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Regional Cortical Thinning and Systemic Inflammation in Older Persons Without Dementia

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To the editor: Regional cortical thinning occurs in aging¹, in Alzheimer's disease (AD)² and its prodromal stages^{2–3}, but little is known about its biological basis. This thinning may reflect the presence of neuroinflammation associated with deposition of AD pathology and neurodegeneration. Aging is associated with upregulation of inflammation-associated genes in the brain as well as microglial activation⁴. Post-mortem examination of older persons without dementia has shown that up to 40% have evidence of AD pathology⁵ and inflammatory mechanisms are upregulated in regions of the aged brain known to be vulnerable to deposition of AD pathology⁶. Brain characteristics of older persons have been linked to level of circulating inflammatory markers: circulating interleukin-6 (IL-6) has been associated with hippocampal, medial prefrontal cortex and cerebellum volumes in middle-aged adults⁷, C-reactive protein (CRP) and tumor necrosis factor-alpha (TNFα) have been associated with white-matter hyperintensities⁸ and total brain atrophy in community-based samples of older persons without dementia or stroke⁹, and it has been shown that neuroinflammation is triggered easily by systemic inflammatory stimuli¹⁰.

Using imaging methodology that measures regional atrophy across the entire cortical mantle^{1–3} and data from the Rush Memory and Aging Project, a prospective

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Author Contributions: Dr. Fleischman had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. She was involved in study concept and design, acquisition of all data, analysis and interpretation of all data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Dr. Arfanakis was involved with acquisition of neuroimaging data, interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual contact. Drs. Kelly, Buchman, Morris and Barnes were involved with acquisition of serum data, interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Dr. Bennett was involved with acquisition of neuroimaging and participant data, interpretation of the data, drafting of the manuscript, and critical revision of the manuscript for important intellectual content. Ms. Rajendran was involved in study concept and design, acquisition, post-processing, analysis and interpretation of all data, and drafting of the manuscript.

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epidemiological, community-based cohort study of aging⁵, we tested the hypothesis that regional cortical thinning is associated with level of systemic inflammation in aging. Twenty-nine older persons without dementia or other neurological and psychiatric conditions and not taking anti-inflammatory medications (age $M = 81.2$, $SD = 4.9$; M education = 14.6, $SD = 2.5$; 76% female) were characterized as having high or low levels of systemic inflammation based on the upper and lower quartiles of a composite measure of circulating CRP and TNF α , prototypical biomarkers of inflammation that have been utilized in many studies of aging. Age and education did not differ significantly between groups and there were no significant correlations between level of inflammation with age, education or sex (all $ps > .05$).

High-resolution T₁-weighted anatomical data were obtained on a 1.5 Tesla GE MRI scanner using an MPRAGE sequence. Thickness across the cortical mantle was estimated using Freesurfer software (<http://surfer.nmr.mgh.harvard.edu>) and an exploratory statistical map was generated using a 2-class general linear model based on computing the effect of inflammation level on cortical thickness at every voxel of each hemisphere with a conservative threshold of $p < 0.012$. Regional clusters in which cortical thickness differed by the level of inflammation were identified and examined independently. The high inflammation group had significant cortical thinning, compared to the low inflammation group in four left-hemisphere and six right-hemisphere regions (Table 1). Two-tailed t-tests indicated that, for each individual region, group differences in thickness were highly significant. All differences survived a Bonferroni-corrected probability level of .00007 except left hemisphere post-central. There was no significant group difference in cortical thickness in a control region chosen a-priori (BA 17, cuneus, left and right hemisphere $ps = .93$ & .24).

We found a pattern of regional cortical thinning that was associated with level of systemic inflammation in older persons without dementia. The pattern was similar to that previously reported for nondemented elders¹ and, notably, included regions of primary motor (pre-central), somatosensory (post-central), auditory (transverse temporal) and visual (pericalcarine, lingual) cortex. The findings suggest that regions of cortex are, indeed, differentially vulnerable to thinning in older persons, that this vulnerability is associated with level of systemic inflammation, and that it occurs not only in expected association areas, but also in regions of primary sensory and motor cortices. The association between cortical thinning and systemic inflammation in the current study was also evident in some of the same regions (superior frontal, superior parietal and precuneus) reported in persons with, or at risk for, clinical AD^{2,3}. The findings suggest that these association areas may be particularly vulnerable to presence of inflammatory mechanisms and that the associated cortical thinning can be seen in older persons who do not have dementia.

Although the participants in this study were sampled from a clinical-pathological study in which a comprehensive clinical evaluation allowed for the relevant exclusions, the sample size was relatively small and the results are preliminary. However, the effect sizes that were obtained were large and the pattern of regional cortical thinning that emerged was consistent with other studies of aging and AD that have used the same methods. Although preliminary, the results of this study are important because they suggest the presence of regional cortical thinning in older persons who do not have dementia and link it to a potential risk factor for neurodegeneration in aging, systemic inflammation.

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Table 1

Thinning by region for high (HI) and low (LI) inflammation groups

Region	Cortical thinning for inflammation groups by region (mm) (SD)		Group mean difference (mm) [*]	Percent thinning	Effect size [*]	P-value
Left Hemisphere $\overline{HI}$ $\overline{LI}$						
Lateral orbital frontal	2.50 (0.35)	2.95 (0.27)	0.45	15.15	1.43	6.50E-4
Inferior temporal	2.94 [†] (0.34)	2.48 (0.23)	0.46	15.65	1.60	1.04E-4
Post-central	1.81 [†] (0.51)	1.30 (0.18)	0.51	28.17	1.34	9.16E-4
Precuneus	1.25 (0.08)	1.46 (0.12)	0.21	14.32	2.05	1.83E-5
Pericalcarine	1.41 (0.09)	1.62 (0.14)	0.20	12.48	1.75	1.08E-4
Lingual	1.23 (0.08)	1.42 (0.14)	0.18	14.95	1.68	8.10E-4
Right Hemisphere $\overline{HI}$ $\overline{LI}$						
Parsorbitalis	2.57 [†] (0.35)	2.03 (0.25)	0.53	20.71	1.73	4.03E-5
Superior frontal	1.71 (0.14)	2.11 (0.19)	0.41	18.85	2.36	1.61E-6
Pre-central	1.99 (0.27)	2.46 (0.37)	0.47	19.28	1.47	1.61E-6
Transverse temporal	1.67 (0.30)	2.18 (0.40)	0.52	23.67	1.47	6.15E-4
Post-central	1.79 (0.24)	2.25 (0.32)	0.46	20.36	1.60	2.60E-4
Superior parietal	1.70 (0.14)	2.09 (0.18)	0.40	19.02	2.45	6.79E-7
Precuneus	1.69 (0.16)	2.09 (0.22)	0.39	18.90	2.03	1.56E-5

^{*} Cohen's d[†] HI>LI