Genetic associations of brain structure to serum transferrin: an MRI and DTI analysis (N=615)

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Introduction

Iron and the proteins that transport it are necessary for normal brain function. Iron is a vital factor for oxidation processes within cells; compared to other organs, oxidation proceeds at one of the highest rates in the brain (Connor et al. 1992). **Iron deficiency** in children leads to **poorer cognitive achievement** (Halterman et al. 2001) and alters dopamine metabolism, particularly in the caudate and putamen (Nelson et al. 1997). **Iron overload** also adversely affects the brain; **neuroimaging** shows abnormal brain iron concentrations in **Huntington's** (Jurgens et al. 2010) and **Alzheimer's** (Bartzokis et al. 1994) diseases. Almost all iron in the plasma is bound to **transferrin** - the protein that transports iron and delivers it to the brain and other tissues. Here we employed a **twin design**, comparing **identical** (MZ) and **fraternal** (DZ) twins, to assess genetic contributions to variability in brain structure (MRI) and microstructure (DTI). We tested whether plasma transferrin levels and variants in transferrin-related candidate genes were associated with differences in the **healthy** adult brain.

Methods and Findings

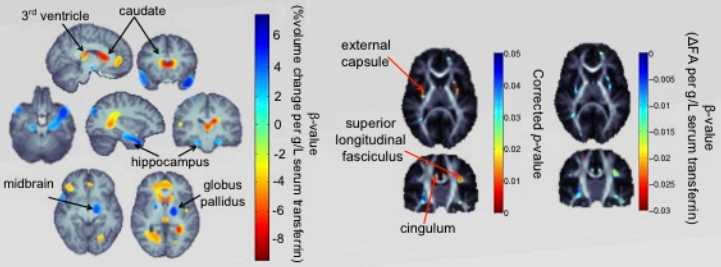
•**Subjects**: High magnetic field (4-Tesla) structural images were acquired from 615 genotyped healthy young adult twins and siblings (mean age: 23.5+/-2.1 years). 544 were also scanned with 4T diffusion tensor imaging (DTI).

•**Transferrin Association**:

•Random effects regression used to control for kinship

•Covariates include age, sex, and total serum iron

•N=615 for structural regressions N=544 for DTI-FA regression



•For multiple comparisons corrections over voxels, we used a searchlight method to regionally control the false discovery rate (Langers et al. 2007).

•**Cross-Trait Cross-Twin Bivariate Genetic Association**:

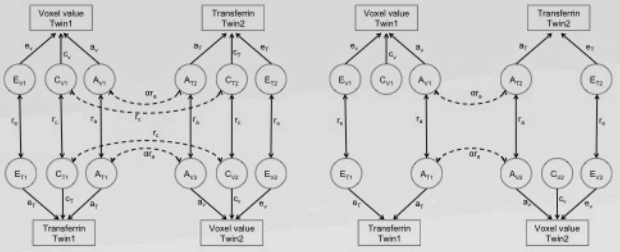
•Find the best fitting bivariate genetic model

•95 pairs of monozygotic twins – share all their genes

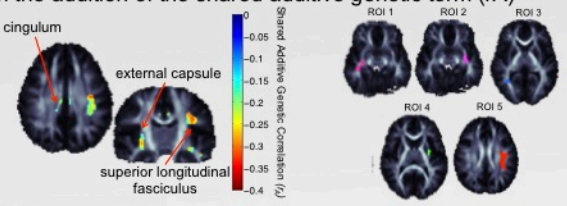
•59 pairs of same-sex dizygotic twins – share ~half of genes

•Break down population variance into:

- •A – additive genetic factors
- •C – shared environmental factors
- •E – unique environmental factors



•Find the regions where the model is significantly improved with the addition of the shared additive genetic term (rA)



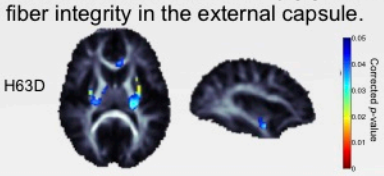
Results and Conclusions

(1) discovered associations of transferrin to variations in the healthy brain

(2) found brain regions where structural variance is partially controlled by the same genes as transferrin levels

(3) identified specific genetic variants associated with the brain differences.

- hemochromatosis H63D mutation (Njajou et al. 2003) was associated with fiber integrity in the external capsule.



•**Genomic Search**

•Significant regions of correlation were clustered into 5 ROIs.

•42 available SNPs (M_{eff}=20; (Gao et al., 2008)) within two transferrin-related candidate genes (*TF* and *HFE*)

•We used a linear mixed effects model to estimate the genetic associations to the mean FA measures at each ROI, controlling for age, sex, total serum iron, and familial relatedness using Efficient Mixed-Model Association (Emma, Kang et al., 2008)

•***HFE* H63D** in ROI-4 has an association that survives multiple comparison correction p=0.002

References & Acknowledgements

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