

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

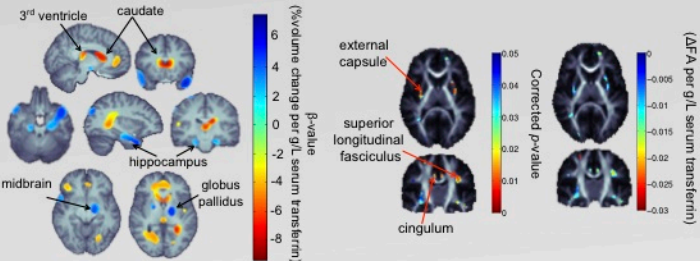
Subjects: High magnetic field (4-Tesla) structural images were acquired from 615 genotyped healthy young adult twins and siblings (mean age: 23.5±2.1 years). 544 were also scanned with 4T diffusion tensor imaging (DTI).

Transferrin Association:

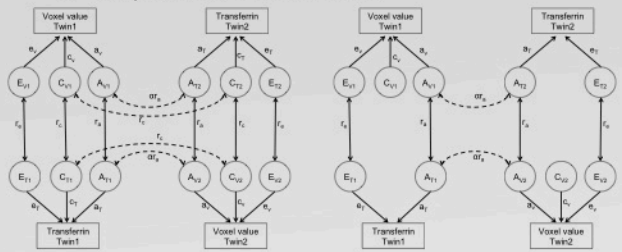
- Random effects regression used to control for kinship
- Covariates include age, sex, and total serum iron
- N=615 for structural regressions N=544 for DTI-FA regression

Cross-Trait Cross-Twin Bivariate Genetic Association:

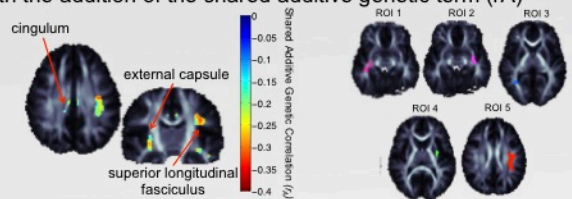
- Find the best fitting bivariate genetic model
- 95 pairs of monozygotic twins – share all their genes
- 95 pairs of same-sex dizygotic twins – share ~half of genes
- Break down population variance into:
 - A – additive genetic factors
 - C – shared environmental factors
 - E – unique environmental factors



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

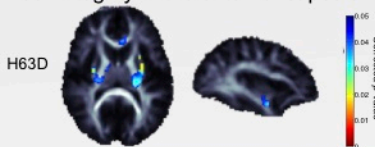


• Find the regions where the model is significantly improved with the addition of the shared additive genetic term (rA)



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 ($M_{\text{eff}}=20$; (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 & Acknowledgments

• Bartzokis, G. et al. (1994). "In vivo evaluation of brain iron in Alzheimer's disease and normal subjects using MRI." *Biol Psychiatry* 35(7): 480-487.
 • Chiang, MC. et al. (2009). "Genetics of brain fiber architecture and intellectual performance." *J Neurosci* 29(7): 2212-2224.
 • Connor, JR. and SA. Benkovic (1992). "Iron regulation in the brain: histochemical, biochemical, and molecular considerations." *Ann Neurol* 32 Suppl: S51-61.
 • Gao, X. et al. (2008). "A multiple testing correction method for genetic association studies using correlated single nucleotide polymorphisms." *Genet Epidemiol* 32(4): 361-369.
 • Halterman, JS. et al. (2001). "Iron deficiency and cognitive achievement among school-aged children and adolescents in the United States." *Pediatrics* 107(6): 1381-1386.
 • Kang, HM. et al. (2008). "Efficient Control of Population Structure in Model Organism Association Mapping." *Genetics*. Vol. 178, 1709-1723.
 • Jurgens, CK. et al. (2010). "MRI T2 Hypointensities in basal ganglia of premanifest Huntington's disease." *PLoS Curr* 2:8
 • Langers, DR. et al. (2007). "Enhanced signal detection in neuroimaging by means of regional control of the global false discovery rate." *Neuroimage* 38(1): 43-56.
 • Nelson, C. et al. (1997). "In vivo dopamine metabolism is altered in iron-deficient anemic rats." *J Nutr* 127(12): 2282-2288.
 • Njajou, OT. et al. (2003). "A population-based study of the effect of the HFE C282Y and H63D mutations on iron metabolism." *Eur J Hum Genet* 11(3): 225-231.



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