lateral orbitofrontal	R	28.4	49.2	-10.5	57.89	0.00038
Fusiform	R	41.6	-34.2	-20.6	19.64	0.00029
Superior temporal	L	-56.4	-11.8	1.3	17.81	0.00032
Pars orbitalis	R	38.5	37.9	-9.0	1.36	0.00070

Note: Talairach coordinates reflect location of peak voxel within cluster. L, left; R, right.

(Raz et al., 2010; Storsve et al., 2014). For example, orbitofrontal and lateral prefrontal volume declined over 30-month follow-up in a study of middle-aged to older adults (Raz et al., 2010), similar to a lifespan study showing declining thickness and surface area over an average of 3.5 years (Storsve et al., 2014). In our study, older age was associated with differences in OFC surface area, but not in thickness. Although there have been reports of orbitofrontal thinning in the OFC with age (Thambisetty et al., 2010), other studies have found that thinning of the OFC plateaus at older ages (Sowell et al., 2003; Fjell et al., 2009a, 2014). This has been reported both in cross-sectional studies, in which the OFC was more preserved than other frontal regions (Salat et al., 2002; Fjell et al., 2009a,b), and in longitudinal studies, in which thinning of the OFC occurred at a slower rate than most ROIs (Sowell et al., 2003). These results suggest that the impact of age on OFC thickness may be minimal within groups of middle-age to older adults, who constituted the sample for the present study.

In contrast to results for the OFC, we found that older age was associated with reduced surface area in the bilateral DLPFC but greater cortical thickness in the right DLPFC. The different direction of the relationships of age

with surface area and thickness is not surprising considering evidence of a negative correlation between these two measures in regions including the prefrontal cortex (e.g., Storsve et al., 2014). We also found a negative relationship between surface area in cortical thickness in the DLPFC, ACC and OFC. Age-related inflammatory changes may explain these findings. There is evidence that inflammation is associated with reductions in gray matter volume and surface area (Jefferson et al., 2007; Marsland et al., 2015), however, the relationship between inflammation and cortical thickness may be more complex. For example, in the Religious Orders Study, inflammation was associated with cortical thinning in some regions, but cortical thickening in others (Fleischman et al., 2010), similar to other reports of a positive relationship between inflammatory markers and cortical thickness (Sörös, 2010; Krishnadas et al., 2013). Given the chronic, low-grade inflammation that increases with age (Cevenini et al., 2010; Solana et al., 2012), older age may be characterized by concomitant surface area decreases and cortical thickness increases.

Inflammation might also contribute to the association between older age and greater cortical thickness in the bilateral ACC in the present study. There is evidence to

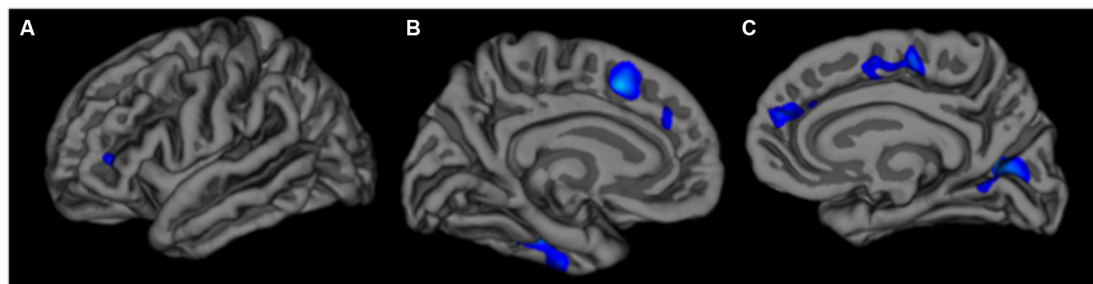


FIGURE 2 | Left lateral (A) left medial (B) and right medial (C) views of associations between older age and reduced surface area in the vertex-wise analysis. The color scale is represented as $\log(p)$.

suggest that the relationship between age and thickness in the ACC is nonlinear, such that thickness of the ACC is reduced at older age until age 60, but is greater at older ages thereafter (Fjell et al., 2014). One hypothesis to explain this observation is that increased thickness of the ACC is an indication of neuroplasticity (Draganski et al., 2006; Engvig et al., 2010) given its role in allocating attentional resources (Bush et al., 2000; Posner et al., 2007; Posner, 2012), and executive control (Westlye et al., 2010). Since we would not expect neuroplasticity to increase after age 60, this explanation would not appear to fully explain the relationship. In contrast, inflammation does increase with age, and thus appears to be a more plausible cause of age-related thickness increases. Longitudinal studies will help to clarify potential mechanisms. The lack of age-related surface area reduction in the ACC is in accordance with previous cross-sectional studies (Fjell et al., 2009a, 2014), as well as a recent longitudinal study of healthy adults in which decelerating changes across the lifespan were observed in some regions of the prefrontal cortex (Storsve et al., 2014). In contrast, other studies have documented age-related differences and decline in these regions (Raz et al., 2005, 2010). For example, older age was associated with smaller volumes in the ACC in a recent investigation of middle-aged to older adults (Hafkemeijer et al., 2014).

Variability in findings across studies of age and brain structure may be due, in part, to differences in the study samples. For example, men and women have been found to have different trajectories of age-related structural changes (Murphy et al., 1996; Coffey et al., 1998; van Velsen et al., 2013). Demographic and clinical variables such as education, vascular disease, and genetic variation may also moderate the relationships of age with brain structure (Decarli et al., 1999; Swan et al., 2000; Seshadri et al., 2004; Raz et al., 2005, 2007b; Luders et al., 2006; Brundel et al., 2010; Dettie et al., 2011; Leritz et al., 2011; Villeneuve et al., 2014; Gonzalez et al., 2015) but have not always been accounted for in previous studies. Additionally, findings from cross-sectional studies may differ from longitudinal studies, as there is evidence that some regions show no cross-sectional differences but do change over time (Fjell et al., 2014).

The present study should be considered within the context of the relatively small sample size, which, together with the lack of young adults in the sample, limited our ability to directly examine nonlinear age effects. The sample size might also explain the discrepancy between the ROI analyses, which revealed a significant association between age and cortical thickness, and the exploratory vertex-wise analyses, which revealed no significant associations. The vertex-wise analyses were exploratory in nature and involved a large number of analyses that included each vertex in the cortex, thus a very strict correction for multiple comparisons was made. In our fairly small sample, small but significant effects are more difficult to detect with such a correction but are apparent in focused, hypothesis-driven ROI analyses. Nonetheless, our results are consistent with previous demonstrations of age-related differences in frontal

lobe structure, and contribute to a relatively small body of literature examining age effects in middle-age to older adults. Our findings also highlight the dissociation between measures of surface area and cortical thickness. Though some studies have shown similar age effects across different structural methods (Lemaitre et al., 2012), these two measurements are dissociable metrics that are confounded in studies of gray matter volume. Some studies have found either no correlation or a weak correlation between thickness and surface area (Winkler et al., 2010; Hogstrom et al., 2013), consistent with evidence that thickness and area are genetically independent and are affected by distinct neurobiological factors, such as myelin growth, during development (Panizzon et al., 2009; Rakic et al., 2009; Rakic, 2009; White et al., 2010). Additional research is needed to clarify the distinct causes of surface area and cortical thickness changes in late life, and to determine whether or not these two measures are differentially related to clinical and functional outcomes.

Overall, the present findings suggest that reductions in surface area and greater cortical thickness in prefrontal regions occur during the later decades of life. Thus, our findings suggest aging differentially affects changes in regional surface area and cortical thickness. Longitudinal studies are needed in middle-age and older adults to confirm these findings.

AUTHOR CONTRIBUTIONS

AJW and VMD designed the study. VMD, SMS, CNS, JWK, MLG, SDA and TMM acquired the data. SMS, MEM, AO, and AJW processed the neuroimaging data. VMD performed the statistical analyses. All authors contributed to data interpretation and writing of the article.

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Conflict of Interest Statement: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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