Age-Dependent Differences in Brain Tissue Microstructure Assessed with Neurite Orientation Dispersion and Density Imaging

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BACKGROUND

- Normal human aging is accompanied by alterations in brain structure in both white and gray matter, and these changes can be visualized with modern imaging techniques (Pannese, 2011).
- Neurite Orientation Dispersion and Density Imaging (NODDI) is a technique that uses magnetic resonance imaging (MRI) to assess the density of axons and dendrites (neurites), the amount they disperse away from each other, and overall water diffusion (Zhang et al., 2012).
- In conjunction with tests of memory and executive function, NODDI may be able to resolve early brain changes and their relation to cognitive functioning with more specificity than traditional brain imaging techniques.

OBJECTIVES

- To determine how age affects the density of neurites and isotropic water diffusion in a group of cognitively healthy older adults.
- To determine if NODDI measures relate to cognitive function.

METHODS

Participants:
- N=117 cognitively healthy adults (mean age 61.7 years, SD 6.1) enriched for parental family history of Alzheimer's disease (AD) and *APOE* ε4 genotype from the Wisconsin Registry for Alzheimer's Prevention (WRAP) and Alzheimer's Disease Research Center (ADRC) cohorts, both designed to identify biological and lifestyle risk factors associated with development of subsequent AD.

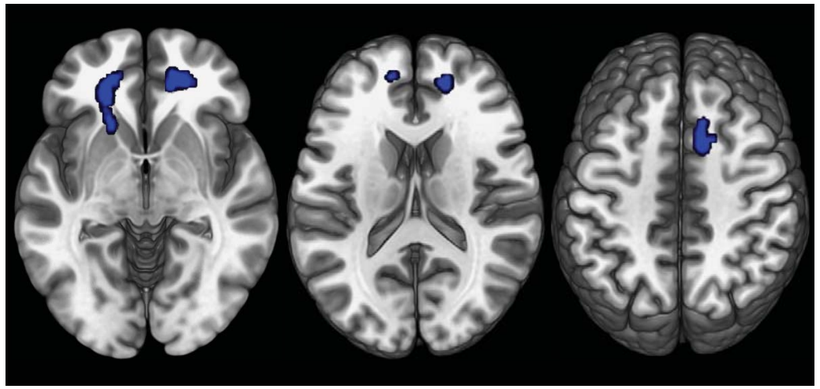
Brain Imaging:
- Participants underwent a 15-minute Hybrid Diffusion Imaging (HYDI) protocol, which acquires 126 diffusion-weighted measurements including those at substantially higher b-values than traditional diffusion tensor imaging, up to 7,500 s/mm^2. Modeling was accomplished with NODDI to produce maps of neurite density, orientation dispersion, and the volume fraction of isotropic water diffusion.

Cognitive Data Collection:
- Subjects completed a comprehensive neuropsychological battery, including tests of episodic memory and executive function: the Rey Auditory Verbal Learning Test (RAVLT), Trail Making Test Part B, and the Mini Mental State Exam (MMSE). Across participants, the average time between brain imaging and neuropsychological testing was 110 days, SD=128 days.

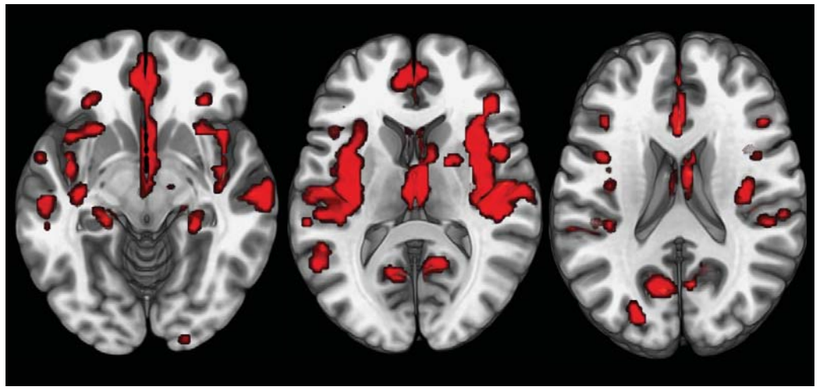
Statistical Analyses:
- NODDI Parameters: Separate voxel-wise regressions were performed in Statistical Parametric Mapping (SPM) 12 for each of the NODDI parameters as dependent variables and age as the independent variable of interest, controlling for the covariates of sex, *APOE* ε4 status, and family history of AD. Significance was inferred at $p<0.05$ with FWE correction with cluster extent > 25 voxels.
- Cognitive Measures: We performed partial correlations between NODDI measures in the statistically significant regions with scores on each cognitive test (controlling for age, sex, FH+, and *APOE* ε4) in SPSS 22.

RESULTS

NEURITE DENSITY DECREASES WITH AGE

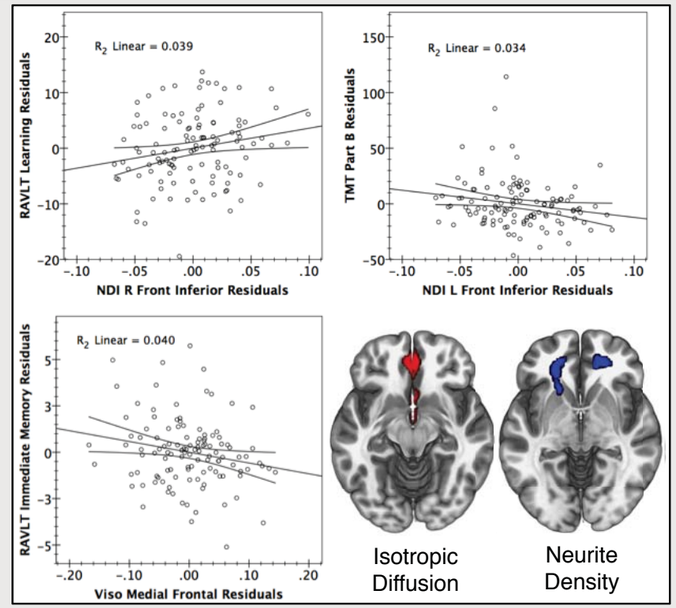


ISOTROPIC WATER DIFFUSION INCREASES WITH AGE



Sample Characteristics	Mean (SD)
Number of Participants	117
Age (Years)	61.7 (6.1)
Sex (% Female)	62%
APOE4 Genotype (%)	40%
Family History of Alzheimer's Disease (%)	72%
Education (Years)	17 (2.5)
MMSE	29.3 (1.0)
RAVLT Trial 1 (Immediate Memory)	6.7 (1.9)
RAVLT Trials 2-5 (Learning)	45.3 (7.0)
RAVLT Delay (Delayed Memory)	10.8 (3.1)
TMT Part B (Seconds)	61.0 (25.3)
Days Between Cognitive Testing and MRI	110 (128)

COGNITIVE SCORES



DISCUSSION

- Widespread increases in water diffusion were observed throughout the brain with increasing age, as well as decreases in neurite density in frontal white matter regions.
- These results suggest that NODDI is capable of measuring age-related brain changes and cognitive functioning, findings that are in agreement with histological studies as well as other diffusion-weighted imaging techniques (Dickstein et al., 2013; Anderson and Rutledge, 1996)
- This study sheds light on the processes underlying normal brain development, knowledge that is crucial for differentiating healthy aging from pathology associated with Alzheimer's disease and other dementias.

WORKS CITED

- Pannese, E. 2011. Morphological changes in nerve cells during normal aging. Brain Structure & Function 216(2), 85-9. doi:10.1007/s00429-011-0308-y.
- Zhang, H. et al (2012), 'NODDI: practical in vivo neurite orientation dispersion and density imaging of the human brain." Neuroimage, vol. 61, no. 4, pp. 1000-1016.
- Dickstein, D.L., Weaver, C.M., Luebke, J.I., Hof, P.R. 2013. Dendritic spine changes associated with normal aging. Neuroscience 251, 21-32. doi:10.1016/j.neuroscience.2012.09.077.
- Anderson, B., Rutledge, V. 1996. Age and hemisphere effects on dendritic structure. Brain 119, 1983-90.

ACKNOWLEDGMENTS

This material is based upon work supported by a NSF Graduate Research Fellowship under Grant No. DGE-1256259 to APM. Any opinions, findings, and conclusions or recommendations expressed in this material are those of the authors(s) and do not necessarily reflect the views of NSF. This research was also supported by NIH grants R01AG037639 (BBB), P50 AG033514 (SA), and AG027161 (SCJ).

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