Quantitative fiber tracking in the normal aging brain: neuropsychological correlates

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Introduction

Normal aging is accompanied by declines in selective cognitive and motor functions[1]. Concurrent declines in white matter microstructure integrity, which are detectable with diffusion tensor imaging (DTI)[2], possibly contribute to waning function. Regional analysis of white matter indicates that fractional anisotropy (FA) decreases and diffusivity increases with age[3]. To date, one aging study used quantitative fiber tracking but reported only on the corpus callosum[4]. Here, we used quantitative fiber tracking to examine age effects on commissural and association fiber tracts and tested functional correlates of these white matter systems.

Methods

Volunteers were 12 young (25.5±4.3yrs) and 12 elderly (77.6±4.9yrs), right-handed, non-smoking, healthy men and women, recruited from the local community. The groups did not differ significantly in education (young=16.25±2.2, elderly=17.08±2.0 yrs) or estimated general intelligence (young IQ=113.67±5.7, elderly IQ=118.17±5.9). DTI data were acquired with an 8-channel head coil at 3.0T after higher-order (nonlinear) shimming. DTI and FSE data were collected with the same slice locations: DTI (2D echo-planar, TR=7300ms, TE=86.6ms, thickness=2.5mm, skip=0, locations=62, b=0 (5 NEX)+15 noncollinear diffusion directions b=860s/mm^2 (2 NEX)+15 opposite polarity noncollinear diffusion directions b=860s/mm^2 (2 NEX), FOV=240mm, x-dim=96, y-dim=96, reconstructed to 128x128, 4030 total images); FSE (2D axial, TR=7850ms, TE=17/102ms, thickness=2.5mm, skip=0, locations=62). T1-weighted SPGR (3D axial IR-prep, TR=6.5ms, TE=1.6ms, thick=1.25mm, skip=0, locations=124) images were precisely aligned, such that 2, 1.25mm slices subtended each 2.5mm thick slice. A fieldmap was generated from a gradient recalled echo sequence, and all DTI images were un-warped with FSL PRELUDE.

To achieve common anatomical coordinates across subjects, SPGR data for each subject were aligned with a brain template made from these 24 subjects ("SRI24 atlas")[5] with group-wise nonrigid registration[6,7]. Each subject's common space SPGR transformations were applied to that individual's FA data sets, which were reformatted into common space to create a group average FA data set. Fiber tracts were identified on the group-average FA images with single point landmarks in 3 dimensions on axial or coronal slices. The commissural fibers (genu, splenium, anterior commissure) were identified at their maximum in the midline; the fornix was also identified in the midline. Bilateral association tracts were identified with anterior-posterior locations: inferior longitudinal, cingulate (superior, posterior and inferior portions), and uncinate fasciculi (Fig 1c,d).

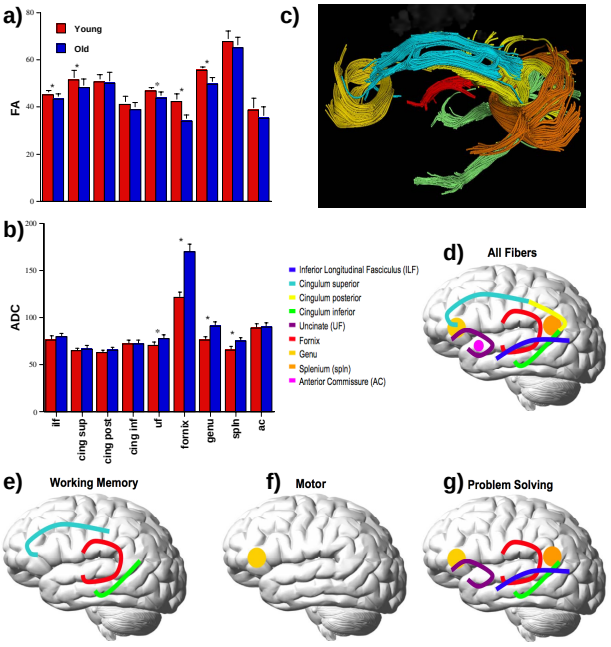

Fig 1: a) mean±SE FA, b) mean± ADC, for young (red) and elderly (blue) subjects. c) Fiber tracking example from a single subject. d) Schematic of all fibers quantified. Correlations between FA or ADC in fiber tracts (marked in color) and e) Working Memory, f) Motor, or g) Problem Solving Behavioral Factors.

The fiber tracking routine[8,9] distributed by G. Gerig [www.cs.unc.edu] used a target-source convention that restricted the fibers to ones originating in source voxels and passing through target voxels. In common space, each landmark was dilated with a morphological operator to produce a 5mm cube as the fiber-tracking target. Sources were 3mm thick planes: a) 5mm bilateral to commissural targets; b) 5mm anterior and 5mm posterior to association and fornix targets. For each subject, the targets and sources for fiber tracking were mapped to that subject's native image space with a numerical inversion of the transformation to common space. Targets, sources, and tensor matrix in native space were passed to the fiber tracking routine, the output of which was a 3D graphic of the fiber paths plus a table of locations. Identified fiber tracts were warped into common space, as were the subject's FA and apparent diffusion coefficient (ADC), for quantification by evaluating DTI metrics in all voxels identified in each fiber's extent.

Results

The older group had disproportionately lower FA and higher ADC in the genu than splenium. Group-by-hemisphere ANOVAs and t-tests indicated lower FA in the inferior longitudinal fasciculus, superior cingulate, uncinate, fornix, and genu and higher ADC in the uncinate, fornix, genu, and splenium of the older than younger groups (p=.034 to .0001; Fig 1a,b). Because group-by-hemisphere interactions were nil to modest, bilateral values were averaged for correlational analyses.

Behavioral test scores were subject to principal component analysis. Three factors emerged: Working Memory (phonological fluency, forward and backward digit span, forward block span, Sternberg verbal memory task), Motor (fine finger movements, grooved pegboard, motor and big/little circle reaction time tasks), and Problem Solving (semantic and figural fluency, backward block span, Stockings of Cambridge, Intra-extra dimensional set-shifting, comprehensive trails, combined postural sway-problem solving task). Problem Solving scores of the older were lower than those of the younger group (p=.0005). Regression analysis across all subjects revealed that Working Memory correlated with inferior cingulum FA (r=.57, p=.0035), superior cingulum ADC (r=-.45, p=.027), and fornix FA (r=.45, p=.028) and ADC (r=-.41, p=.045; Fig 1e). The Motor measure correlated with genu ADC (r=-.45, p=.029; Fig 1f). The Problem Solving measure correlated with inferior cingulum, inferior longitudinal fasciculus, uncinate, fornix and genu FA (range r=.43 to .64, p=.03 to .0008) and uncinate, fornix, genu and splenium ADC (range r=.45 to .66, p=.02 to .0004; Fig 1g).

Discussion and Conclusion

Quantitative fiber tracking revealed aging effects in FA or ADC in 6 of the 9 quantified fiber systems. Age effects were prominent in anterior tracts, specifically, the uncinate, fornix and genu. Functional correlates of these age effects provide convergent validity to the biological meaningfulness of the fiber tracked loci and metrics. Conversely, the DTI-functional correlations support the possibility of regional degradation of white matter fiber integrity as a biological source of age-related functional compromise.

Acknowledgements

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