Interrelationships of brain microstructural and macrostructural abnormalities in the oldest old.

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Background: Diffusion Tensor Imaging and Magnetization Transfer imaging have been recently used in geriatric neuroepidemiology (2, 3) to uncover the presence of microstructural brain abnormalities that would otherwise remain hidden with conventional MRI sequences and markers. However, the relationships between micro- and macro- structural abnormalities have not been examined in the oldest old. Understanding these relationships is useful to improve measurements of subtle brain changes with aging and to understand the mechanisms underlying responses to treatment and brain plasticity in older adults.

Hypothesis: Micro structural abnormalities of neurons and fibers (i.e.: fractional anisotropy [FA], mean diffusivity [MD], relative peak height [RPH]) are associated with greater burden of macro structural abnormalities (i.e.: white matter hyperintensities [WMH] volumes and gray matter atrophy index [AI]) and associations are stronger for those with lower burden of macrostructural abnormalities.

Methods: We analyzed an initial sample of 59 subjects from a large epidemiology study of 303 subjects with mean age of 82.8 years. Images were obtained with a 3T Siemens Trio Tim and acquired with the following pulse sequences, MPRAGE (224*224, Axial 176 slices, 1*1*1 mm, TR=2.3secs, TE=3.43ms), FLAIR (212*256, Axial 48 slices, 1*1*3 mm, TR=9.16 secs, Tl=2.5secs), magnetization transfer imaging (MTI) (Sagittal 120 slices, 256*256, 0.89*0.89*1.5 mm, ON and OFF pulses) and diffusion tensor imaging (DTI) (Axial 40 slices, 128*128, 13 directions repeated 4 times). Using in-house developed framework from publicly available software (ITK, FSL (1) and MIPAV), the following whole brain measures were calculated: total brain volume, white matter measures (WMH burden, Mean FA and RPH) and gray matter measures (AI, Mean MD and RPH). Partial correlation coefficients of between macrostructural and microstructural measures were obtained using SPSS, controlling for brain volume.

Results: All macrostructural and microstructural measures were significantly associated with each other except GM-RPH (Table 1). WM measures showed significant inverse correlations with the WM microstructural measures and the macrostructural GM measures showed a significant direct correlation with mean diffusivity. The white matter FA and normalized-WMH shows a significant quadratic relationship ($R^2= 0.374$), The quadratic curve showed the expected pattern of increased microstructural abnormality (decreased FA) leveling-off with continued increases in macrostructural abnormality (increased volume of WMH). The other measures do not support the model.

Conclusion: In this study we found significant correlations between several measures of micro- and macrostructural abnormalities in the oldest old. The pattern of the relationships between the imaging markers partially supports our hypothesis that the microstructural abnormalities detect brain changes even for lower burden of macrostructural abnormalities. The association between GM-RPH and AI indicates that MTI and DTI are measuring different aspects of GM changes. Future studies to explain these differential relationships are warranted.

References:
1. Smith et.al, NeuroImage, 23(S1): 208-219, 2004

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