Multivariate-defined spatial networks of age-associated atrophy

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Introduction: Structural magnetic resonance imaging (MRI) can be used to understand the morphological consequences of normal aging and how these changes impact cognitive abilities. Studies that have used manual tracing volumetric approaches or voxel-based morphometry (VBM) to understand the impact of age on neuromorphology suggest a relatively-greater age-associated loss of tissue in the frontal lobes than in more posterior regions. However, these studies generally have not considered the interrelationship among brain regions because they treat each unit of measurement (i.e., region-of-interest [ROI] or voxel) as an independent source of variance. Further, the exact impact of age-associated change in neuromorphology on cognitive function is still poorly understood.

By applying novel multivariate statistical analytic techniques to VBM, age-associated "networks" of grey and white matter tissue loss can be identified and the extent to which these age-associated patterns are expressed can be related to cognitive abilities. Multivariate approaches allow for the explicit examination of the spatial *distribution* of aging effects and infer connectivity by testing the relationship among the units of measurement. Here, we present data in which a version of principal components analysis (PCA), termed Scaled Subprofile Model (SSM), was applied to VBM to identify networks of age-associated atrophy in grey and white matter (Brickman, Habeck, et al., 2006). The degree to which each individual's pattern was expressed was related to performance on a brief battery of neuropsychological tests to elucidate the age-associated changes that potentially underlie age-related differences in cognition. To examine the stability of the identified topography, we determined how well the patterns could distinguish older from younger adults in a new sample that was independent of the one used to define the topography.

Methods: Subject groups included 113 participants, comprising medically, psychiatrically, and neurologically healthy Younger (n=84, mean age ± SD = 24.02 ± 3.83) and Older (n=29, mean age ± SD = 73.14 ± 6.72) adults. An independent sample of 42 younger adults (age = 23.38 ± 2.24) and 35 older adults (age = 72.29 ± 6.91) was considered for forward application of the covariance pattern. T1 weighted spoiled gradient (SPGR) images were acquired on all subjects with a 1.5T Philips Intera MRI scanner (TE/TR = 3ms/34 ms; flip angle = 45°; FOV = 240 mm x 240 mm; slice thickness/gap = 1.5mm/1mm); matrix = 256 x 256). Subjects were assessed with a brief neuropsychological battery including measures of attention, memory, language, and IQ.

Image analysis: Images were first spatially normalized to the same stereotactic space, defined by the Montreal Neurological Institute template, and then segmented into grey matter, white matter, and CSF using SPM. Data from younger and older subjects were combined and individual voxel densities were the measurement units used to conduct the multivariate analysis. The SSM approach captures the major sources of between- and within-group variation for both the grey and white matter images and produces a series of principal components (PCs). We sought to identify the optimal number of PCs that should be included as predictors in a linear regression model, using group membership (i.e., Younger vs. Older) as the outcome variable. The age-related covariance patterns were defined by the linear combination of PCs that best distinguished the two groups, while simultaneously accounting for a major portion of the variance in the data. The defined patterns were prospectively applied to the second sample to probe to what extent they were manifest and could be used to distinguish age groups.

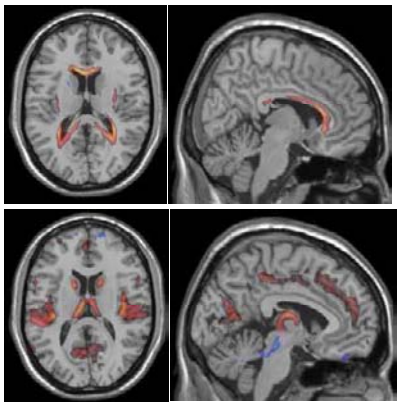

Fig 1. Axial and sagittal view of white (top) and grey (bottom) regions implicated in the covariance analysis. Negative factor loadings, indicating collateral age-related decreases, are displayed in "hot" colors.

Results: Grey and white matter covariance patterns that distinguished between groups were identified and comprised the linear combination of 7 PCs for grey matter and 6 PCs for white matter. Negative factor loadings, indicating collateral age-associated decreases in density, were observed throughout the entire brain, including cortical and subcortical regions (see Figure 1). As expected, the mean expression of this pattern was significantly greater in older subjects than in younger subjects, t (111) = 19,02, p < .001 and specificity and sensitivity for classification were greater than 98% and 92%, respectively, for grey and white matter (see Figure 2). When the covariance patterns were prospectively applied, there was excellent group classification accuracy for grey matter (97% accuracy, odds ratio = 5.34, p = .04) and for white matter (91% accuracy, odds ratio = 2.97, p < .001; see Figure 2). The degree of grey and white matter pattern expression was significantly associated with performance across neuropsychological tests of attention, memory, and executive function; these relationships generally remained significant when controlling for age.

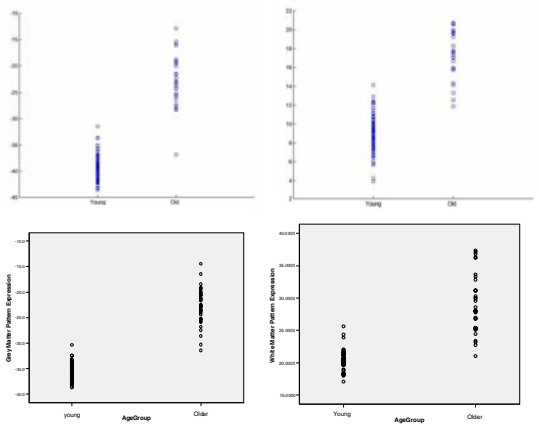

Fig 2. Distribution of the degree to which younger and older participants expressed the grey (left) and white (right) matter topographies (top) and forward application of the same topographies to independent sample.

Discussion: The results suggest that identifiable networks of widespread grey and white matter regions systematically decline with age and that pattern expression is linked to age-related cognitive decline. Further, the identified patterns discriminated older from younger adults in an independent sample with high levels of accuracy, suggesting the stability of these age-associated networks across samples. Multivariate approaches to analyze structural MRI data can compliment univariate approaches by identifying the distribution of the effects of aging in the brain. Future work should focus on the combination of multivariate analyses with the identification of moderators and mediators in the relationships among normal aging, neuromorphology, and cognition.