

Systemic inflammation in non-demented elderly human subjects is associated with altered diffusion characteristics of brain white matter

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Introduction: Aging is associated with upregulation of inflammation-associated genes in the brain¹. Inflammation has been linked to functional disability², frailty³, and mortality⁴ in the elderly. The exact mechanisms underlying the development of inflammation and its effects on the brain are not fully understood. MRI has been used to study structural brain abnormalities linked to inflammation mainly in young and middle-age adults^{5,6}. The purpose of this study was to test the hypothesis that, high levels of systemic inflammation in a community sample of non-demented elderly individuals are associated with altered diffusion characteristics of brain white matter (WM).

Materials and Methods: Serum from 97 non-demented participants (age = 85.3 ± 5.7 years) of the Rush Memory and Aging Project⁷ was assayed for two circulating inflammatory markers, C-reactive protein (CRP) and tumor necrosis factor-alpha (TNF α). A composite measure of systemic inflammation was constructed as the sum of the z-scores of the log-transformed CRP and TNF α . All subjects were imaged with a 1.5 T GE MRI scanner (Waukesha, WI) using a) T1-weighted 3D MPRAGE with: TE=2.8 ms, TR=6.3 ms, preparation time=1000 ms, 1.25 mm³ voxel size, 160 sagittal slices, and two repetitions, b) T2-weighted FLAIR with: TE=120 ms, TR=8 s, inversion time=2 s, 3 mm³ voxel size, c) spin-echo EPI diffusion tensor imaging (DTI) with: TE=84.6 ms, TR=5.4 s, 10.5 mm³ voxel size, two b=0 sec/mm² volumes, 12 diffusion directions at b-value=900 s/mm², and 6 repetitions. For each participant, the MPRAGE and FLAIR data were co-registered, and WM hyperintense (WMH) lesions commonly present in the brain of elderly persons were automatically segmented using a support vector machine classifier, considering both the MPRAGE and FLAIR information. Bulk motion, distortions due to eddy currents and field non-uniformities were corrected in the DTI data, the B-matrix was reoriented, and diffusion tensors were estimated using TORTOISE⁸ (<http://www.tortoisediti.org>). Maps of the fractional anisotropy (FA), trace of the diffusion tensor, axial and radial diffusivity, were produced for each subject. The WMH lesion map of each participant was converted to the space of the corresponding processed DTI data. FA, trace, axial and radial diffusivity, and WMH information was projected onto a white matter skeleton using Tract-Based Spatial Statistics⁹ (TBSS). Linear regression was then used to test for associations of DTI parameters with the composite measure of systemic inflammation, while controlling for age, sex, level of education, and presence of WMH lesions. The null distribution was built using the "randomise" tool in FSL (FMRIB, University of Oxford, UK) and 5000 permutations of the data. Differences were considered significant at p<0.05, Family Wise Error (FWE) corrected. The Threshold-Free Cluster Enhancement (TFCE) method was used to define clusters with significant differences.

Results: Significant negative correlations between FA and systemic inflammation were detected in a large portion of the corpus callosum, in the left inferior fronto-occipital and superior longitudinal fasciculi, and several other WM regions (Fig. 1A). Significant positive correlation between FA and inflammation was found only in the cerebral peduncle and left corona radiata (Fig. 1A). In most voxels of the skeleton where higher systemic inflammation was associated with lower FA, both the trace and radial diffusivity were significantly positively correlated with inflammation (Fig. 1B, 1D). A few small WM clusters showed negative, as well as positive correlations between axial diffusivity and inflammation (Fig. 1C).

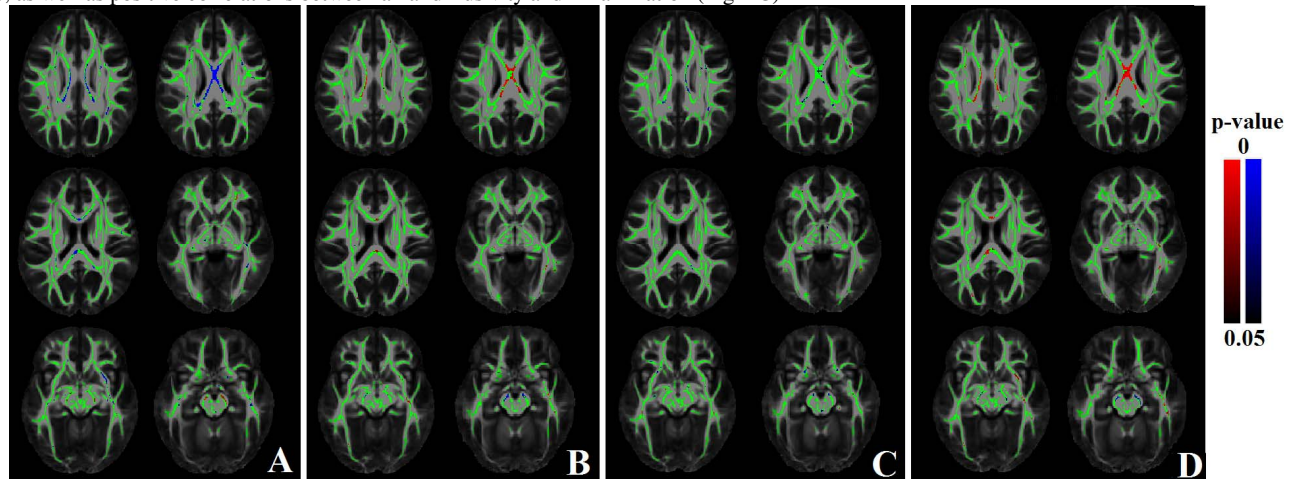


Figure 1: WM regions with positive (red) and negative (blue) correlations of (A) FA, (B) trace, (C) axial diffusivity, and (D) radial diffusivity with systemic inflammation, presented on the WM skeleton (green).

Discussion: In this work, it was demonstrated that, in elderly persons without dementia, high levels of systemic inflammation were associated with significantly lower FA in several WM structures. This relationship was driven, in most structures, by a significant positive correlation of systemic inflammation with radial diffusivity. Furthermore, radial diffusivity also explained most of the significant positive correlations between trace and inflammation levels. The negative correlation between WM FA and inflammation is in agreement with the only study previously published on this subject⁶. However, that work reported significant effects only in the frontal lobe. This may be due to the fact that the previous study focused on younger subjects, involved traditional voxel-based analysis (sensitive to misregistration), measured only one inflammatory marker (more noise), did not control for WMH on a voxel-by-voxel basis (less appropriate statistical model). Although the previous work translated lower FA in brain WM as lower microstructural integrity⁶, edema may be another potential explanation for our findings. Therefore, further histological investigation of WM microstructure is necessary. Nevertheless, high levels of systemic inflammation in non-demented elderly may be a risk factor for abnormal diffusion properties of brain WM.

References: [1] Lee CK, et al., *Nature Genetics* 2000;25:294-297. [2] Cohen HJ, et al., *J Gerontol A Biol Sci Med Sci* 1997;52:M201-208. [3] Ershler WB, et al., *Annu Rev Med* 2000;51:245-270. [4] Reuben DB, et al., *J Am Geriatr Soc* 2002;50:638-644. [5] Marsland AL, et al., *Biol Psychiatry* 2008;64:484-490. [6] Wersching H, et al., *Neurology* 2010;74:1022-1029. [7] Bennett DA, et al., *Curr Alzheimer Res* 2012;9:646-663. [8] Pierpaoli C, et al. *ISMRM* 2010, p.1597. [9] Smith SM, et al. *Neuroimage* 2006;31:1487-1505.