ENVIRONMENTAL FACTORS SURPASS GENETIC INFLUENCES IN DETERMINING FIBER MICROSTRUCTURE AS THE BRAIN DEVELOPS: DIFFUSION TENSOR IMAGING IN 705 TWINS

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Introduction (574 characters): In young adults, white matter fiber integrity is under strong genetic control and correlates with intellectual performance [1]. However, it is still unclear how genetic influences vary as the brain's fiber circuitry develops. Here we scanned 705 twins and their siblings using diffusion tensor imaging (DTI), an imaging method exquisitely sensitive to white matter integrity, quantified by the fractional anisotropy (FA) of water diffusion. FA is a widely accepted index of white matter integrity. By fitting a quantitative gene-environment interaction model [2] at each point of the brain, we mapped dynamic changes in white matter heritability as the brain matures.

Methods (1,213 characters): We acquired 30-gradient DTI at 4 Tesla from 705 twins and their non-twin siblings, including 531 healthy adults (aged 20 or older) and 174 adolescents (aged 12 and 16), from 358 different families. High angular resolution diffusion-weighted scans (b=1145.7 s/mm^2). were acquired using single-shot echo planar imaging with a twice-refocused spin echo sequence, to reduce eddy-current distortions. Total scan time was 3.05 minutes. We used FSL software (http://www.fmrib.ox.ac.uk/fsl/) to pre-processing and linearly align the diffusion images. FA maps computed from the linearly-registered DT data were fluidly registered to a mean FA template. We assessed age-related differences in heritability of white matter integrity between adolescence (age < 20 years) and adulthood (age$\geq$ 20 years) by modeling age as a moderator that linearly interacts with additive genetic and unique environmental variance components [2]. Direct age effects on FA were modeled. We used the false discovery rate method to adjust for multiple comparisons across voxels.

Results (633 characters): Between age 12 and adulthood, brain fiber organization and coherence, measured by FA, increased by up to 10% in most of the white matter (**Figure 1;** MNI coordinates of the slices, in mm, are shown at the bottom). We also detected significant age x heritability interaction. White matter integrity in the left inferior and middle frontal gyri, the splenium of the corpus callosum on the left, and the right inferior longitudinal fasciculus (ILF)/inferior fronto-occipital fasciculus (IFO), was significantly more heritable in the adolescents than adults. In adolescents, around 70-80% of the variation in FA was attributable to genetic factors, but in adults, only 30-40% of the variation in FA was attributable to genetic factors.

Conclusion (287 characters): Heritability of white matter integrity decreases as subjects get older. Environmental influences, e.g., learning, education, life experiences, diet, and exercise, start to dominate and increasingly determine brain fiber networks as one matures into adulthood.

[1] Chiang MC et al. (2009). *J Neurosci*. 29:2212-2224.

[2] Purcell S (2002). *Twin Res*. 5:554-571.

Figure 1