

Basal Ganglia Iron Content and Myelination in Adolescents

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Introduction

- Iron is important for critical processes in the brain, including myelination and neurotransmitter synthesis.
- Adolescents, particularly females, are at high risk for iron deficiency, due to menstruation and rapid growth.
- In fact, an estimated 38.6% of female adolescents in the US have iron deficiency.
- Even without anemia, iron deficiency has been associated with disrupted brain development and more severe symptoms of depression and anxiety.
- The basal ganglia (BG), including the caudate nucleus (Cd), putamen (Pu), and globus pallidus (GP), are rich in iron.
- Previously, we have shown that iron deficiency was associated with lower Cd and Pu QSM-based susceptibility, consistent with lower iron content.
- Here, using brain imaging, we examined the association between BG susceptibility and myelination in adolescents.

Methods

Participants: Unmedicated 10- to 17-year-old participants, with and without internalizing disorders were enrolled. Participants with anemia, other serious general medical conditions, or contraindications to completing an MRI scan were excluded.

Two hundred and six adolescents (58% ♀, age: 13.6±2.2yrs, 30% with Iron deficiency without anemia) provided usable data.

Procedures: 3T MRI, including structural (T1- and T2-weighted, 1 mm isotropic), diffusion tensor imaging (DTI, 2.2 x 2.2 x 2 mm), and quantitative susceptibility mapping (QSM, 0.75 x 0.75 x 1 mm).

Analyses:

- QSM reconstruction using QSMbox and susceptibility quantification within BG regions of interests and averaged between hemispheres.
- T1w/T2w ratio image normalized (2 mm smoothing) to a study-specific template.
- Fractional anisotropy (FA) calculated from DTI, normalized, and skeletonized (using FSL tract-based spatial statistics, TBSS) within the analyzed cohort.
- The associations between BG susceptibility values and FA, examined using tract-based special statistics (TBSS), adjusting for age.
- The associations between BG susceptibility values and T1w/T2w ratio examined using voxel-based statistics analyses and vertex-wise cortical surface analysis, adjusting for age.

Results

- Age was strongly associated with white matter FA and T1w/T2w ratio across the brain.
- After adjusting for age in 111 female adolescents and correcting for family-wise error, the combination of Cd/Pu/GP susceptibility (with dominant Pu contribution) was positively associated with FA, with the strongest cluster spanning the SLF (Fig 1).
- In 119 female adolescents, Pu susceptibility was positively associated with the T1w/T2w ratio across a broad area of the white matter and in subcortical structures with appreciable amount of myelinated fibers, e.g., brainstem, thalamus, GP, cerebellum, etc. (Fig 2).
- In vertex-wise cortical surface analysis, the combination of Cd/Pu/GP susceptibility (with dominant Pu contribution) was associated with the T1w/T2w ratio in right Brodmann area 44 (Fig 3).

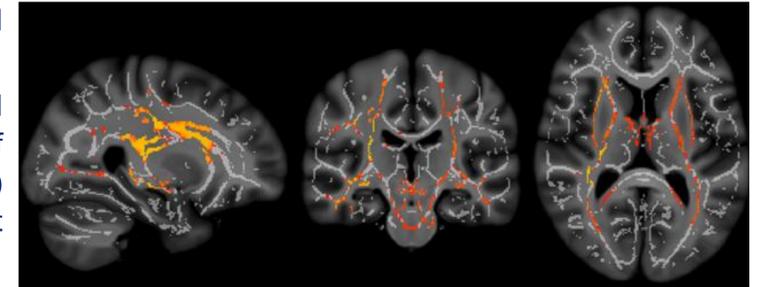


Fig 1: Association between BG susceptibility and FA, adjusting for age, in 111 female adolescents, particularly in the SLF and the internal and external capsules. Red voxels are significant at $p < 0.05$, while orange ones are significant at $p < 0.01$.

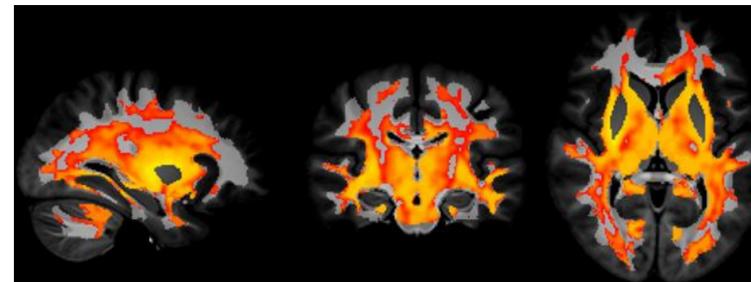
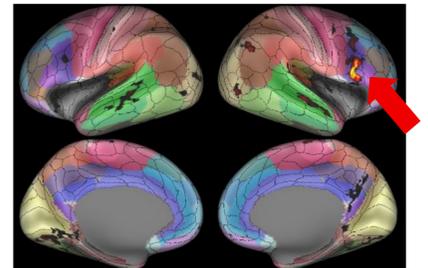


Fig 2: Association between putamen susceptibility and T1w/T2w ratio, adjusting for age, in 119 female adolescents. Red voxels are significant at $p < 0.05$, while orange ones are significant at $p < 0.025$.

Fig 3: Association between basal ganglia susceptibility and T1w/T2w ratio in the cortex, adjusting for age, in 119 female adolescents. Red arrow pointing at right Brodmann Area 44. Voxels significant at $p < 0.05$.



• **No significant associations were observed in male participants, and no negative associations were identified.**

Conclusions

- BG susceptibility, which is strongly correlated with its iron content, is positively correlated with white matter maturation in female adolescents. This process appears altered by the presence of iron deficiency.
- The lack of such association in male adolescents parallels a similar lack of reduced BG iron content in male adolescents with ID in our recent publication.
- Our findings provide new insights into the microstructural underpinnings whereby iron deficiency may disrupt brain development and contribute to psychopathology.
- Clinicians should consider screening for iron deficiency in adolescents, particularly females, to optimize brain development and reduce the risk for psychopathology and cognitive impairment.

The authors have no conflicts of interest to disclose.

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