SUPPLEMENTARY MATERIAL

# Brain Iron Levels in Attention-Deficit/Hyperactivity Disorder Normalize as a Function of Psychostimulant Treatment Duration

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## 1. Supplementary material and methods

### *1.1. Group Comparisons of Brain Iron Indices Controlling for Age*

While the control and attention-deficit/hyperactivity disorder (ADHD) groups did not statistically differ in age, supplementary magnetic field correlation (MFC) and R2* relaxation rate group analyses controlling for age was conducted in the same regions-of-interest (ROIs) as the main manuscript. A univariate ANCOVA (age as a covariate) was conducted for normally distributed measures and a ranked ANCOVA for non-normally distributed measures; partial eta-squared ($\eta_p^2$) reported for effect size. A sequential Bonferroni-type false discovery rate (FDR) corrected $p < 0.05$ (Benjamini and Hochberg, 1995) was indicative of a statistically significant difference.

### *1.2. Effects of Group, Age and Their Interaction on Brain Iron Indices*

To further examine the effects of group, age and their interaction on brain iron indices, we conducted supplementary multiple regression analysis with group, age (mean centered) and their interaction as independent variables and MFC or R2* as the dependent variable. Measures with non-normally distributed residuals were log or reciprocal transformed to meet normality requirements and the FDR corrected $p < 0.05$ was applied to control for multiple comparisons.

*1.3. Correlation Analyses Between Behavioral Ratings and Brain Iron Indices*

To examine whether brain iron indices were related to symptom severity, supplementary correlation analyses of MFC and R2* with T-scores from the Behavioral Rating Inventory of Executive Function (BRIEF) (Gioia et al., 2000) were conducted within each group using Pearson's correlation ($r$) for normally distributed measures and Spearman's correlation ($r_s$) for non-normally distributed measures. An FDR corrected $p < 0.05$ was applied to control for multiple comparisons. While both parents and teachers were instructed to rate the participant's behavior when off all medication, the teacher BRIEF ratings reflected a mix of behaviors off or on medication and were not available for all participants. As such, we restricted our analysis to the BRIEF ratings from parents.

BRIEF T-scores provide information about the participant's behavior relative to a normative sample and consist of the Behavioral Regulation Index (BRI) which represents the participant's ability to shift cognitive set and modulate emotions and behavior via inhibitory control, the Metacognition Index (MI) which reflects the participant's ability to cognitively self-manage tasks and monitor his or her performance, and the Global Executive Composite (GEC) which serves a summary score (Gioia et al., 2000). High T-scores indicate greater degrees of executive dysfunction, with scores $\geq$ 65 indicating potential clinical significance.

*1.4. Volumetric Analyses*

Regional brain volumes ($mm^3$) of the globus pallidus (GP), putamen (PUT), caudate nucleus (CN), thalamus (THL) and total brain volume were extracted from the automated segmentation of each participant's high-resolution structural T1-weighted magnetization-prepared rapid acquisition gradient-echo (MPRAGE) image using the Freesurfer software (http://surfer.nmr.mgh.harvard.edu). Regional volumes were corrected for total brain volume by dividing the regional volume by total brain volume (Sussman et al., 2016). Volumetric analysis was conducted on the regional volume relative to whole brain (reported as percentages). Given the unavailability of automated segmentation of the red nucleus (RN) and the lack of clear anatomical RN boundaries in the MPRAGE image to guide reliable manual segmentation, accurate calculation of RN volumes could not be made. Accordingly, the RN was excluded from this supplementary analysis.

To examine whether regional brain volume was related to brain iron indices in the GP, PUT, CN and THL, we conducted supplementary partial correlation analyses of MFC and R2* with relative regional volume within each group. In the control group, age was controlled for in the analyses due to its significant correlation with brain iron (Hallgren and Sourander, 1958; Table 3) and brain volume (Sussman et al., 2016). In the ADHD group, age and medication duration were controlled for in the analyses as brain iron indices significantly correlated with medication duration (which was collinearly related to age; Table 3). Pearson's partial correlation was conducted for normally distributed measures, Spearman's partial correlation for non-normally distributed measures and the FDR corrected $p < 0.05$ was applied to control for multiple comparisons.

To test whether regional brain volume mediated the relationship between age and brain iron indices in the control group, we conducted regression analysis using the non-parametric Preacher and Hayes bootstrap method (Preacher and Hayes, 2004) implemented with the PROCESS macro, version 3.3 (Hayes and Rockwood, 2017) in SPSS (v24.0; IBM, Armonk, NY). The indirect effect was tested using a percentile bootstrap estimation approach with 10,000 samples (Shrout and Bolger, 2002).

## 2. Supplementary results

### *2.1. Group Comparisons of Brain Iron Indices Controlling for Age*

There were no significant MFC or R2* group differences between the control and ADHD groups in any of the ROIs when age was controlled for as a covariate (Supplementary Table S2).

### *2.2. Effects of Group, Age and Their Interaction on Brain Iron Indices*

Multiple regression was carried out to investigate whether group, age and their interaction could significantly predict MFC in the GP, PUT, CN, THL and RN. The model was a significant predictor of MFC in the GP, PUT, CN, THL and RN (FDR corrected; Supplementary Table S3A). In the GP, PUT and CN, age contributed significantly to the model but group and the group x age interaction did not. In the THL, only the group x age interaction contributed to the model, but its significance did not survive FDR correction. In the RN, only the constant significantly contributed to the model. The same findings were replicated in the MFC analysis of the cohort with R2* data (Supplementary Table S3C).

Multiple regression analyses of R2* found that the model was a significant predictor of R2* in the GP, PUT and CN (FDR corrected; Supplementary Table S3B), with a trend in the THL. However, none of the individual predictors contributed significantly to the model in any of the ROIs (there was a trend for age in the GP and PUT and a trend for the group x age interaction in the THL).

### *2.3. Correlation Analyses Between Behavioral Ratings and Brain Iron Indices*

In the control group, the BRIEF measures (BRI, MI, GEC) did not significantly correlate with MFC or R2* in any of the ROIs (Supplementary Table S10). In the ADHD group, higher BRI measures were significantly correlated with lower MFC in the PUT and CN but these findings did not survive FDR correction (Supplementary Table S10A). BRI did not correlate with MFC in the other ROIs and there were no significant correlations between BRI, MI and GEC with R2* in any of the ROIs (Supplementary Table S10B).

*2.4. Volumetric Analyses*

In the control group, higher brain iron indices correlated with lower regional brain volume in the CN (iron as indexed by MFC; Supplementary Table S8A) and in the GP (iron indexed by R2* and MFC; Supplementary Table S8B-C) but these findings did not survive FDR correction. There were no significant correlations between MFC or R2* with regional brain iron volumes in the remaining ROIs. In the ADHD group, no significant correlations were detected between brain iron indices (MFC or R2*) and regional brain volume in any of the ROIs (Supplementary Table S8).

Regression analysis was used to investigate the hypothesis that regional brain volume mediates the effect of age on brain indices in the control group. For the GP, PUT, CN and THL, results indicated that higher age was a significant predictor of lower regional brain volume (Sussman et al., 2016) but that regional brain volume was not a significant predictor of MFC (Supplementary Table S9A). These results do not support the mediation hypothesis and is reflected in the non-significant indirect $\beta$ coefficients for volume. In the GP, PUT, CN and THL, age remained a significant predictor of MFC after controlling for the mediator (regional brain volume). Similar results were detected for R2* in all the ROIs examined (Supplementary Table S9B).

## 3. Supplementary references

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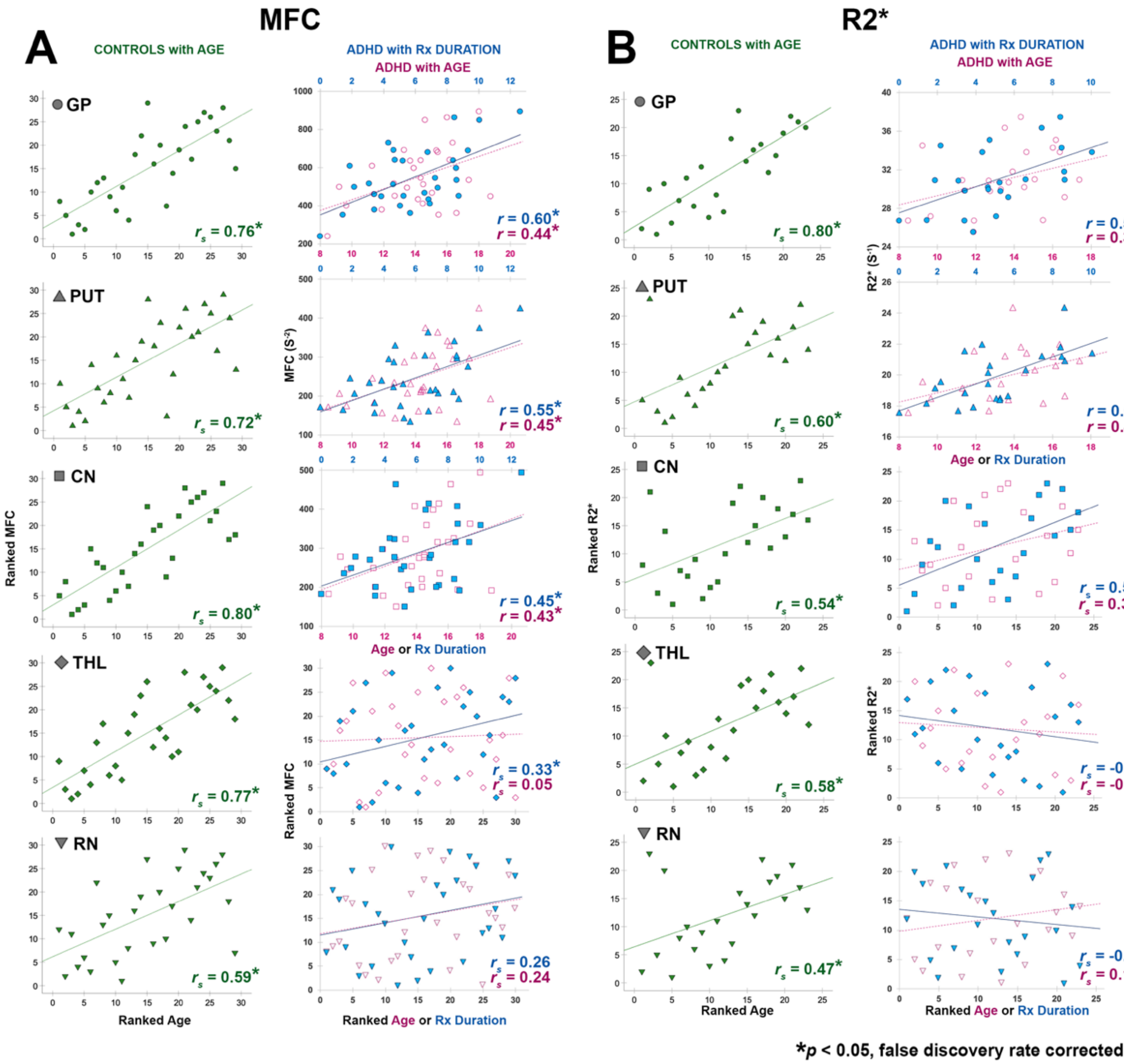
## 4. Supplementary figure




**Supplementary Figure S1. Simple Correlation of Brain Iron Indices with Age or Rx Duration**

**A.** In the control group (green), magnetic field correlation (MFC) indices of brain iron significantly increased with age in the globus pallidus (GP), putamen (PUT), caudate nucleus (CN), thalamus (THL) and red nucleus (RN). In the ADHD group, MFC significantly increased with psychostimulant medication (Rx) duration in the GP, PUT, CN and THL (blue) and with age in the GP, PUT and CN (purple). **B.** Similar results were found with R2* indices of brain iron except correlations with age in the ADHD group (GP, PUT) did not survive false discovery rate correction. *r*: Pearson's correlation, $r_S$: Spearman's correlation (ranked values plotted).

## 5. Supplementary tables

**Supplementary Table S1. Demographics (MFC & R2* data)**

| | Control Group ($n$ = 23) | ADHD group ($n$ = 23) | Group Comparison | |
|---|---|---|---|---|
| | | | $t$ | $p$-value |
| Age (years, mean ± SD) | 13.2 ± 3.6 | 13.5 ± 2.4 | §254 | 0.8 |
| Age Range (years) | 8.2 – 18.6 | 8.5 – 17.4 | --- | --- |
| Ethnicity (C:AA:O) | 20:3:0 | 20:3:0 | --- | †1.0 |
| **KBIT-2** | | | | |
| Verbal IQ | 110.0 ± 10.8 | 107.1 ± 14.0 | -0.8 | 0.4 |
| Nonverbal IQ | 105.4 ± 12.7 | 109.1 ± 12.9 | §254 | 0.8 |
| Composite IQ | 109.3 ± 11.4 | 109.8 ± 13.0 | 0.1 | 0.9 |
| **ADHD Subtype** | | | | --- |
| Combined | --- | 16 | --- | --- |
| Inattentive | --- | 6 | --- | --- |
| Hyperactive | --- | 1 | --- | --- |
| **BRIEF-Parent** | | | | |
| Behavioral Regulation Index | 47.8 ± 8.1 | 62.2 ± 9.9 | 5.4 | <0.001 |
| Metacognition Index | 47.4 ± 9.4 | 69.4 ± 7.0 | 9.0 | <0.001 |
| Global Executive Composite | 48.3 ± 9.9 | 68.5 ± 7.4 | 7.9 | <0.001 |
| **BRIEF-Teacher** | | | | |
| Behavioral Regulation Index | 48.9 ± 4.9 | 60.2 ± 15.1 | §88 | 0.018 |
| Metacognition Index | 50.7 ± 9.2 | 67.5 ± 15.4 | 4.0 | <0.001 |
| Global Executive Composite | 50.0 ± 7.1 | 66.1 ± 15.6 | 3.9 | 0.001 |

All participants, male, right-handed, comorbid-free, positive history of psychostimulant medication; MFC: magnetic field correlation; R2*: R2* proton transverse relaxation rate; C: Caucasian; AA: African American; O: other; KBIT-2: Kaufman Brief Intelligence Test, second edition; BRIEF-Parent: Behavioral Rating Inventory of Executive Function-Parent version (T-scores); BRIEF-Teacher: Teacher version (T-scores, Controls = 19, ADHD = 17); $t$: Student's $t$-test (two-tailed); §Mann-Whitney $U$ test (Exact Sig. two-tailed); †Fisher's Exact Test (Exact Sig. two-sided); SD: standard deviation; df: degrees of freedom; --- not applicable.

**Supplementary Table S2. Group Comparisons (Control for Age)**

| | Control Group ($n$ = 29) | ADHD Group ($n$ = 30) | Group Comparison | | |
|---|---|---|---|---|---|
| **A.** MFC ($s^{-2}$) | Est. Marginal Mean (SE) | Est. Marginal Mean (SE) | *F* | *p*-value | effect size: $\eta_p^2$ |
| GP | 1.13 (2.48) | -1.09 (2.44) | 0.41 | 0.526 | 0.007; small |
| PUT | -1.07 (2.53) | 1.03 (2.49) | 0.35 | 0.558 | 0.006; small |
| CN | -0.02 (2.45) | 0.02 (2.41) | 0.00 | 0.990 | 0.000; small |
| THL | -3.54 (2.78) | 3.42 (2.74) | 3.18 | 0.080 | 0.053; small |
| RN | 0.09 (2.88) | -0.09 (2.83) | 0.00 | 0.966 | 0.000; small |
| | Control Group ($n$ = 23) | ADHD Group ($n$ = 23) | Group Comparison | | |
| **B.** R2* ($s^{-1}$) | Est. Marginal Mean (SE) | Est. Marginal Mean (SE) | *F* | *p*-value | effect size: $\eta_p^2$ |
| GP | -0.12 (2.14) | 0.12 (2.14) | 0.01 | 0.940 | 0.000; small |
| PUT | -1.53 (2.24) | 1.53 (2.24) | 0.93 | 0.340 | 0.021; small |
| CN | -1.99 (2.49) | 1.99 (2.49) | 1.28 | 0.264 | 0.028; small |
| THL | 1.20 (2.60) | -1.20 (2.60) | 0.42 | 0.519 | 0.009; small |
| RN | 0.92 (2.52) | -0.92 (2.52) | 0.27 | 0.608 | 0.006; small |
| **C.** MFC ($s^{-2}$) | Est. Marginal Mean (SE) | Est. Marginal Mean (SE) | *F* | *p*-value | effect size: $\eta_p^2$ |
| GP | 1.16 (2.68) | -1.16 (2.68) | 0.37 | 0.545 | 0.008; small |
| PUT | -0.55 (2.13) | 0.55 (2.13) | 0.13 | 0.718 | 0.003; small |
| CN | 0.20 (2.56) | -.20 (2.56) | 0.01 | 0.911 | 0.000; small |
| THL | -2.70 (2.34) | 2.70 (2.34) | 2.65 | 0.111 | 0.057; small |
| RN | 1.39 (2.54) | -1.39 (2.54) | 0.60 | 0.441 | 0.014; small |

GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; RN: red nucleus; *F*: ranked ANCOVA, age covariate (two-tailed); $\eta_p^2$: partial eta-squared; SE: standard error.

**Supplementary Table S3. Effects of Group, Age and Their Interaction on Brain Iron Indices**

| Region | GP | PUT | CN | THL | RN |
|---|---|---|---|---|---|
| **A.** MFC ($s^{-2}$) | ($n$ = 59) | | | | |
| Model | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value)$^T$ | $\beta$ ($p$-value)$^T$ |
| Constant | 544.9 (0.000)* | 243.5 (0.000)* | 284.2 (0.000)* | 5.0 (0.000)* | 5.4 (0.000)* |
| Group | 37.2 (0.311) | 0.7 (0.967) | 1.2 (0.947) | -0.07 (0.205) | -0.01 (0.919) |
| Age | 28.3 (0.009)* | 13.5 (0.008)* | 15.1 (0.005)* | 0.01 (0.401) | 0.02 (0.398) |
| Group x Age | 16.6 (0.201) | 6.4 (0.291) | 5.6 (0.380) | 0.04 (0.033)$^{\#}$ | 0.04 (0.249) |
| Adjusted $R^2$ | 0.41 | 0.39 | 0.39 | 0.29 | 0.12 |
| F(3,55) | 14.5 | 13.2 | 13.3 | 8.9 | 3.6 |
| $p$-value | 0.000* | 0.000* | 0.000* | 0.000* | 0.019* |
| **B.** R2* ($s^{-1}$) | ($n$ = 46) | | | | |
| Model | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value)$^T$ | $\beta$ ($p$-value) | $\beta$ ($p$-value) |
| Constant | 30.9 (0.000)* | 19.9 (0.000)* | 0.05 (0.000)* | 18.7 (0.000)* | 23.5 (0.000)* |
| Group | 0.3 (0.756) | -0.3 (0.620) | 0.002 (0.148) | 0.1 (0.845) | 0.4 (0.739) |
| Age | 0.5 (0.050) | 0.3 (0.055) | -0.001 (0.148) | -0.0 (0.716) | 0.2 (0.632) |
| Group x Age | 0.3 (0.235) | 0.1 (0.669) | 0.0 (0.800) | 0.2 (0.062) | 0.2 (0.642) |
| Adjusted $R^2$ | 0.37 | 0.25 | 0.16 | 0.11 | -0.01 |
| F(3,42) | 10.0 | 5.9 | 3.9 | 2.8 | 0.9 |
| $p$-value | 0.000* | 0.002* | 0.016* | 0.052 | 0.455 |
| **C.** MFC ($s^{-2}$) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value)$^T$ |
| Constant | 530.9 (0.000)* | 236.1 (0.000)* | 275.2 (0.000)* | 147.6 (0.000)* | 5.3 (0.000)* |
| Group | 37.5 (0.369) | 4.1 (0.821) | 1.3 (0.944) | -5.5 (0.531) | 0.04 (0.704) |
| Age | 28.5 (0.025)$^{\#}$ | 12.9 (0.021)$^{\#}$ | 15.7 (0.008)* | 0.6 (0.803) | 0.01 (0.714) |
| Group x Age | 20.1 (0.184) | 9.2 (0.163) | 6.2 (0.368) | 7.7 (0.018)$^{\#}$ | 0.06 (0.177) |
| Adjusted $R^2$ | 0.45 | 0.47 | 0.45 | 0.31 | 0.12 |
| F(3,42) | 13.2 | 14.1 | 13.5 | 7.7 | 3.0 |
| $p$-value | 0.000* | 0.000* | 0.000* | 0.000* | 0.040* |

Multiple regression; Group: ADHD = 0, Controls = 1; GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; RN: red nucleus; $^T$ transformed data; *$p < 0.05$, two-tailed (false discovery rate corrected); $^{\#}p < 0.05$, two-tailed.

**Supplementary Table S4. MFC Group Comparisons (*n* = 46)**

| | Control Group (*n* = 23) | ADHD Group (*n* = 23) | Group Comparison | | |
|---|---|---|---|---|---|
| MFC ($s^{-2}$) | Mean (SD) | Mean (SD) | statistic | *p*-value | effect size |
| GP | 561.1 (219.0) | 535.1 (155.7) | *t* = 0.5 | 0.645 | *d* = 0.1; small |
| PUT | 236.9 (99.0) | 238.1 (68.1) | *U* = 245 | 0.679 | $r_{rb}$ = 0.1; small |
| CN | 273.3 (92.8) | 277.6 (81.8) | *t* = -0.2 | 0.869 | *d* = 0.0; small |
| THL | 140.8 (40.3) | 147.7 (30.4) | *U* = 197 | 0.142 | $r_{rb}$ = 0.2; small |
| RN | 228.5 (84.5) | 229.5 (124.4) | *U* = 237 | 0.557 | $r_{rb}$ = 0.1; small |

GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; RN: red nucleus; *t*: Student's *t*-test (two-tailed); *U*: Mann-Whitney *U* test (Exact Sig. two-tailed); SD: standard deviation; *d*: Cohen's *d*; $r_{rb}$: rank biserial correlation.

**Supplementary Table S5. MFC Correlations with Age and Psychostimulant Medication Duration (*n* = 46)**

| | Control Group (*n* = 23) | ADHD Group (*n* = 23) | | | |
|---|---|---|---|---|---|
| MFC ($s^{-2}$) | vs. Age | vs. Rx Duration | vs. Age | vs. Rx Duration (control for Age)§ | vs. Age (control for Rx Duration)§ |
| Region | $r_s$ (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) |
| GP | 0.81 (<0.001)* | 0.59 (0.002)* | 0.45 (0.016)* | 0.45 (0.018)[#] | 0.17 (0.232) |
| PUT | 0.78 (<0.001)* | 0.55 (0.003)* | 0.46 (0.013)* | 0.39 (0.037)[#] | 0.22 (0.169) |
| CN | 0.82 (<0.001)* | 0.41 (0.026)* | 0.47 (0.012)* | 0.20 (0.192) | 0.31 (0.081) |
| THL | 0.80 (<0.001)* | 0.24 (0.140) | 0.05 (0.407) | 0.25 (0.130) | -0.11 (0.322) |
| RN | 0.61 (0.001)* | $r_s$ = 0.07 (0.380) | $r_s$ = 0.16 (0.227) | $r_s$ = -0.03 (0.443) | $r_s$ = 0.15 (0.243) |

GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; RN: red nucleus; Rx: psychostimulant medication; *r*: Pearson's correlation; $r_s$: Spearman's correlation; §: partial correlations; *$p$ < 0.05, one-tailed (false discovery rate corrected); [#]$p$ < 0.05, one-tailed.

**Supplementary Table S6. Group Comparisons – Exclude Cases with Non-psychostimulant Medication History**

| | Control Group ($n$ = 29) | ADHD Group ($n$ = 20) | Group Comparison | | |
|---|---|---|---|---|---|
| **A.** MFC ($s^{-2}$) | Mean (SD) | Mean (SD) | statistic | $p$-value | effect size |
| Age | 13.9 (3.5) | 14.3 (2.7) | $U$ = 288 | 0.976 | $r_{rb}$ = 0.0; small |
| GP | 579.4 (204.6) | 544.4 (182.2) | $t$ = 0.6 | 0.534 | $d$ = 0.2; small |
| PUT | 242.9 (92.7) | 244.8 (86.0) | $t$ = -0.1 | 0.941 | $d$ = 0.0; small |
| CN | 284.1 (88.8) | 286.7(95.1) | $U$ = 280 | 0.848 | $r_{rb}$ = 0.0; small |
| THL | 143.5 (36.8) | 153.0 (43.8) | $U$ = 249 | 0.414 | $r_{rb}$ = 0.1; small |
| RN | 230.9 (77.6) | 261.2 (142.1) | $U$ = 276 | 0.786 | $r_{rb}$ = 0.0; small |
| | Control Group ($n$ = 23) | ADHD Group ($n$ = 15) | Group Comparison | | |
| **B.** R2* ($s^{-1}$) | Mean (SD) | Mean (SD) | statistic | $p$-value | effect size |
| Age | 13.2 ± 3.6 | 13.6 ± 2.7 | $U$ = 163 | 0.791 | $r_{rb}$ = 0.1; small |
| GP | 31.0 (3.6) | 30.8 (3.6) | $t$ = 0.2 | 0.817 | $d$ = 0.1; small |
| PUT | 19.5 (2.3) | 19.8 (1.4) | $t$ = -0.4 | 0.711 | $d$ = 0.2; small |
| CN | 18.4 (1.6) | 19.2 (2.7) | $U$ = 149 | 0.497 | $r_{rb}$ = 0.1; small |
| THL | 18.7 (1.3) | 18.9 (1.4) | $U$ = 172 | 1.000 | $r_{rb}$ = 0.0; small |
| RN | 23.8 (4.0) | 24.0 (3.2) | $U$ = 170 | 0.953 | $r_{rb}$ = 0.0; small |
| **C.** MFC ($s^{-2}$) | Mean (SD) | Mean (SD) | statistic | $p$-value | effect size |
| GP | 561.1 (219.0) | 535.3 (179.3) | $t$ = 0.4 | 0.693 | $d$ = 0.1; small |
| PUT | 236.9 (99.0) | 235.9 (76.5) | $U$ = 165 | 0.836 | $r_{rb}$ = 0.0; small |
| CN | 273.3 (92.8) | 272.0 (84.5) | $t$ = 0.05 | 0.964 | $d$ = 0.0; small |
| THL | 140.8 (40.3) | 143.5 (36.2) | $U$ = 151 | 0.535 | $r_{rb}$ = 0.1; small |
| RN | 228.5 (84.5) | 245.7 (149.8) | $U$ = 164 | 0.813 | $r_{rb}$ = 0.0; small |

GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; RN: red nucleus; $t$: Student's $t$-test (two-tailed); $U$: Mann-Whitney $U$ test (Exact Sig. two-tailed); SD: standard deviation; $d$: Cohen's $d$; $r_{rb}$: rank biserial correlation.

**Supplementary Table S7. Correlations with Age and Psychostimulant Medication Duration – Exclude Cases with Non-psychostimulant Medication History**

| | Control Group | ADHD Group | | | |
|---|---|---|---|---|---|
| Iron Index | vs. Age | vs. Rx Duration | vs. Age | vs. Rx Duration (control for Age)§ | vs. Age (control for Rx Duration)§ |
| | (*n* = 29) | (*n* = 20) | | | |
| **A.** MFC ($s^{-2}$) | $r_s$ (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) |
| GP | 0.76 (<0.001)* | 0.66 (0.001)* | 0.38 (0.048)$^{\#}$ | 0.61 (0.003)* | -0.22 (0.189) |
| PUT | 0.72 (<0.001)* | 0.58 (0.004)* | 0.38 (0.048)$^{\#}$ | 0.48 (0.019)* | -0.09 (0.357) |
| CN | 0.80 (<0.001)* | 0.48 (0.015)* | 0.41 (0.036)$^{\#}$ | 0.29 (0.113) | 0.09 (0.360) |
| THL | 0.77 (<0.001)* | $r_s$ = 0.44 (0.026)* | $r_s$ = 0.16 (0.253) | $r_s$ = 0.46 (0.020)* | $r_s$ = -0.23 (0.165) |
| RN | 0.59 (<0.001)* | $r_s$ = 0.46 (0.021)* | $r_s$ = 0.23 (0.166) | $r_s$ = 0.43 (0.030)* | $r_s$ = -0.14 (0.277) |
| | (*n* = 23) | (*n* = 15) | | | |
| **B.** R2* ($s^{-1}$) | $r_s$ (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) |
| GP | 0.80 (<0.001)* | 0.57 (0.013)* | 0.27 (0.163) | 0.55 (0.022)* | -0.18 (0.266) |
| PUT | 0.60 (0.001)* | 0.70 (0.002)* | 0.41 (0.063) | 0.63 (0.008)* | -0.11 (0.356) |
| CN | 0.54 (0.004)* | $r_s$ = 0.59 (0.010)* | $r_s$ = 0.20 (0.233) | $r_s$ = 0.63 (0.006)* | $r_s$ = -0.34 (0.111) |
| THL | 0.58 (0.002)* | $r_s$ = -0.07 (0.405) | $r_s$ = -0.37 (0.089) | $r_s$ = 0.27 (0.166) | $r_s$ = -0.44 (0.050) |
| RN | 0.47 (0.012)* | $r_s$ = -0.33 (0.113) | $r_s$ = -0.10 (0.357) | $r_s$ = -0.36 (0.094) | $r_s$ = 0.18 (0.262) |
| **C.** MFC ($s^{-2}$) | $r_s$ (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) | *r* (*p*-value) |
| GP | 0.81 (<0.001)* | 0.70 (0.002)* | 0.38 (0.083) | 0.65 (0.006)* | -0.18 (0.272) |
| PUT | 0.78 (<0.001)* | 0.58 (0.012)* | 0.36 (0.092) | 0.48 (0.041)$^{\#}$ | -0.04 (0.448) |
| CN | 0.82 (<0.001)* | 0.38 (0.080) | 0.44 (0.051) | 0.13 (0.325) | 0.27 (0.179) |
| THL | 0.80 (<0.001)* | 0.30 (0.137) | 0.14 (0.315) | 0.29 (0.160) | -0.09 (0.374) |
| RN | 0.61 (0.001)* | $r_s$ = 0.29 (0.148) | $r_s$ = 0.21 (0.229) | $r_s$ = 0.21 (0.230) | $r_s$ = 0.01 (0.480) |

GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; RN: red nucleus; Rx: psychostimulant medication; *r*: Pearson's correlation; $r_s$: Spearman's correlation; §: partial correlations; *$p < 0.05$, one-tailed (false discovery rate corrected), $^{\#}p < 0.05$, one-tailed.

**Supplementary Table S8. Brain Volume Correlations with Brain Iron Indices**

| | | Control Group | ADHD Group |
|---|---|---|---|
| | | vs. Volume (control for Age) | vs. Volume (control for Age & Rx Duration) |
| **A.** | MFC ($s^{-2}$) | ($n$ = 29) | ($n$ = 30) |
| | Region | $r_s$ ($p$-value) | $r$ ($p$-value) |
| | GP | -0.30 (0.120) | -0.01 (0.970) |
| | PUT | -0.06 (0.768) | 0.00 (0.991) |
| | CN | -0.41 (0.030)# | 0.03 (0.896) |
| | THL | 0.11 (0.567) | $r_s$ = 0.06 (0.746) |
| **B.** | R2* ($s^{-1}$) | ($n$ = 23) | ($n$ = 23) |
| | Region | $r_s$ ($p$-value) | $r_s$ ($p$-value) |
| | GP | -0.48 (0.025)# | $r$ = 0.21 (0.356) |
| | PUT | -0.09 (0.681) | -0.27 (0.240) |
| | CN | -0.14 (0.527) | -0.26 (0.261) |
| | THL | -0.28 (0.204) | -0.03 (0.913) |
| **C.** | MFC ($s^{-2}$) | $r_s$ ($p$-value) | $r$ ($p$-value) |
| | GP | -0.45 (0.036)# | 0.22 (0.338) |
| | PUT | -0.35 (0.113) | $r_s$ = 0.11 (0.649) |
| | CN | -0.31 (0.168) | 0.22 (0.333) |
| | THL | 0.10 (0.657) | 0.01 (0.953) |

Volume: regional volume relative to whole brain volume (%); GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; Rx: psychostimulant medication; *r*: Pearson's partial correlation; $r_s$: Spearman's partial correlation; # $p < 0.05$, two-tailed.

**Supplementary Table S9. Mediation Analysis of Regional Brain Volume on Age and Brain Iron Indices in Controls**

| Region | GP | PUT | CN | THL |
|---|---|---|---|---|
| **A.** Age→Volume→MFC | | ($n$ = 29) | | |
| Model: Volume | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) |
| Constant | 0.270 (0.000)* | 0.936 (0.000)* | 0.569 (0.007)* | 1.069 (0.000)* |
| Direct Effect: Age | -0.003 (0.008)* | -0.011 (0.006)* | -0.008 (0.037)* | -0.006 (0.153) |
| $R^2$ | 0.24 | 0.25 | 0.15 | 0.07 |
| F(1,27) | 8.3 | 9.0 | 4.8 | 2.2 |
| Model: MFC ($s^{-2}$) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) |
| Constant | 261.5 (0.468) | -106.1 (0.532) | 121.4 (0.213) | 9.8 (0.898) |
| Direct Effect: Age | 41.3 (0.000)* | 20.8 (0.000)* | 19.0 (0.000)* | 7.7 (0.000)* |
| Indirect Effect: Volume | -1136.0 (0.375) | 77.0 (0.656) | -220.6 (0.158) | 26.5 (0.701) |
| Indirect Effect LCI, UCI | -5.2, 14.5 | -6.2, 3.6 | -0.3, 5.7 | -1.9, 0.4 |
| $R^2$ | 0.60 | 0.57 | 0.69 | 0.52 |
| F(2,26) | 19.7 | 17.1 | 29.1 | 14.2 |
| $p$-value | 0.000* | 0.000* | 0.000* | 0.000* |
| **B.** Age→Volume→ R2* | | ($n$ = 23) | | |
| Model: Volume | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) |
| Constant | 0.265 (0.000)* | 0.906 (0.000)* | 0.585 (0.000)* | 1.012 (0.000)* |
| Direct Effect: Age | -0.003 (0.041)* | -0.009 (0.037)* | -0.009 (0.036)* | -0.001 (0.863) |
| $R^2$ | 0.18 | 0.19 | 0.19 | 0.002 |
| F(1,21) | 4.7 | 5.0 | 5.0 | 0.03 |
| Model: R2* ($s^{-1}$) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) | $\beta$ ($p$-value) |
| Constant | 31.8 (0.000)* | 14.2 (0.032)* | 17.8 (0.000)* | 17.8 (0.000)* |
| Direct Effect: Age | 0.7 (0.000)* | 0.4 (0.008)* | 0.2 (0.025)* | 0.2 (0.004)* |
| Indirect Effect: Volume | -43.6.0 (0.067) | 0.3 (0.967) | -4.9 (0.279) | -1.8 (0.642) |
| Indirect Effect LCI, UCI | -0.009, 0.3 | -0.1, 0.1 | -0.05, 0.2 | -0.02, 0.1 |
| $R^2$ | 0.71 | 0.35 | 0.37 | 0.35 |
| F(2,20) | 24.2 | 5.4 | 5.9 | 5.3 |
| $p$-value | 0.000* | 0.013* | 0.010* | 0.014* |

Volume: regional volume relative to whole brain volume (%); GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; LCI: lower confidence interval; UCI: upper confidence interval; 95% confidence intervals; *$p < 0.05$, two-tailed (false discovery rate corrected); $^{\#}p < 0.05$, two-tailed.

**Supplementary Table S10. Correlations of Brain Iron Indices with BRIEF Parent Ratings**

| | Control Group | | | ADHD Group | | |
|---|---|---|---|---|---|---|
| Iron Index | vs. BRI | vs. MI | vs. GEC | vs. BRI | vs. MI | vs. GEC |
| | | ($n$ = 29) | | | ($n$ = 30) | |
| **A.** MFC ($s^{-2}$) | $r_s$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) |
| GP | -0.13 (0.516) | 0.24 (0.212) | 0.11 (0.580) | -0.17 (0.358) | 0.09 (0.630) | -0.03 (0.888) |
| PUT | -0.16 (0.420) | 0.23 (0.212) | 0.06 (0.744) | -0.41 (0.025)[#] | 0.13 (0.488) | -0.13 (0.512) |
| CN | -0.13 (0.488) | $r_s$ 0.35 (0.059) | $r_s$ 0.27 (0.159) | -0.44 (0.015)[#] | 0.16 (0.389) | -0.11 (0.550) |
| THL | -0.06 (0.741) | 0.24 (0.211) | 0.14 (0.459) | $r_s$ 0.10 (0.618) | $r_s$ 0.08 (0.687) | $r_s$ 0.11 (0.566) |
| RN | -0.08 (0.691) | 0.18 (0.362) | 0.03 (0.873) | $r_s$ 0.30 (0.102) | $r_s$ 0.04 (0.839) | $r_s$ 0.20 (0.287) |
| | | ($n$ = 23) | | | ($n$ = 23) | |
| **B.** R2* ($s^{-1}$) | $r$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) | $r$ ($p$-value) |
| GP | -0.10 (0.635) | 0.16 (0.463) | 0.18 (0.406) | -0.05 (0.810) | -0.05 (0.809) | -0.06 (0.777) |
| PUT | -0.13 (0.571) | 0.15 (0.502) | 0.09 (0.690) | -0.37 (0.084) | -0.15 (0.501) | -0.29 (0.182) |
| CN | -0.26 (0.224) | 0.03 (0.897) | -0.03 (0.906) | $r_s$ -0.33 (0.122) | $r_s$ -0.14 (0.516) | $r_s$ -0.27 (0.209) |
| THL | -0.18 (0.404) | 0.29 (0.182) | 0.11 (0.628) | $r_s$ -0.06 (0.803) | $r_s$ 0.06 (0.803) | $r_s$ -0.04 (0.845) |
| RN | $r_s$ -0.33 (0.125) | $r_s$ 0.27 (0.207) | $r_s$ 0.02 (0.929) | $r_s$ -0.36 (0.091) | $r_s$ -0.13 (0.550) | $r_s$ -0.25 (0.242) |

GP: globus pallidus; PUT: putamen; CN: caudate nucleus; THL: thalamus; RN: red nucleus; BRIEF: Behavioral Rating Inventory of Executive Function (off medications); BRI: Behavioral Regulation Index (T-scores); MI: Metacognition Index (T-scores); GEC: Global Executive Composite (T-scores); $r$: Pearson's correlation; $r_s$: Spearman's correlation; [#] $p < 0.05$, two-tailed.