Enigma DTI: Toward multicenter genome-wide association analysis of white matter integrity

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KP and JN contributed equitably to this research

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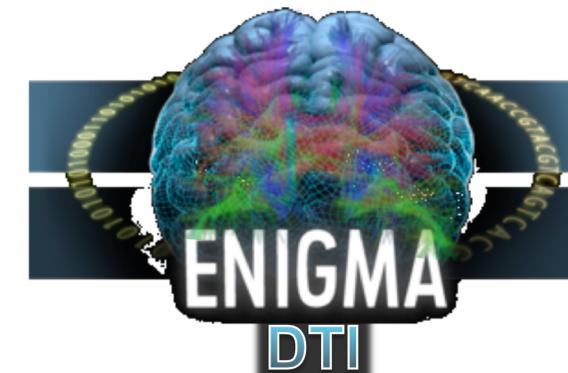
Introduction

- Fractional Anisotropy (FA) of cerebral WM is sensitive index of the microstructural integrity
- FA is a sensitive index of brain maturation, aging and disorders
- Individual FA values are under strong genetic control: 40-60% of its intersubject variability is explained by genetic factors
- Localization of genes that exert control over FA values is important for understanding normal and disorder-specific variations in brain integrity.

Specific Aims

- Develop multi-center DTI atlas and TBSS template
- Validate the template by comparing heritability measurements across the cohorts
- Perform a multi-center, mega-genetic, GWAS analysis of tract-wise and voxel-wise FA values
- Develop efficient and accurate corrections for multiple testing

Methods

- Subjects: 2,000+ data sets have been committed. Including founding sites
  - *GOBS : 862 (Age=44.1±14.6, Age range=20-85 years) randomly selected from 50 large families.*
  - *QTIM : 500 twins and siblings (263F, Age range=20-29 years) from 263 families.*
  - *BFS : 129 (Age range=16-60 yeas), unrelated healthy controls.*
  - LBC: 500 (Age range = 50-90 years), *unrelated healthy controls.*

HARDI-DTI data were collected with various protocols at 3T and 1.5T.

Results: Enigma TBSS Template and Atlas

- Built based on 400 subjects from founding sites
  - 100 subjects per site
- Improved resolution of peripheral WM tracts (Fig. 1)
- Greatly reduced warping effort (20-60%)
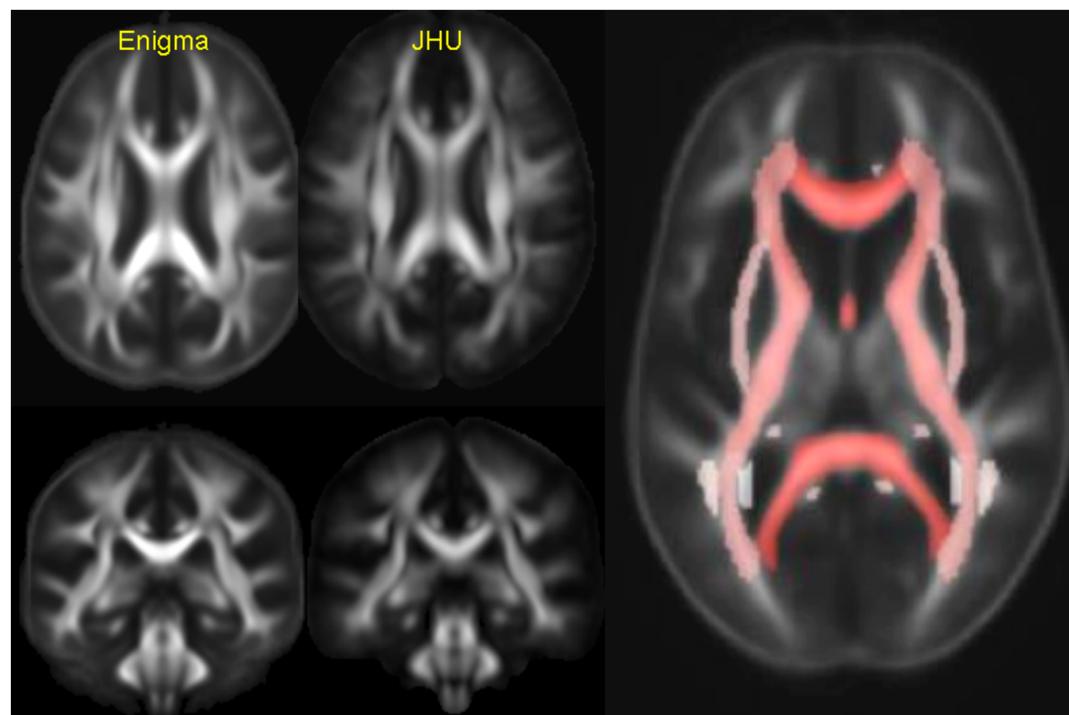
Figure 1. Enigma and JHU templates   Figure 2. JHU labels on Enigma template

- Fully compatible with JHU atlas (Fig. 2)
- Includes manually detailed TBSS skeleton
- Enigma atlas will extend JHU labels to periphery

Results: Comparison of tract-wise heritability

- Heritability for 9 major, JHU WM tracts was calculated for GOBS (pedigree: SOLAR) and QTIM (twins: A-E model)
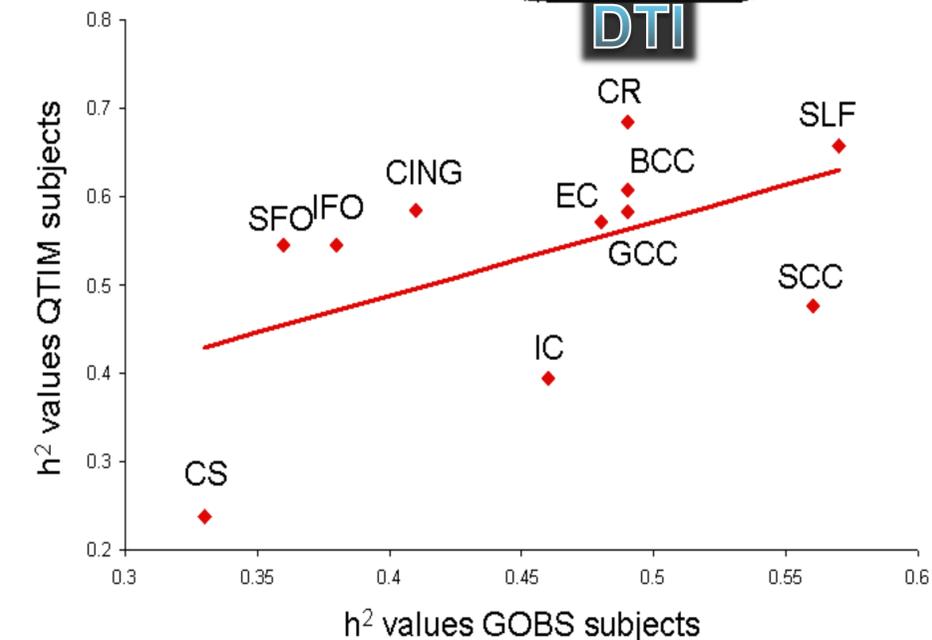
Figure 3. Scatter plot of tract-wise heritability values for 9 major tracts calculated in GOBS and QTIM samples

- A positive correlation of (r=0.51) between tract-wise heritability calculate for GOBS and QTIM samples (Fig. 3)

Conclusions

I)   Enigma experience provides support to multi-center, mega-genetic imaging studies
II) Enigma template and methods are available at http://www.nitrc.org/projects/se_linux/
III) Novel GWAS and multiple testing algorithms are being developed
IV) Other sites with genetically informed subjects are invited to join at http://enigma.loni.ucla.edu/