Increased levels of systemic inflammation in the elderly are associated with reduced microstructural integrity of brain tissue

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Introduction: Aging is associated with upregulation of inflammation-associated genes in the brain [1]. Inflammatory mechanisms are shown to be upregulated in regions of the aged brain known to be vulnerable to deposition of Alzheimer's disease pathology [2]. Also, population-based studies have found that elevated levels of inflammation are related to cognitive decline [3]. The purpose of this work was to test the hypothesis that high levels of circulating inflammatory markers in the elderly are associated with changes in the microstructural integrity of white matter tissue, as assessed with diffusion tensor MRI [4].

Methods: Serum samples from 320 non-demented elderly participants of the Rush Memory and Aging Project [5], not taking anti-inflammatory medications, were assayed for C-reactive protein (CRP) and tumor necrosis factor-alpha (TNFα), biomarkers of systemic inflammation. Subjects were stratified into groups of high and low systemic inflammation based on a composite measure of CRP and TNFα. There were 85 participants within the upper and lower quartiles of composite inflammation. The first 15 MRI-eligible participants from the upper quartile (age = 81.2 ± 3.6 years, education = 13.4 ± 2.5 years) and the first 14 participants from the lower quartile (age = 81.2 ± 6.1 years, education = 15.9 ± 1.8 years) were entered into the current investigation. Diffusion tensor imaging (DTI) data [4] were collected for all subjects on a 1.5T GE MRI scanner using a 2D spin-echo echo-planar DTI sequence with these parameters: TE=84.6 ms, TR=5.4 s, 36 oblique-axial slices, FOV=24 cm, slice thickness=3 mm, acquisition matrix=128×128, NEX=6, two b=0 s/mm^2 images, 12 diffusion directions at b-value=900 s/mm^2, for a scan time of 7 min and 33 s. Eddy-current distortions and motion were corrected by 3D affine registration, and the diffusion tensors were estimated in each voxel, using the software package TORTOISE [6]. Fractional anisotropy (FA) and trace maps were produced. FA maps were spatially normalized to population space using high-order diffeomorphic registration with Tract-Based Spatial Statistics (TBSS) [7]. Voxelwise t-tests were then used to compare FA and trace values between the groups with high and low levels of inflammation (through TBSS). Only differences with $p<0.05$ were considered significant after correction for multiple comparisons. Correlations between the composite measure of inflammation and age, sex and education, were also investigated.

Results: FA was significantly lower in several white matter regions in the group of subjects with high levels of inflammation than in the group with low levels of inflammation (Fig.1A): corpus callosum, internal capsule, external capsule, superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus, uncinate fasciculus, cingulum, corona radiata, posterior thalamic radiations. There were no regions with significantly lower FA in the group of subjects with low levels of inflammation. Trace was significantly higher in several white matter regions in the group of subjects with high levels of inflammation than in the group with low levels of inflammation (Fig.1B): corona radiata, corpus callosum, external capsule, posterior thalamic radiations. There were no regions with higher trace in the group of subjects with low levels of inflammation. No significant effects for age, sex, and education were detected.

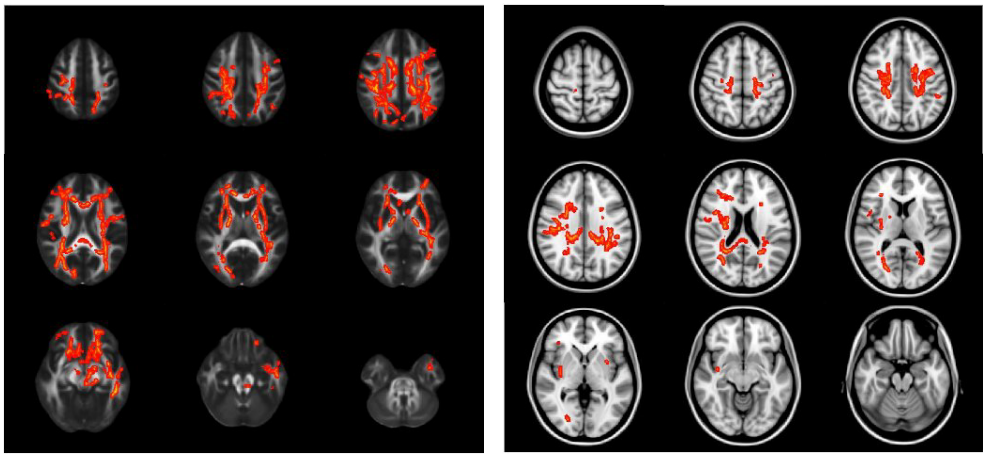

Figure 1: Regions with significantly lower FA values (left) and significantly higher trace values (right) in the group of subjects with high levels of inflammation compared to the group with low levels of inflammation.

Discussion: This work demonstrated that in elderly persons without dementia, high levels of systemic inflammation were associated with significantly lower FA and higher trace values in white matter throughout the brain. These results are in agreement with the findings of a recent study that showed an association of inflammation with the microstructural integrity in brain tissue of younger subjects (mean age approximately 18 years lower than that of the present study) [8]. However, the previous investigation considered only FA changes, while we considered both FA and trace changes. Furthermore, the recently published study showed FA changes primarily in frontal regions, while our study revealed FA and trace changes throughout the brain (likely due to the use of TBSS in the present study which limits the problem of multiple comparisons). Finally, our study used a diffusion-encoding scheme with twice as many diffusion directions (only 6 were used in the previous study), significantly improving DTI results [9]. In conclusion, our work suggests that high levels of systemic inflammation in the elderly may be a risk factor for reduced microstructural integrity of brain tissue.

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