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Profiles of White Matter Microstructure in a Population-Based Cohort of Elderly Patients

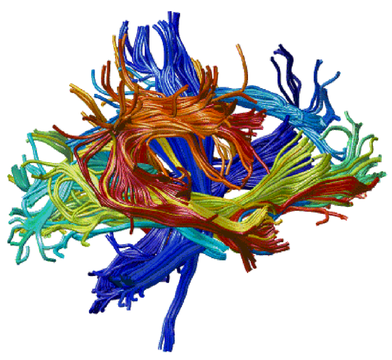
Daniel Peterson[1], Natalie Koh[1], Mary Askren[1], Chris Gatenby[1], Tara Madhyastha[1], Thomas Grabowski[1]

[1]Integrated Brain Imaging Center (IBIC), University of Washington, Seattle, WA

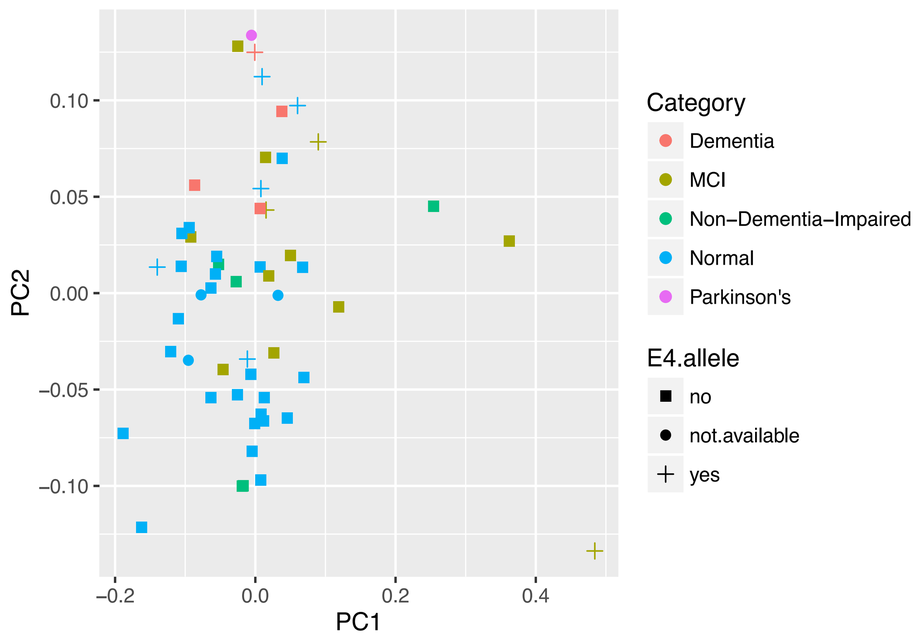
Introduction

Neurodegenerative diseases are among the most costly to society. While much has been learned about the underlying mechanism of neurodegeneration in recent decades, improvements in the standard of care remain elusive. One barrier in translating research to the clinic is that studies are often conducted with a carefully chosen set of inclusion and exclusion criteria in order to reduce uncontrolled variation in the sample, while in the clinic patients often present with mixed pathology and complex comorbidities.

In this study, we present an exploratory cross-sectional analysis of white matter microstructure in a population sample of elderly patients that were recruited as a sample of the general population, some of whom later went on to develop neurodegenerative diseases.



20 Major White Matter Tract Measures
(Mean Fractional Anisotropy in Each Tract)



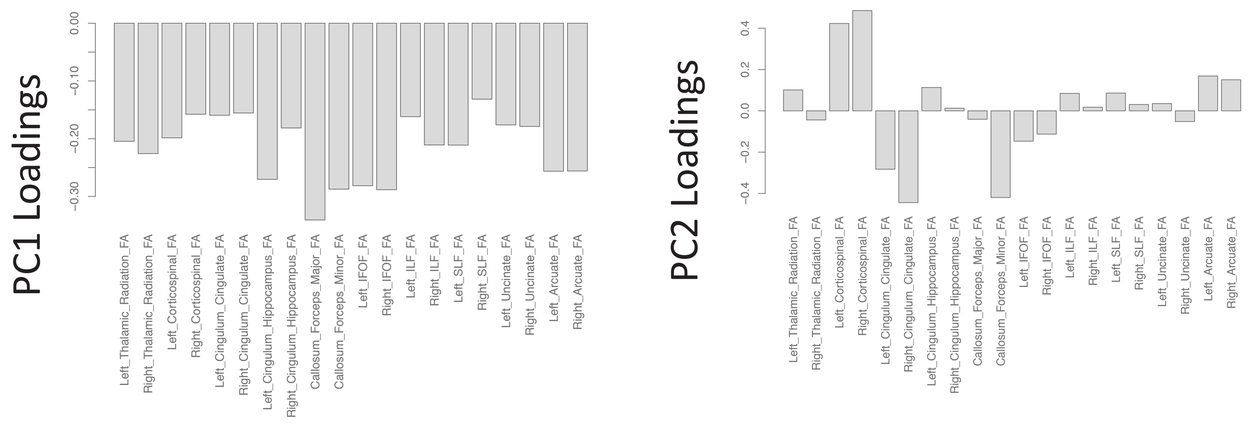


Figure 1: *Mean FA values of 20 major white matter tracts were subjected to Principal Components Analysis. PC2 was found to be sensitive to disease status.*

Methods

Sample

Subjects were recruited as part of a longrunning study called Adult Changes in Thought (ACT)[Montine 2012]. The ACT study approaches subjects selected at random from the Group Health Cooperative health insurance system, and follows their outcomes longitudinally. ACT phenotyping includes genetic testing for APOE status. Neuroimaging data were collected on 54 Subjects (28 F, 26 M), Age Mean(SD)= 79.28 (6.1). Poor data quality and contraindications to MRI were the only exclusion criteria. Diffusion data were acquired at 3T.Subsequent to enrollment, subjects were grouped into the following categories, based on expert consensus diagnosis: Parkinson's Disease (n=1) Dementia (n=4), Mild Cognitive Impairment (n=12), Normal Cognition (n=32) and Non-Dementia Impaired (n=5). This last category included individuals with psychiatric disorders, continuing symptoms of traumatic brain injury, or other CNS disorders not on the neurodegenerative spectrum.

Imaging

Diffusion data were acquired at 2mm isotropic resolution, along 64 directions, plus two b0 images. Distortion correction was accomplished with FSL's 'topup' [Andersson 2003], and motion correction with 'eddy'[Andersson 2016]. The DTI model was fit using RESTORE [Chang 2005]. The microstructure of major white matter tracts was assessed with Automated Fiber Quantification (AFQ)[Yeatman 2012].

Analysis

Mean Fractional Anisotropy (FA) values of 20 major white matter tracts were extracted for Principal Components Analysis (PCA), as implemented in R [R Development Core Team 2008]. No diagnostic, behavioral or demographic information was included in the PCA. Group differences were assesed with Wilcoxon rank-sum tests, and correlations with Spearman rho.

Results

- The first principal component (PC1) was found to explain 40% of the variance, and PC2 was found to explain 13%
- PC1 was correlated with in-scanner framewise displacement (p=0.0019), as well as with age (p=0.008). PC1 loadings were fairly uniform, indicating that PC1 is similar to a FA global mean.
- The second principal component (PC2) was found to be sensitive to disease status (Figure 1). PC2 was higher in subjects with MCI or Dementia, compared to subjects with Normal Cognition (p=0.0052). Additionally, PC2 was higher in subjects with an E4 allele, regardless of category (p=0.03) as well as among those with Normal Cognition (p=0.013).
- Inspection of the loadings on PC2 revealed a large contribution from the forceps minor, and from the left and right cingulum bundle (Figure 2). Both of these FA measures were decreased in subjects with MCI or Dementia, compared to subjects with Normal Cognition (p=0.0098 for the cingulum, p=0.00023 for the forceps minor).

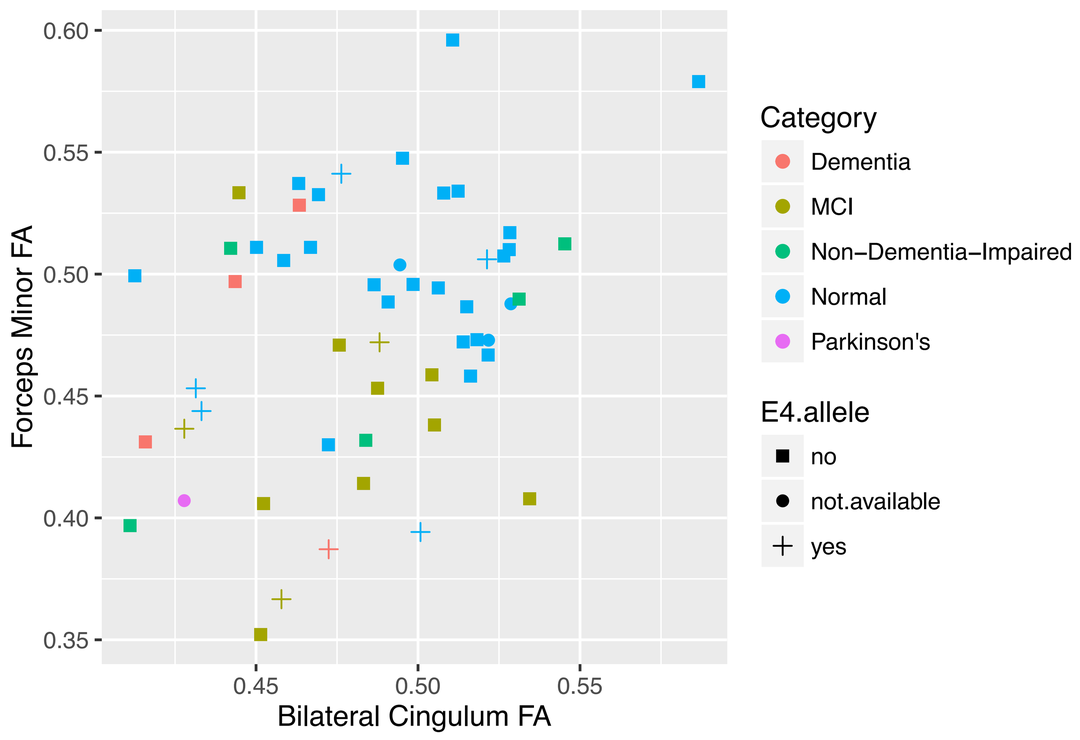


Figure 2: *Inspection of the loadings on PC2 revealed a large contribution from FA within the forceps minor, and the left and right cingulum bundle. Both these measures were decreased in subjects with MCI or Dementia, and among cognitively normal subjects with an APOE E4 allele, which carries an increased risk of cardiovascular and neurodegenerative disease*

Conclusions

By applying PCA to measures derived from an automated fiber-tracking and parcellation procedure, we were able to identify a mode of variation that is associated with cognitive status. Cognitively normal patients with the APOE-E4 allele strongly express this mode, and show a white matter microstructural profile that is similar to impaired patients. This includes reduced FA in the forceps minor and the cingulum bundle. Both of these tracts form part of the structural basis of the default mode network [Greicius 2009].

This investigation demonstrates that measures derived from DTI-based fiber-tracking can be sensitive to disease status in a heterogeneous, clinically realistic cohort. These results suggest that FA in the cingulum bundle and in prefrontal comissural tracts may serve as a biomarker for neurodegenerative disease. These subjects will be followed longitudinally, and these measurements may be useful in predicting future cognitive status.

References

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Correspondence may be sent to djpeters@uw.edu

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