

# BASAL GANGLIA IRON CONTENT IN ADOLESCENTS WITH IRON DEFICIENCY

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## Introduction

- Brain iron is necessary for mitochondrial aerobic metabolism, neurotransmitter synthesis, myelination, and neurogenesis,.
- Adolescence is a critical period for brain development, with significant changes in neural connectivity, maturation, and plasticity.
- Iron Deficiency (ID) is the most common nutritional deficiency worldwide, and females and adolescents are particularly susceptible, due to various factors including menstruation and rapid growth. In the US, about 38.6% of female adolescents have ID.
- Even without anemia, ID has been associated with disrupted brain development, cognitive impairment, and psychiatric symptom severity.
- This study examines the impact of iron deficiency without anemia (IDWoA) on basal ganglia (BG) iron content in adolescents, using MRI-based quantitative susceptibility mapping (QSM).
- The BG, including the caudate nucleus (Cd), putamen (Pu), and globus pallidus (GP), are rich in iron.

## Methods

**Participants:** Unmedicated 10- to 17-year-old females, with and without depressive or anxiety disorder, were enrolled. We excluded participants with anemia, elevated C-reactive protein concentration (CRP) indicating acute inflammation, other serious general medical conditions, or contraindications to completing an MRI scan.

**Procedures:** Participants underwent a blood draw to measure hemoglobin, serum ferritin (sF), and CRP. QSM data were acquired at 3T with a 3D GRE multi-echo sequence with voxel resolution of 0.7 mm × 0.7 mm × 1 mm. T1-weighted (T1w) images were acquired at 1 mm isotropic resolution.

### Analyses:

- Iron deficiency status was based on sF, with a cutoff of 15 ng/mL indicating ID.
- The GRE phase images were reconstructed into QSM images using the state-of-the-art QSMbox. The Cd, Pu, and GP regions of interest were manually defined in our study-specific QSM-T1w hybrid template and were transformed to the native QSM image space for susceptibility values.
- Group averages for participants with and without IDWoA were compared.
- Multivariable regression analysis examined the association between IDWoA status (or sF groups) and basal ganglia susceptibility, accounting for age and sex.

## Results

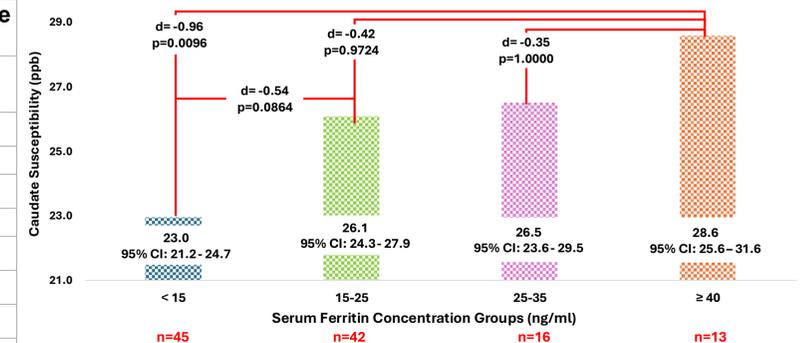
**Table 1: Demographic and Clinical Characteristics of the Participants**

	IDWoA N = 62	No ID N = 147	P value
Female Sex, n (%)	45 (73)	77 (52)	<b>0.007</b>
Age, yrs	13.7±2.0	13.4±2.3	>0.30
Black or Hispanic, n (%)	41 (66)	74 (50)	<b>0.036</b>
BMI Z-score	0.55±0.69	0.35±0.77	<b>0.078</b>
Vocabulary T-score	47.5±8.3	49.9±8.2	<b>0.058</b>
Post-Menarche, n (%)	35 (80)	44 (59)	<b>0.025</b>
Age at Menarche, yrs	11.5±1.3	11.3±1.2	>0.60
Hemoglobin, g/dL	13.3±1.0	14.1±1.1	<b>&lt;0.0001</b>
sF, ng/ml	10.0±2.9	30.9±17.1	<b>&lt;0.0001</b>
Internalizing Dis, n (%)	40 (65)	72 (49)	<b>0.0397</b>

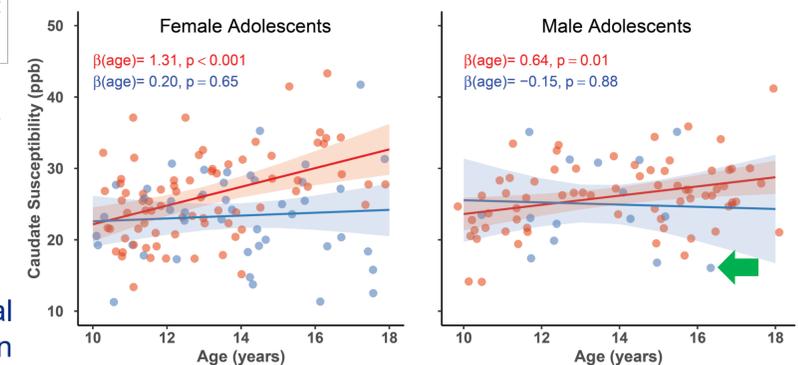
Vocabulary T-score: based on the Wechsler Abbreviated Scale of Intelligence II, vocabulary subtest. Internalizing Disorders: DSM-5-based depressive or anxiety disorder.

After controlling for age and sex and compared to sF >15 ng/mL, IDWoA was associated with lower susceptibility in the caudate and putamen in the total sample (Cohen's  $d = -0.41$ ,  $p = 0.01$  &  $d = -0.38$ ,  $p = 0.02$ ) and in females, specifically ( $d = -0.64$ ,  $p = 0.001$  &  $d = -0.47$ ,  $p = 0.01$ ).

After adjusting for age and estimated total intracranial volume, females in the upper median for caudate susceptibility had significantly smaller putamen volumes ( $d = -0.41$ ,  $p = 0.03$ ), whereas males in the upper median for putamen susceptibility had smaller putamen and pallidum volumes ( $d = -0.85$ ,  $p = 0.001$  &  $d = -0.79$ ,  $p = 0.002$ ).



**Figure 1:** A dose effect is apparent in adolescent females, with those having the lowest serum ferritin concentration (sF) showing the largest difference in caudate susceptibility compared to those with the highest sF. The analysis adjusted for age.



**Figure 2:** Age is associated with a significant increase in caudate susceptibility in iron replete (red dots) participants but not in those with IDWoA (blue dots). This difference was significant in female adolescents but not in males, likely due to the smaller number of males with IDWoA and the fact that the oldest male is ~ 16 years old (green arrow), limiting statistical power.

## Conclusions

- During adolescence, a time when brain iron accrues, ID is associated with lower susceptibility in the Caudate and Putamen, indicating lower iron content, particularly in females.
- This effect appears to get more accentuated with duration of exposure to ID and with the severity of ID, even in the absence of anemia.
- Our findings provide new insights into the impact of ID on brain development.
- Given that the disruption in brain iron accrual in adolescence may contribute to psychopathology, screening for and managing ID in adolescents should be considered to optimize brain development and reduce the risk for psychopathology.

The authors have no conflicts of interest to disclose.  
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