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Genetic Influences on Microstructure of White Matter. A tract-based study of DTI-derived Parameters

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Introduction

We examined genetic control over measures of white-matter microstructure in randomly-ascertained large extended pedigrees. In this preliminary study we examined genetic influence over intersubject variability in measurements extracted from magnetic resonance diffusion tensor imaging (DTI)

Methods

Subjects: 470 subjects (182/288 M/F) from 39 families, ages 19-90
Imaging: Hi-res (1.7x1.7x3 mm) SE-EPI, 55 dir (b=0,700)
FSL DTI Processing:

- Tensor fitting: FDT
- Intersubject Normalization: TBSS
- By tract-measurements: JH-DTI atlas (Figure 1)

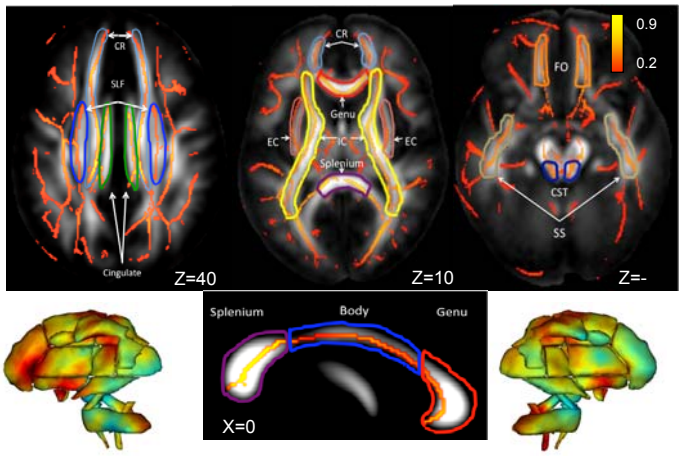

Figure 1. Average FA/MD/L1/$L_\perp$ were calculated for 12 major WM tracts

Results-Heritability

Parameter	Average h^2	N of significant tracts
MD	.24±.09	9
L1	.19±.08	7
$L_\perp$	.31±.07	11
FA	.53±.11	12

Table 1. Heritability for whole-brain average DTI parameters

FA values showed the highest heritability among DTI parameters (Table 1)
•Average FA values for all major tracts were heritable (Table 2)
• Transverse Diffusivity ($L_\perp$) was second most heritable parameter
• Analysis of aging trends provides a physical explanation for differences in heritability

- Diffusivity is a function on the temperature
- Transverse diffusivity is a measurement of myelination
- Ratio of $L_\perp$ /L1 has higher correlation with age than either $L_\perp$ (r2=0.38) or L1 (r2=0.14) (Figure 2)
  - This eliminates intersubject variability due to body temperature

Result (cont)

Tract	Fiber^	Interconnections	Heritability*	p-value
Corpus Callosum (CC)	C	Medial Cerebral Hemispheres	0.667 (0.10)[a,c,d]	$9.7x10^{-11}$
Internal Capsule (IC)	P	Subcortical/Brainstem/Cortex	0.303 (0.12)[a]	$3.2x10^{-03}$
Corona Radiata (CR)	P	Cortical/Subcortical	0.560 (0.11)[a,b,d]	$4.4x10^{-08}$
Posterior Thalamic Radiation (PTR)	P	Thalamus/Parietal lobe	0.411 (0.10)[a,c]	$3.0x10^{-06}$
Sagittal Stratum (SS)	A/P	Subcortical/Temporal/Occipital	0.385 (0.12)[a]	$2.4x10^{-04}$
Superior Fronto-Occipital Fasciculus (SFO)	A	Frontal/Parietal/Occipital	0.418 (0.10)[a,d]	$3.4x10^{-05}$
External Capsule (EC)	A	Frontal/Temporal/Occipital	0.421 (0.11)[a]	$2.7x10^{-05}$
Inferior Fronto-Occipital Fasciculus (IFO)	A	Lateral Frontal/Occipital	0.397 (0.13)[a]	$3.1x10^{-04}$
Superior Longitudinal Fasciculus (SLF)	A	Frontal/Temporal/Occipital	0.624 (0.11)[a]	$1.1x10^{-08}$
Uncinate Fasciculus (UNF)	A	Inferior Frontal/Anterior Temporal	0.508 (0.13)[a]	$3.2x10^{-05}$
Cingulum (CG)	A	Cingulated Gyrus/Hippocampus	0.432 (0.13)[a,b]	$1.8x10^{-04}$

Table 2. Heritability Estimates for White Matter Tracts
^C=Commissural, P=Projection, A=Association; *Heritability estimate, h^2, and standard error; Significant Covaraites: a. Age, b. Sex, c. Age x Sex, d. Age^2

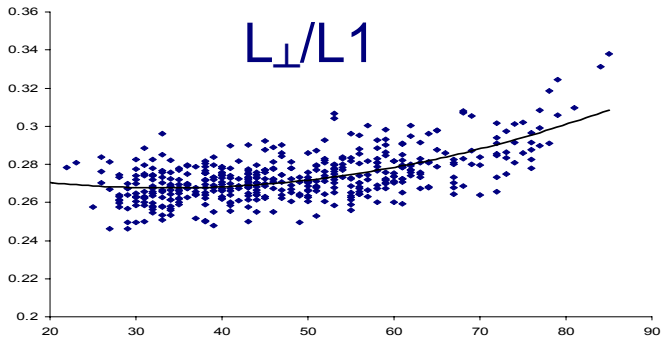

Figure 2. Ratio of $L_\perp$/L1 versus age

Results-Linkage

No significant linkage found
High heritability and absents of linkage indicates that:
• FA/Myelination is a complex polygenetic trait
• Myelination is a dynamic process. Degree of myelination varies with age

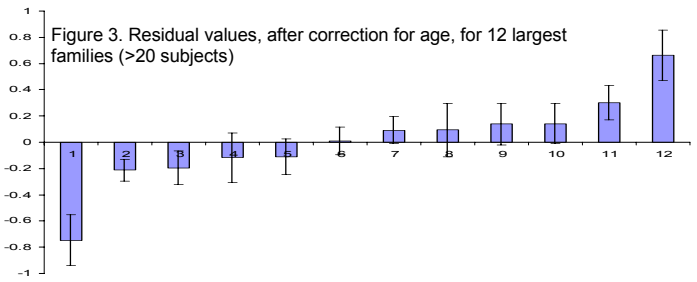

Figure 3. Residual values, after correction for age, for 12 largest families (>20 subjects)

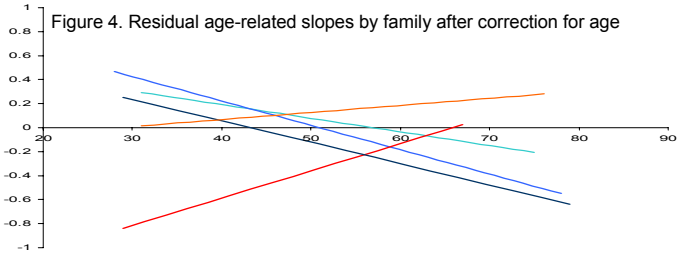

Figure 4. Residual age-related slopes by family after correction for age

Acknowledgements

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