Relationship Among Markers of Cerebral Integrity with Aging
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Introduction: Fractional anisotropy (FA), derived from diffusion tensor imaging (DTI), is an index of white matter (WM) integrity and is known to decline with age. We aimed to clarify the underlying physiological mechanisms for age-related decline in FA values. To this end, we used a multimodal MRI protocol, which combined DTI with ¹H MRS and 3D WM lesion mapping protocols to ascertain changes in biologically important spectroscopy markers and white matter lesion burden associated with changes in FA values. The data were collected in two samples: middle-aged and elderly healthy adults. We hypothesized that a significant proportion of inter-subject difference in FA values will be explained by the difference in the concentrations of biologically important neurochemicals. Further, we hypothesized that these trends will be similar in both groups of subjects.

Methods: Using a Siemens 3-T MR system, data were acquired from 20 healthy middle-aged participants (mean age: 38.3 ± 5.7, range: 28-49 years) and 25 healthy elderly participants (mean age: 66.6 ± 6.2, range: 57-80 years). The imaging protocol consisted of a high-resolution diffusion tensor imaging (1.7x1.7x3-mm, 55 and 86 directions), a 3-D 1-mm³ turbo-spin-echo FLAIR sequence, and a single voxel PRESS spectroscopy sequence (TR/TE = 1500/135-ms, VOI ~ 3.4-cm³, NEX = 256, 1024 complex points, and 1.2k-Hz spectral width) performed bilaterally in a purely white matter voxel placed in the anterior corona radiata (ACR). The following measurements were performed in both cohorts: ACR FA values, the volume of deep-cortical and periventricular WM lesions, and metabolite concentrations of N-acetylaspartate (NAA), phosphocreatine plus creatine (tCr), and choline-containing compounds (tCho), quantified using LCMModel (1).

Results: The elderly adults showed an expected negative correlation between FA values and age (r=-0.314, p=0.135) (Figure 1A). This trend was less pronounced in the middle-aged group (r=-0.169, p=0.476). When combined, the trend was (r=-0.877, p=0.01). In the elderly group, NAA, tCr, and tCho were strongly and positively correlated (r=0.746, 0.561, 0.480, p<0.05). Table 1 shows the correlation between ACR FA values and WM lesions reached significance (r = -0.447, p<0.05). In the middle-aged group, NAA was the sole metabolite that correlated with ACR FA values (r=0.634, p<0.05), and there was no significant correlation between ACR FA values and WM lesions (r=-0.252, p=0.283).

Discussion: Our findings demonstrate that age-related decline in FA values is associated with a decline in NAA concentrations in both middle-aged and elderly individuals. This trend was more pronounced in the elderly group where a significant correlation was also observed with other metabolites, and the intersubject differences in metabolic concentrations and WM lesions volumes explained 62% of the variance in FA values. In the middle-aged group, intersubject differences in the NAA concentrations and WM lesion volumes explained 54% variance in the FA values. One of NAA’s many roles is in development and maintenance of cerebral myelination. It is transported from neurons to oligodendrocytes where its acetate moiety is removed and utilized for myelin synthesis (3). Our data suggests a potential mechanism for age-related decline in FA values; whereby, neuronal death leads to reduced axonal NAA concentrations and subsequent reduction in available acetate, which results in age-related impaired myelin lipid turnover and potentially lower FA values. This process appears to be accelerated in the elderly, where tCr and tCho are also significantly correlated with FA values. tCho and tCr concentrations are sensitive markers of cerebral inflammation (4) and compensatory metabolic processes (5), respectively, indicating compromised cerebral integrity. In addition, this data also suggests that WM lesions disrupt the health of white matter as indicated by higher lesion volume correlating with reduced FA values. Therefore, combination of multiple magnetic resonance techniques provides detailed insight into compromised white matter integrity as a function of aging.


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Figure 1. (A) This plot shows the decline in ACR FA values as function of age and (B) shows a representative 135-ms TE spectrum acquired from a 3.4-cm³ voxel placed in the anterior corona radiata.