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Authors
Rast, P
Kennedy, KM
Rodrique, KM
et al.

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APOEε4 Genotype and Hypertension Modify Eight-year Cortical Thinning: Five Occasion Evidence from the Seattle Longitudinal Study


*aDepartment of Psychology, University of California-Davis, 1 Shields Avenue, Davis, CA 95616, prast@ucdavis.edu, +1 530-754-9435

*bCenter for Vital Longevity, School of Behavioral and Brain Sciences, The University of Texas at Dallas, 1600 Viceroy Dr., Suite 800, Dallas, TX 75235, USA, kristen.kennedy1@utdallas.edu; krodrigue@utdallas.edu

*cIntegrated Brain Imaging Center (IBIC), Department of Radiology, University of Washington, 1959 NE Pacific St, Seattle, WA 98195, USA, tgrabow@u.washington.edu

*dDepartment of Epidemiology, Johns Hopkins Bloomberg, School of Public Health, Baltimore, MD, USA

*eBiospective, Montreal, Canada

*fSeattle Longitudinal Study, Department of Psychiatry & Behavioral Sciences, University of Washington, 2500 6th Ave N., Seattle, WA, USA oldage@u.washington.edu; schaie@u.washington.edu

*These authors contributed equally.

*Corresponding Author.
Abstract
We investigated individual differences in longitudinal trajectories of brain aging in cognitively-normal healthy adults from the Seattle Longitudinal Study covering 8-years of longitudinal change (across 5-occasions) in cortical thickness in 249 midlife and older adults (52-95 years-old). We aimed to: understand true brain change; examine the influence of salient risk factors that modify an individual’s rate of cortical thinning; and compare cross-sectional age-related differences in cortical thickness to longitudinal within-person cortical thinning. We used Multivariate Multi-Level Modeling to simultaneously model dependencies among five lobar composites (Frontal, Parietal, Temporal, Occipital, Cingulate) and account for the longitudinal nature of the data. Results indicate 1) all five lobar composites significantly atrophied across 8-years, showing nonlinear longitudinal rate of cortical thinning decelerated over time, 2) longitudinal thinning was significantly altered by hypertension and APOEɛ4, varying by location: frontal and cingulate thinned more rapidly in APOEɛ4 carriers. Notably, thinning of parietal and occipital cortex showed synergistic effect of combined risk factors, where individuals who were both APOEɛ4 carriers and hypertensive had significantly greater 8-year thinning than those with either risk factor alone or neither risk factor, 3) longitudinal thinning was three-times greater than cross-sectional estimates of age-related differences in thickness in parietal and occipital cortices.

Keywords: Aging, APOE, Cortical thinning, Hypertension, Longitudinal modeling
Aging is associated with adverse cognitive outcomes believed to be associated with changes in the macrostructure of the brain (Raz and Rodrigue 2006; Rodrigue & Kennedy, 2011; MacDonald et al. 2009). Cross-sectional and longitudinal MRI studies of aging of brain structural properties, such as cortical and subcortical volume (Good et al. 2001; Jernigan et al., 1991; Liu et al. 2003; Pfefferbaum et al. 1994; Scanhill et al. 2003; Raz et al. 2005; Carmichael et al. 2012), white matter quality and connectivity (Lebel et al. 2012; Sullivan et al., 2010; Raz et al., 2012; Kennedy & Raz, 2009; Salat et al., 2005), have shown detrimental effects across the lifespan that are modified by individual difference variables, such as genetic and health risk factors (e.g., Kennedy & Raz, 2009; Salat et al., 2012; Swan et al., 1998). More recently, it has been suggested that cortical thinning in individuals at risk for dementia may be even more sensitive to early preclinical pathological changes than measures of cortical volume (Burggren et al. 2008), and that cortical thinning is the primary contributor to reductions in cortical volume with aging and thus, may be a more specific index of structural brain changes with advancing age (Thambisetty et al. 2010; Storsve et al. 2014).

Primarily, inferences about effects of aging on brain structure, including cortical thinning, are drawn from cross-sectional research (Salat et al. 2004; Fjell et al. 2009; Gautam et al. 2011, 2013; Leritz et al. 2011). Although cross-sectional designs allow for the comparison of a wide age range (e.g., 20s vs 80s), they do not allow measurement of true within-person change over time (cf. Hofer et al. 2006). Further, it is suggested that cross-sectional studies have underestimated actual changes in individual brain size as we age (Kennedy and Raz 2015). Thus, only longitudinal follow-up of individuals over time can assess the accurate rate of brain aging. Accordingly, there is a growing body of longitudinal studies of structural brain aging (Raz et al. 2005, 2010; Fjell et al. 2014; Walhovd et al. 2014; Pfefferbaum et al., 2013; Pacheco et al. 2015; Pillai et al. 2012; Jiang et al. 2014; Storsve et al. 2014; Thambisetty et al. 2010; Doré et al. 2013; Jiang et al. 2014). To better understand the effects of age and developmental change on the brain, longitudinal studies need to follow individuals on multiple occasions and for several
years (to take advantage of advanced multi-sampling data analysis techniques), examine multiple brain regions (for investigation of regional patterns), include potential modifying predictor variables, sample widely from the lifespan as preclinical changes often occur in midlife, and accommodate non-linear time trajectories. Therefore, there remain two major issues to address in the need to document within cognitively normal adults the regional variability in thinning across the cortex: long-term longitudinal designs and advanced statistical procedures need to be applied to understand actual change and variability of change, and to examine the salient factors that modify an individual’s rate of cortical thinning. The current study sought to incorporate these strengths.

The majority of longitudinal studies of brain aging have underutilized the richness of the data by using suboptimal analysis methods such as using simple repeated-measures t-tests or other univariate linear models rather than mixed models or latent growth curve modeling (but for example, see Raz et al., 2005; 2010; 2012 for exceptions). Multivariate multilevel modeling approaches (MMLM; MacCallum et al. 1997) are sophisticated data analysis techniques that are more appropriate to capture and model the richness of multivariate longitudinal data when more than two measurement occasions have been collected. These models are able to take into account not only the dependence of individual data points due to repeated measurements but also due to the similarity in cortical thickness among brain regions within individuals. Moreover, multilevel or mixed-effects models make full use of all available data, do not require that all participants have the same number of follow-up time points, nor do they require that all participants be measured at the same time intervals (cf. Raudenbush 2001).

Two salient vascular risk factors have been often studied because they convey increased risk for Alzheimer’s disease and alter cognition and brain structure in normal aging: APOEε4 genotype and diagnosis of hypertension. APOEε4 is the strongest genetic risk factor for sporadic AD (Corder et al., 1993), with 60% of AD individuals carrying at least one ε4 allele. These ε4 carriers display structural alterations in APOE protein, which impacts lipid and beta-amyloid binding, reducing its function in
neuronal integrity maintenance (Frieden and Garai, 2012). Individuals who are ε4 positive accumulate greater amyloid, and at an earlier age of onset (Fleisher et al., 2013), likely because the APOEε4 isoform reduces amyloid clearance and increases Aβ aggregation (Verghese et al., 2011). Without adequate clearance, beta-amyloid can form oligomers and plaque which may be neurotoxic to neurons (Liu et al., 2013; Scheltens et al., 2016; but see Hardy 2009 for a different viewpoint). This neurotoxicity brings with it damaged neuronal repair, neuronal inflammation, weakened blood barrier integrity, upregulated tau phosphorylation and neurofibrillary tangle formation (Mahley and Huang, 2012). Thus, APOE has been associated with increased risk for AD, modified cognitive and brain aging, and exacerbated cerebrovascular dysfunction. Carrying a diagnosis of hypertension in midlife has also been associated with increased later life dementia risk (Kivipelto et al., 2001). Hypertension diagnosis has been associated with greater 5-year shrinkage of brain volumes in otherwise healthy adults (Raz et al., 2005) and this shrinkage was associated with poorer fluid intelligence (Raz et al., 2008). Vuorinen and colleagues (2013) found that hypertension in midlife was associated with differences in cortical thickness 28 years later. Although this was not a longitudinal study, it suggests that carrying a diagnosis of hypertension over many years may lead to thinning of the cortex. Finally, Donix et al., (2010) found that APOEε4 carriers had greater thinning over 2 years in the medial temporal lobe structures.

Thus, in the present study we sought to examine the regional pattern of cortical thinning of association cortices in a large sample of cognitively normal adults with a wide age range including midlife through older age (52 – 95 years). In the Seattle Longitudinal Study we have collected five measurement occasions of data spanning eight years and here we use MMLM to optimally model within-person change and variability of change. We further investigate individual difference factors that likely contribute substantially to variance in rate of cortical thinning; APOEε4 status and diagnosis of hypertension. Beyond these primary aims, we also sought to compare cross-sectional age-related differences in cortical thickness with longitudinal within-person change in thickness.
Materials and Methods

Seattle Longitudinal Study

Data were obtained from community-living, non-demented participants in the Seattle Longitudinal Study (SLS), a cohort-sequential longitudinal study of the relationship between aging, health, cognition and lifestyle (Schaie 2013). SLS members at recruitment represented a stratified-by-age and gender random sample of the membership of the Group Health Cooperative of Puget Sound, a large health maintenance organization in western Washington State. Cognitive and behavioral assessments have been conducted every 7 years starting in 1956 on a mixed age cohort (age 22 - 88) with follow-up and recruitment of new samples every seven years (1956 through 1998). This study has been approved by the Group Health Cooperative of Puget Sound Internal Review Board. All participants provided written informed consent.

Participants

The current analyses included 249 individuals from the SLS who had MRI scans between 2006 and 2014. The interval between the MRI scans was two years and some participants had up to five scans ($n = 69$ participants had five scans, 49 had four, 50 had three, 55 had two, and 26 participants had one scan; Interval 1 between wave 1 and 2 was on average 23 months with SD = 1.9, interval 2 mean was 24 months and SD=3.6, interval 3 mean was 24 months and SD=3.9, and interval 4 was 17 months and SD=2.5). The mean age at the first MRI scan was 66.3 years ($SD = 8.0$ years); mean education was 16 years; sex distribution: 45% male. Racial composition included 241 Caucasian, 3 African American, 4 Asian, and 1 Hispanic participant. The racial composition of the MRI sample is similar to that of the total SLS population and to the health maintenance organization at the time of recruitment. Note that the MRI sample is a longitudinal sample who have been participating in the SLS for at least 14 years prior to the first MRI scan. Participants were assessed using an expanded CERAD neuropsychological battery (Morris et al. 1989, 1993; Schaie 2013) within 3 years of baseline scan and assessed at 2-3 year intervals.
thereafter. MMSE and WAIS Vocabulary scores at time of first scan are reported in Table 1.

Neuropsychological test performance was reviewed by two neuropsychologists, taking into consideration age norms and participant education and occupational status. No participants met criteria for dementia or mild cognitive impairment at baseline scan. Since the baseline scan, 12 participants have been assessed as demented and 2 participants as having mild cognitive impairment (MCI). Participants assessed as demented or MCI after the first scan were included in the analyses. Further, 13 participants are now deceased.

Participants were selected from the larger SLS sample with cognitive assessments in middle age. Selection criteria were: i) had undergone two or more cognitive assessments in midlife and/or old age, ii) participated in the 2005 SLS longitudinal data wave, iii) were cognitively normal based on cognitive assessment and consensus review, and iv) were willing and capable of undergoing multiple MRI scans.

Of the 249 participants, 161 entered the study in 2006, 46 entered in 2008 and 42 entered the study in 2010. Regarding attrition, of the participants that entered the study in 2006, 91% returned for the second occasion after that, 80% returned to the third, 75% to the fourth and 85% to the fifth occasion. Of those who entered in 2008, 91% returned for the second occasion after that, 83% returned to the third and 74% returned to the fourth measurement occasion. The attrition was larger for the group that had their first scan in 2010. Of those participants, 81% returned for their second measurement occasion and after that 53% returned for their third occasion. Dropouts from the first recruitment did not differ from the study sample in age, education, or neuropsychological test scores.

Risk Factor Predictor Variables

Apolipoprotein-E (APOE). APOE genotyping was performed at Northwest Lipid Research Laboratory, Seattle using restriction isotyping (Hixson and Vernier 1990) on 221 participants. Individuals were categorized as APOEε4 allele carriers (homozygotes and heterozygotes) vs. non-carriers for
Individual differences in cortical thinning

analysis. Of these, 32% possessed at least one ε4 allele (Table 1). Given the unknown effect of an APOE ε2 allele in the ε2ε4 carriers (five participants) we ran sensitivity analyses excluding these participants. Given that the results without the ε2ε4 carriers were almost identical, we included the five individuals in the final sample.

Hypertension. Hypertension status was determined based on medical records and confirmed on self-report provided at baseline. According to these self-reports 119 participants (48%) were hypertensive and 129 participants (52%) were normotensive. One person did not provide information on her hypertension status and thus was not included in the final model.

Hence, the final model with both predictors, APOE and hypertension, was based on 220 participants. Participants with hypertension or an APOEε4 allele did not differ in education or neuropsychological test scores from normotensives or non ε4-carriers.

MRI Acquisition and Processing

T1-weighted high-resolution structural imaging employed a magnetization-prepared rapid gradient echo (MP-RAGE) imaging sequence on a Philips 3.0 T Achieva scanner using the following parameters: repetition time = 7 milliseconds (ms), echo time = 3.20 ms; flip angle = 8 degrees; matrix = 256x256; NEX = 2; FOV = 256x256; and 0.859 millimeter thick sagittal slices. Cortical reconstruction was performed with FreeSurfer v5.1.0 (Dale et al. 1999; Fischl and Dale 2000; Fischl et al. 1999a, 1999b). After automatic analysis, the gray/white matter surfaces were visually inspected, and when deemed necessary, two trained raters made control point and white matter edits to improve pial and white matter boundary-finding. Analyses were then reiterated to ensure that tissue classification was as accurate as possible. The mapping to standard spherical coordinates allowed for automated anatomical parcellation of the cortical surface into 34 gyral parcels per hemisphere (Desikan et al. 2006). The time points for the present analyses were obtained from Freesurfer’s cross-sectional pipeline. Following Reuter and colleagues’ (2012) recommendation we did not use the data points from Freesurfer’s longitudinal pipeline.
due to the potential risks of “underestimating change and accuracy … when measuring longitudinal change over longer periods of time” (Reuter et al., 2012, p. 1404).

Creation of lobar composites.

For data reduction purposes, we aggregated cortical parcels across biological regions of interest to create lobar composites as follows. Cortical thickness values for each of the 68 parcels for each subject were first obtained at all time points. Given our interest in association and paralimbic cortices, likely to be most susceptible to age-related cortical thinning, we included a subset of 46 parcels that were used to define 13 regions and five composites (cf. Table 2 and Figure 1), plus visual cortex as a control region. To allow broader levels of analysis and to minimize comparisons required, parcels were averaged to form relevant regions (e.g., pars triangularis, pars opercularis, and pars orbitalis combined to form inferior frontal gyrus) which were combined to also form appropriate lobar composites: Frontal, Parietal, Temporal, Occipital, and Cingulate. To account for different sizes of the Desikan parcels when averaging, we computed average weighted means for each region and each composite. Due to difficulties in obtaining adequate parcellation of the entorhinal cortex that were not resolved after careful manual edits of individual segmentations we decided to remove this region from our analyses.

– insert Table 2 and Figure 1 about here –

Statistical Modeling Approach: Multivariate Multilevel Models (MMLM)

The longitudinal data used here have several levels of dependency that need to be included in the statistical models. For one, the measurements of the composites, regions and parcels are nested in two hemispheres within individuals who have been measured repeatedly over time. Cortical thickness measures of different regions taken from the same individual share the same history of growth, atrophy and exo- and endogenous influences making data points dependent as they cannot be considered random draws. In addition, repeated measures over time will result in thickness measures that are more similar within individual than across individuals thus adding another layer of data dependency. Currently,
multilevel or mixed-effects models are best suited to account for these dependencies and to obtain unbiased parameter estimates and standard errors of cortical thickness and atrophy rates.

To account for the multivariate nature of the data resulting from multiple regions (Carmichael et al. 2012) or composites measured at the same time across both hemispheres, and to jointly examine the longitudinal cortical thinning among these composites and regions, we applied multivariate multilevel models (MMLM; MacCallum et al., 1997). In addition to estimating average effects of cortical thickness and cortical atrophy (fixed effects), these models also estimate individual differences expressed as variances of the fixed effects (random effects). The multivariate approach allows us to model simultaneously the interplay (covariances between cortical thickness and annual atrophy rate) among the five composites and the effect of the predictor variables on atrophy.

In contrast to ANOVA, the MMLM approach takes advantage of different coding techniques to directly test comparisons of interest, omitting the need for post-hoc testing. Further, multilevel techniques shrink group-level variances toward the mean, reducing the number of statistically significant comparisons, and with it counterbalancing the risk of Type I errors arising from multiple comparisons (cf. Gelman et al. 2012).

In the Supplemental Material we provide a detailed formal description of the statistical model and the approach to derive the best model for these data. While the current analyses focus on cortical thickness changes across composites (cf. Table 2), we provide additional analyses of change within each of the five composites across its regions in the Supplemental Material. Briefly, we employed a series of nested joint MMLM models to analyze cortical thickness of the five broad lobar composites: Frontal, Temporal, Parietal, Occipital, and Cingulate. This process consisted of 4 modeling steps that incrementally modified model complexity, starting with the Intercept Model that only includes intercept terms of cortical thickness. Next, we expanded that model to the Baseline Model which includes age-at-study-entry and time-in-study effects. In a third step, we constrained (co)variance parameters to be equal
Individual differences in cortical thinning across composites to reduce overall model complexity while maintaining model fit (*Constrained Baseline Model*). The final, *Full Model*, expanded that latter model to include explanatory variables such as APOEε4 and hypertension, to explain differences in between-person cortical thickness and within-person thinning rates. All estimates reported in Table 3, as well as Figures 2 and 3 are based on the *Full Model*. Model fitting steps and resulting parameters (from Intercept to Constrained Baseline Model) are reported as Supplemental Materials.

All models were estimated using the statistical software package R with the LME command from the NLME library (Pinheiro and Bates 2000; R Core Team 2017). The code for the final model is provided in the Supplementary Material (Code section). The significance of random effects was obtained using likelihood ratio (LR) tests.

**Results**

*MMLM of Cortical Thinning in Lobar Composites and Risk Modifiers*

The Full Model is the major test of our hypotheses and results are presented in Table 3. The significant effects in Table 3 are noted in bold font and are explained in turn here. For each of the 5 lobar composites, we examined Age, Time, Time², APOEε4, and Hypertension effects and the interactions among these effects.

-- insert Table 3 about here --

*Age* indicates the significance of cross-sectional age differences in cortical thickness and refers to age at baseline. Significant cross-sectional age-differences were found for all 5 composites indicating thinner cortex with older age. *Time* indicates the significance of linear slope (rate of thinning) across the longitudinal occasions for a given composite at study entry -- also referred to as instantaneous rate of change. Linear change over time was found in Parietal, Temporal and Occipital composites; however, a significant quadratic function would supersede these effects of linear change. *Time²* term was included to investigate *curvilinear* (accelerated or decelerated) thinning over time. We found significant *Time²* effects
for all 5 composites indicating that the rate of atrophy significantly reduced as time passed; in other words, participants’ cortex tended to thin out at a slower pace as the study occasions progressed. Interestingly, for the Frontal, Temporal, and Cingulate cortex there was additionally a significant Age x Time² interaction, indicating that this deceleration of rate of thinning was stronger in older participants.

**Risk Modifiers**

Interestingly, neither the main effects of APOE nor hypertension (HT) were significant for any composite, indicating that at study entry cortical thickness did not differ between carriers and noncarriers or hypertensives and normotensives. However, there was a significant Time x APOE interaction for Frontal and Cingulate composites, indicating that thinning rate depended on APOE status, with ε4 carriers having larger atrophy rates, amounting to a 0.24% initial thinning per year compared to non-carriers. Hypertension did not affect the rate of thinning in any lobar composite, neither on initial thickness nor on the atrophy rate. Rather, a significant Time x APOE x Hypertension interaction was found in the Parietal and Occipital composites and indicated that participants who were both hypertensive and APOEε4 carriers showed significantly faster thinning over time than their non-risk counterparts (Figure 2). As such, atrophy rates for those participants evidenced an additional loss of cortical thickness of 0.3% to 0.4% per year, over and above the overall atrophy rate of approximately 0.7% per year (Table 3).

--- insert Figure 2 about here ---

Notably, APOE genotype explained 20% of the variance between participants in initial slope (change) in longitudinal thinning associated with the Frontal, Cingulate, and Temporal composites, 16% in the Parietal and 10% in the Occipital composite, indicating that APOE is a major explanatory factor in individual differences in cortical thinning. APOE genotype also explained 11% of between-hemisphere differences in the Temporal composite. As a comparison, participants’ age explained 4% of slope variance in the Frontal and 10% of the slope variance in the Cingulate composite while it explained less than 1% in all other regions.
After accounting for individual differences due to APOE and hypertension, large individual differences persist (cf. Supplementary Table 4), as there is a myriad of factors that influence brain aging. Both cortical thickness at study entry and thinning rates differed among individuals. These individual differences in cortical thinning are illustrated in Figure 3. All lines represent predicted individual cortical thickness trajectories from the full model for each of the five lobar composites for both hemispheres. Each line represents individual estimates across the 8-year duration of the study.

--- insert Figure 3 about here ---

_Cross-Sectional versus Longitudinal Estimates of Aging of Cortical Thickness._ Longitudinal data offer the possibility to compare change due to the passage of _time within individuals_ (longitudinal) and the differences in time lived _across individuals_, operationalized as _age-differences_ (cross-sectional). Both of these sets of estimates are reported in Table 3. For both Age and Time the unit of change is one year. The differences/changes reported in the table reflect the slope of Time and Age at study entry for a, on average, 65 year old. At later points in the study or for different ages, these slopes and their ratios will differ due to the quadratic term in the model which makes a comparison of these two effects difficult as they are contingent on centering choices. However, given that cross-sectional studies essentially correspond to the first measurement occasion in longitudinal studies the comparison of atrophy rates at the first measurement occasion with cross-sectional age effects are still informative. In the Parietal, Temporal and Occipital composites the significant main effect of longitudinal thinning (Time) indicated an annual -0.7%Δ for Parietal and Occipital and -0.3%Δ for Temporal composites. The longitudinal thinning rate in the Parietal and Occipital composites was almost _three times larger_ than the effect of cross-sectional age-differences in cortical thickness. This suggests that for these brain regions, cross-sectional estimates are underestimated compared to true within-person change over time. For the Temporal composite, however, longitudinal thinning and cross-sectional age-differences were identical. In the Frontal and Cingulate composites only APOEε4 carriers’ cortices thinned initially by
approximately -0.25% per year compared to non-carriers. Again, in both of these composites longitudinal thinning was similar or slightly larger compared to cross-sectional thickness differences but, overall, atrophy rates decelerated over the course of the study.

**Discussion**

This study aimed to contribute to our understanding of aging of brain structure in two important ways: by utilizing long-term multiple occasion longitudinal designs with appropriate sophisticated statistical procedures needed to understand true brain change, and by examining the potential influence of salient risk factors that modify an individual’s rate of brain structural loss. To this end, we used multivariate multilevel modeling (MMLM) to measure 8-year longitudinal change (across five occasions) in cortical thickness in cognitively healthy midlife and older adults in the Seattle Longitudinal Study, as well as the modifying effects of APOEε4 and hypertension. As a secondary aim, we compared cross-sectional age-related differences in cortical thickness with true within-person cortical thinning over time, as it is believed that for some cortical composites, cross-sectional aging studies routinely underestimate an individual’s rate of actual shrinkage over time. This design and modeling approach allowed us to detect three major results: 1) in all five areas examined (frontal, parietal, temporal, occipital, cingulate) there was significant loss of cortical thickness across 8 years and this thinning rate decelerated over time in midlife through older age when change is assessed via quadratic rather than only linear trajectories, 2) thinning of parietal and occipital cortex was dependent on combined risk factors, where individuals who were both APOEε4 carriers and hypertensive had significantly greater 8-year thinning than those with either risk factor alone or neither risk factor, and 3) that for some brain regions (parietal, occipital) longitudinal loss of thickness was three times greater than cross-sectional estimates of age-related thickness differences. To our knowledge, this is the first report of long-term longitudinal change in cortical thickness extending over both midlife and old age and reporting synergistic modifying effects of APOE genotype and hypertension status.
Risk Modifiers of Within-Person Brain Aging. Humans age at different rates and this is apparent across all organs and systems. Underlying this variability are individual difference factors that include one’s genetic, health, and lifestyle/environmental factors. Some individuals maintain sharp cognitive prowess as they age, whereas others less so, and still others develop neurodegenerative conditions such as Alzheimer’s disease or other dementias. Two of the major risk factors that have been linked to cognitive and brain aging and pathology are the presence of APOEε4 allele and diagnosis of hypertension. Elevated blood pressure and hypertension have been associated with poorer brain health, including greater white matter hyperintensity lesions (Raz et al., 2007; 2012), decreased white matter connectivity (Kennedy and Raz, 2009; Salat et al., 2012), smaller regional brain volumes (Raz et al., 2005; 2007), and most recently thinner cortical regions (Leritz et al., 2011; Vuorinen et al., 2013). Hypertension putatively exerts its negative effects on the brain because it brings about cerebral dysautoregulation and alters perfusion of the cortex. We find effects of hypertension on thinning of posterior cortices (parietal and occipital) in the Time x APOE x HT interaction, in line with studies of loss of regional posterior volumes (Raz et al., 2007) and of decreased white matter integrity (Kennedy and Raz, 2009; Raz et al., 2007). Given the perfusion of the posterior cortices is limited to the posterior cerebral arteries territory, as compared to the better perfused anterior territories of the brain, posterior brain regions would be more susceptible to negative effects of hypertension (Sorond et al., 2005). These vascular alterations are associated with an increased risk for Alzheimer’s disease and other dementias (Kivipelto et al., 2001). Indeed, it has been proposed that hypertension, and other vascular risk factors, may increase risk for dementia possibly because of an association with decreased cortical thickness (Alosco et al., 2014; Villeneuve and Jagust, 2015; Villeneuve et al., 2014).

APOEε4 positivity, in addition to a genetic risk for AD, also increases risk for cerebrovascular dysfunction as its mechanisms are, in part, through clearance and transport of cholesterol and beta-amyloid protein. APOEε4 carriers have been found to have greater hippocampal shrinkage (Moffat et al.,
Individual differences in cortical thinning

2000), smaller regional brain volumes and thickness (Liu et al., 2010), and poorer white matter integrity (Persson et al., 2006). APOEε4 carriers also show greater reduced metabolism in temporal cortex across 2 years (Reiman et al., 2001) and greater beta-amyloid deposition in temporal cortex with increased APOEε4 dose (Reiman et al., 2009). Notably, in the current study, APOE’s effects on rate of thinning over time exceeded those of the effects of age, explaining 20% of the variance in change in Frontal, Temporal, and Cingulate cortices.

Of particular importance is the impact of multiple risk factors. Meta-analyses have identified at least 10 major risk factors suggesting that brain atrophy is likely due to multiple risk factors in any individual (Anstey et al., 2013; Deckers et al., 2014; Exalto et al., 2014). Interestingly, Rodrigue et al (2013) found in a cross-sectional study that among cognitively healthy older adults, individuals with both hypertension and APOEε4 risk factors had significant elevation in beta-amyloid deposition. Quite similarly, we report here accelerated rate of thinning across 8 years in ε4 carriers in frontal and cingulate cortex, but also a significantly greater rate of thinning in the parietal and occipital cortex in ε4 carriers who were also hypertensive. These synergistic effects on brain health markers may suggest that there is a threshold at which the brain can no longer resist damage. For example, having a genetic risk for AD may not have detrimental effects on the brain unless another exacerbating condition is present, such as hypertension.

Although the larger and longer longitudinal studies of cortical thinning have not systematically investigated the effects of APOE genotype or hypertension, a few smaller longitudinal investigations have done so (Thompson et al, 2011). Donix et al (2010) examined 2-yr longitudinal change in cortical thickness in cognitively normal older adults varying by APOEε4 status. Those with an APOEε4 allele exhibited greater cortical thinning in entorhinal cortex, and all medial temporal cortex regions compared to non-carriers. In relation to the moderating effect of hypertension on cortical thinning, Walhovd et al, (2014) examined effects of several cardiovascular-related factors (omega-3 fatty acids, vitamin D,
physical exercise, cholesterol, systolic blood pressure and body mass) and reported that better cardiovascular indices related to less cortical thinning in temporal and frontal regions. In a cross-sectional study, hypertensives exhibited lower perfusion in temporal and occipital cortices, along with thinner temporal, frontal, parietal cortex than non-hypertensives (Alosco et al. 2014). Overall, it seems fairly consistent that hypertension has an effect on posterior cortical thickness, and although the mechanism behind this is yet unknown, it may be due in part to altered perfusion of those territories in hypertensives. Indeed, we show that APOE by itself has an effect on thinning in frontal and cingulate regions; however, it required the synergistic effect of both APOE and hypertension risk factors to affect change in the most posterior regions (parietal and occipital). This finding mirrors and extends the previous findings of posterior regions being most affected longitudinally by hypertension in white matter hyperintensities and volume loss (Raz et al., 2007) to cortical thinning loss.

**Comparison of magnitude of Cross-Sectional vs Longitudinal findings across regions**

There has been debate regarding the magnitude of cross sectional age differences vs. longitudinal annual rate of atrophy. This is a very important issue, both methodologically, and for the proper understanding of true effects of aging on a person’s brain. Some researchers have suggested that neural longitudinal effects may be larger than cross sectional-age difference estimates (Raz and Lindenberger 2010; Kennedy and Raz 2015; Pfefferbaum and Sullivan 2015). Similar to prior cross-sectional studies, we found age differences in all composites.

Although few in number thus far, longitudinal evidence suggests that there are *regional differences* in rate of cortical thinning and highlight the considerable individual variability in rates of thinning. Although some longitudinal studies report general agreement with cross-sectional studies regarding regions showing age effects (Resnick et al. 2003), other longitudinal studies report patterns of associations that differ from cross-sectional reports (Raz et al. 1997; Du et al. 2006; Pfefferbaum and Sullivan 2015). The primary problem with cross-sectional studies of aging, however is that it is
impossible to know whether these ubiquitous detrimental effects of “aging” on the brain are actually due
to the passage of time, or from differences across individuals in the sample. Longitudinal designs, in
contrast, hold variation at the individual level constant, essentially utilizing each person as his or her own
control subject. Therefore, although limited by shorter time windows, longitudinal designs are the only
way to measure true (e.g. intraindividual) change in brain structure as a person ages. We found that
although initial atrophy rates tended to be larger than cross-sectional differences (in some regions three
times greater), atrophy rates also were nonlinear, decelerating over the course of the study reducing the
rate of atrophy as time went by.

*Individual differences and between- vs. within-person variance*

Importantly, in some brain regions, APOE genotype predicted from 13% to 20% of the variance
among participants (compared to hypertension, which explained less than 1% of between-person
variance). This is an impressive amount of variance to be explained in atrophy in normally aging
individuals. Despite this, even after including person-level predictors, the amount of individual
heterogeneity in cortical thickness and atrophy rates remains substantial, given that there are multitude of
variables that affect how people age. In contrast, within-person variability was much smaller, with the
main source residing at the measurement (i.e., FreeSurfer) level, comprising both fluctuations due to
longitudinal change over five time points (thinning and stability and thickening) and to measurement
error. This remaining unexplained variance in brain aging leaves opportunities for the investigation in
future studies of additional risk factors.

*Study-specific considerations*

Any study’s findings should be interpreted with regard to the study design and sample
characteristics. As noted previously, there is naturally a much wider age range (35 years) available for
examining cross-sectional age differences, compared to an 8-year interval for examining longitudinal
within-subject thinning effects. This may have implications for directly comparing magnitude of age
differences and age-related change. The prevalence of significant longitudinal effects and individual differences in atrophy rates in all five composites indicates that age-related thinning can be reliably assessed across five measurement occasions spanning eight years (cf. Rast and Hofer, 2014) and corroborates findings from studies with just two years (e.g. Fjell et al. 2014).

Additionally, sample characteristics must be considered in interpreting study findings. The sample represents cognitively healthy adults of above average educational level within the midlife to old age range. No participants were diagnosed as MCI or demented at baseline. The restriction of the age range to midlife and old age has both advantages and limitations. Lack of a younger adult group restricts comparisons to other longitudinal studies that do include a younger age group. On the other hand, restricting the age range studied allows for an increase in power and the number of participants studied in midlife, which is the critical period for examining preclinical levels of brain and cognitive decline. Likewise, the inclusion of older adults in the high 80’s has extended these findings to an undersampled population of older ages. Related, given the lengthy latent prodromal phase of AD, it is unknown what portion of the sample transitions to dementia over time. Future time points of the Seattle Longitudinal Study will reveal which individuals, if any, are on a trajectory toward dementia and it will be important to relate AD onset to brain aging and preclinical information obtained in the early phases of the study. This extension in age-range, however, may have also increased age-differential selectivity in the sense that the older participants have fared particularly well in terms of brain atrophy. This might be a contributing factor to smaller cross-sectional age differences compared to atrophy rates at study entry.

**Summary**

In conclusion, we used sophisticated multivariate multilevel modeling to demonstrate with longitudinal data spanning eight years and five time points that regional cortical thickness is lost in heteromodal association cortex in middle-aged and older adults ranging in age from 51-86 years. This loss of cortex is decelerated with time, and negatively modified by at least two markers of vascular risk,
APOEε4 genotype and presence of hypertension. Parietal and Occipital cortex appear to be particularly vulnerable to the synergistic combination of both APOEε4 allele and hypertensive vascular risk factors. Because hypertension is amenable to treatment, especially in midlife, it may be a viable strategy for Alzheimer’s disease prevention (Villeneuve and Jagust 2015).
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### Tables

*Table 1. Descriptive Statistics and Sample Characteristics*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Sample</th>
<th>APOE</th>
<th>Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>E4</td>
<td>Noncarrier</td>
</tr>
<tr>
<td>N (%)</td>
<td>249</td>
<td>71</td>
<td>150</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(32%)</td>
<td>(68%)</td>
</tr>
<tr>
<td>M/F (%F)</td>
<td>112/137</td>
<td>30/41</td>
<td>65/85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(55%)</td>
<td>(33%)</td>
</tr>
<tr>
<td>Age lst scan</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M (SD)</td>
<td>66 (8.0)</td>
<td>65 (7.2)</td>
<td>67 (8.5)</td>
</tr>
<tr>
<td>Range</td>
<td>52—89</td>
<td>53—87</td>
<td>52—89</td>
</tr>
<tr>
<td>Education (SD)</td>
<td>16.2 (2.5)</td>
<td>16.5 (2.6)</td>
<td>16.1 (2.4)</td>
</tr>
<tr>
<td>MMSE (SD)</td>
<td>29 (1.1)</td>
<td>29.4 (0.8)</td>
<td>29.2 (1.2)</td>
</tr>
<tr>
<td>WAIS Voc (SD)</td>
<td>60.8 (7.3)</td>
<td>61.8 (5.8)</td>
<td>60.3 (7.8)</td>
</tr>
</tbody>
</table>

*1 APOE allele was available on N = 221 subjects. 2 Chi square of APOE x Hypertension = 6.05, p<.01. Fewer e4 carriers were hypertensive than expected. APOEe4 carriers vs non carriers differed significant in age, but not in education or cognitive scores. Hypertensive vs non hypertensive differed significantly (p < .01) in age, but not in education or cognitive scores.*
Table 2. Component construction of lobar Composites, from aggregated Regions, from relevant association cortex Parcels

<table>
<thead>
<tr>
<th>Composite</th>
<th>Region</th>
<th>Desikan Parcel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>Superior Frontal Gyrus (SFG)</td>
<td>Superior Frontal Gyrus</td>
</tr>
<tr>
<td></td>
<td>Middle Frontal Gyrus (MFG)</td>
<td>Rostral Middle Frontal Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caudal Middle Frontal Gyrus</td>
</tr>
<tr>
<td></td>
<td>Inferior Frontal Gyrus (IFG)</td>
<td>Parsopercularis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pars Triangularis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pars Orbitalis</td>
</tr>
<tr>
<td></td>
<td>Medial Frontal (mF)</td>
<td>Rostral Anterior Cingulate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Medial Orbital Frontal</td>
</tr>
<tr>
<td>Parietal</td>
<td>Inferior Parietal Lobule (IPL)</td>
<td>Supramarginal Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior Parietal Gyrus</td>
</tr>
<tr>
<td></td>
<td>Precuneus (PREC)</td>
<td>Precuneus Cortex</td>
</tr>
<tr>
<td>Temporal</td>
<td>Parahippocampal (PHC)</td>
<td>Parahippocampal Gyrus</td>
</tr>
<tr>
<td></td>
<td>Fusiform Gyrus (FG)</td>
<td>Fusiform Gyrus</td>
</tr>
<tr>
<td></td>
<td>Superior Temporal Gyrus (STG)</td>
<td>Superior Temporal Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Transverse Temporal Gyrus</td>
</tr>
<tr>
<td></td>
<td>Lateral Temporal (LT)</td>
<td>Middle Temporal Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inferior Temporal Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Banks of Superior Temporal Gyrus</td>
</tr>
</tbody>
</table>
Table 2 cont’d

<table>
<thead>
<tr>
<th></th>
<th>Visual Cortex (VC)</th>
<th>*Pericalcarine Sulcus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Occipital</td>
<td>Cuneus (CUN)</td>
<td>Cuneus</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Cingulate (CING)</th>
<th>Posterior Cingulate Gyrus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cingulate</td>
<td></td>
<td>Caudal Anterior Cingulate Gyrus</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Isthmus Cingulate Gyrus</td>
</tr>
</tbody>
</table>

*We included early visual cortex (pericalcarine sulcus and cuneus) as non-heteromodal association control regions.
### Table 3. Full Model fixed effects estimates from joint Multivariate Multilevel Model (MMLM) of Cortical Thinning of the Five Lobar Composites

<table>
<thead>
<tr>
<th>Lobar Composite</th>
<th>Intercept</th>
<th>Time</th>
<th>Age</th>
<th>APOE</th>
<th>HT</th>
<th>Time²</th>
<th>Time×Age</th>
<th>Time×APOE</th>
<th>Time×HT</th>
<th>APOE×HT</th>
<th>Age×Time²</th>
<th>APOE×HT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frontal</td>
<td>2.3766</td>
<td>-0.0031</td>
<td>-0.0038</td>
<td>-0.0159</td>
<td>-0.0087</td>
<td>0.0007</td>
<td>0.0003</td>
<td>-0.0056</td>
<td>-0.0001</td>
<td>0.0106</td>
<td>-0.0001</td>
<td>-0.0005</td>
</tr>
<tr>
<td>Δ%</td>
<td>-0.13</td>
<td>-0.16</td>
<td>-0.67</td>
<td>-0.37</td>
<td>0.03</td>
<td>0.01</td>
<td>-0.24</td>
<td>0.00</td>
<td>0.45</td>
<td>0.00</td>
<td>-0.02</td>
<td></td>
</tr>
<tr>
<td>Parietal</td>
<td>2.2419</td>
<td>-0.0155</td>
<td>-0.0058</td>
<td>-0.0096</td>
<td>-0.0107</td>
<td>0.002</td>
<td>-0.0001</td>
<td>-0.0016</td>
<td>-0.0006</td>
<td>0.0337</td>
<td>0.0000</td>
<td>-0.0066</td>
</tr>
<tr>
<td>Δ%</td>
<td>-0.69</td>
<td>-0.26</td>
<td>-0.43</td>
<td>-0.48</td>
<td>0.09</td>
<td>0.00</td>
<td>-0.07</td>
<td>-0.03</td>
<td>1.5</td>
<td>0.00</td>
<td>-0.29</td>
<td></td>
</tr>
<tr>
<td>Temporal</td>
<td>2.4876</td>
<td>-0.0074</td>
<td>-0.0074</td>
<td>-0.0117</td>
<td>-0.0189</td>
<td>0.0012</td>
<td>0.0001</td>
<td>-0.0011</td>
<td>0.0509</td>
<td>-0.0001</td>
<td>-0.0037</td>
<td></td>
</tr>
<tr>
<td>Δ%</td>
<td>-0.30</td>
<td>-0.30</td>
<td>-0.47</td>
<td>-0.76</td>
<td>0.05</td>
<td>0.00</td>
<td>-0.04</td>
<td>-0.04</td>
<td>2.05</td>
<td>0.00</td>
<td>-0.15</td>
<td></td>
</tr>
<tr>
<td>Occipital</td>
<td>1.6417</td>
<td>-0.0119</td>
<td>-0.0034</td>
<td>0.0026</td>
<td>-0.0043</td>
<td>0.0011</td>
<td>-0.0002</td>
<td>-0.0004</td>
<td>0.0003</td>
<td>0.0058</td>
<td>0.0000</td>
<td>-0.0068</td>
</tr>
<tr>
<td>Δ%</td>
<td>-0.72</td>
<td>-0.21</td>
<td>0.16</td>
<td>-0.26</td>
<td>0.07</td>
<td>-0.01</td>
<td>0.02</td>
<td>0.02</td>
<td>0.35</td>
<td>0.00</td>
<td>-0.41</td>
<td></td>
</tr>
<tr>
<td>Cingulate</td>
<td>2.3764</td>
<td>0.0019</td>
<td>-0.0050</td>
<td>0.0169</td>
<td>0.0134</td>
<td>0.0006</td>
<td>0.0004</td>
<td>-0.0057</td>
<td>-0.001</td>
<td>0.0128</td>
<td>-0.0001</td>
<td>-0.0011</td>
</tr>
<tr>
<td>Δ%</td>
<td>0.08</td>
<td>-0.21</td>
<td>0.71</td>
<td>0.56</td>
<td>0.03</td>
<td>0.02</td>
<td>-0.24</td>
<td>-0.04</td>
<td>0.54</td>
<td>0.00</td>
<td>-0.05</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 cont’d

Note. Bolded estimates are statistically significant at $p < .05$. $N = 220$. Composites are dependent variables modeled simultaneously from a MMLM (see Analysis Plan). APOE and HT are dummy coded with the reference group being the non-carriers of the ε4 allele and the normotensives (e.g., the interaction term Time $\times$ APOE represents the deviation of APOE-ε4 carriers in the atrophy rate from non-carriers). ∆% represents average annual percent change with respect to initial cortical thickness for a 65 year-old person. ∆% for dummy coded variables represents the change in APOE-ε4 carriers or hypertensives with respect to non-carriers or normals. Age is centered at 65 years of age and represents age at Wave 1. Time captures the atrophy rate of the cortex on an annual basis and $\text{Time}^2$ represents quadratic rate of change. Comp = lobar Composite; Int = model Intercept term.
Figure Captions

*Figure 1.* Representation of the five lobar composites (Frontal, Parietal, Occipital, Temporal and Cingulate) and the 13 subordinate regions of interest.

*Figure 2.* Cortical thinning in Parietal and Occipital cortex over 8 years depend on APOE and Hypertension status. Breakdown of significant Time x APOE x Hypertension interaction. Bars show annual percent change in cortical thickness illustrated in four risk groups: participants with “No Risk” factors (i.e., APOE-, normotensive); participants with one risk factor, either Hypertension (HT) or APOEε4+ (APOE); and participants with both risk factors (APOEε4+, hypertensive). Annual percent change for Occipital (Panel A) and Parietal (Panel B).

*Figure 3.* Spaghetti Plots for each Lobar Composite Hemisphere Rate of Cortical Thinning Loss. Each line represents an individual across the occasions of study. Predicted cortical thickness based on the full model with all predictors across five composites and both hemispheres. LH = Left Hemisphere; RH = Right Hemisphere. N = 220 individuals.