Psychostimulant Medication Duration Correlates with Increased Brain Iron Levels in Attention-Deficit/Hyperactivity Disorder

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Target Audience: Scientists and clinicians interested in the application of magnetic resonance imaging indices of brain iron and dopamine.

Purpose: Dopamine (DA) deficiency is implicated in attention-deficit/hyperactivity disorder (ADHD) pathophysiology [1,2]. Psychostimulant medications are the first line of treatment for ADHD and act primarily by increasing synaptic DA levels in the striatum and basal ganglia regions [3]. As brain iron is required for DA synthesis and metabolism [4], it may serve as a possible indirect biomarker of DA status that can be measured *non-invasively* with magnetic resonance imaging (MRI) [5] – radioactive labels are required for direct DA measurement. By utilizing an MRI method called magnetic field correlation (MFC) imaging [6-8], we recently reported significantly reduced striatal and thalamic iron levels in medication-naïve ADHD patients compared to typically developing controls. In contrast, brain iron levels in ADHD patients with a history of psychostimulant treatment were comparable to controls [9]. The purpose of this study is to examine the effect of psychostimulant treatment duration on brain iron levels in a separate cohort of psychostimulant-medicated ADHD patients and healthy controls. Brain iron is detected in MRI mainly via the effect of magnetic field inhomogeneities (MFIs) on MR signal dephasing. MFC has a more direct relationship to MFIs than R2*, in part because it is independent of dipolar relaxation mechanisms [5-8]. The globus pallidus (GP), caudate nucleus (CN), putamen (PUT) and thalamus (THL) were chosen as regions of interest (ROI) because they are targets of psychostimulants and have comparatively high iron levels (Figure 1A) [1,10].

Methods: This IRB approved study involved a total of 23 males recruited from our institution's medical center and the local community: 11 with comorbidity-free ADHD (mean age 13.8 ± 2.4 years; range 9.7-17.4 years) and 12 age- and IQ-matched typically developing controls (mean age 13.3 ± 3.6 years; range 8.9-18.0 years). ADHD patients met current DSM-IV criteria for ADHD (subtype: 7 combined, 3 inattentive, 1 hyperactive) [11] and are psychostimulant-medicated (methylphenidate, dexmethylphenidate, dextroamphetamine/amphetamine, L-lysine-D-amphetamine). Imaging was conducted on a 3T MR system (Siemens Trio) with a 32 channel head coil. Imaging parameters for each sequence are: MFC asymmetric spin echo images: TR/TE = 5550/40 ms, voxel = 1.7 mm³, slices = 40, averages = 4, flip angle = 90°, EPI factor = 33, bandwidth = 1346 Hz/pixel, refocusing pulse time shifts of 0, -4 and -16 ms and acquisition time = 6 min, 40 sec. T2* gradient echo images: TR/10TEs = 4380/4.92, 9.84, 14.76, 19.68, 24.60, 29.52, 34.44, 39.36, 44.28, 49.20 ms, voxel = 1.7 × 1.7 × 1.0 mm³, slices = 82, average = 1, flip angle = 20°, bandwidth = 260 Hz/pixel, and acquisition time = 5 min, 34 sec. MFC and T2* images all have zero interslice gap, FOV = 220 × 220 mm², and acquisition matrix = 128 × 128. T1-weighted MPRAGE images: TR/TE = 1900/2.26 ms, matrix = 192 × 256 × 256, voxel = 1 mm³, and acquisition time = 4 min, 26 sec. The MFC and R2* parametric maps were calculated with in-house software as previously described [9]. For each age, putative postmortem non-heme iron concentrations (C_{PM}) in healthy brain regions were derived from Hallgren and Sourander's equations and data (Figure 1B) [10]. For each subject, automatic ROI segmentation of the MPRAGE was performed using Freesurfer (http://surfer.nmr.mgh.harvard.edu, Boston). All segmented ROIs and parametric maps were then normalized with ART2 [12,13] to the standard brain template provided by MRIcron (ch2bet.nii, http://www.sph.sc.edu/comd/roden/mricron). For each normalized ROI, a consensus mask for the region was generated representing only voxels with 100% overlap among all subjects. Anatomical accuracy was verified by visual inspection. This consensus ROI was applied to the normalized parametric maps to extract ROI means from each subject. Within group linear regressions were conducted for each MRI brain iron index with C_{PM}, age and medication duration (ADHD only). Student's two sample t-test was used to test for group differences (2-tailed, unequal variances assumed).

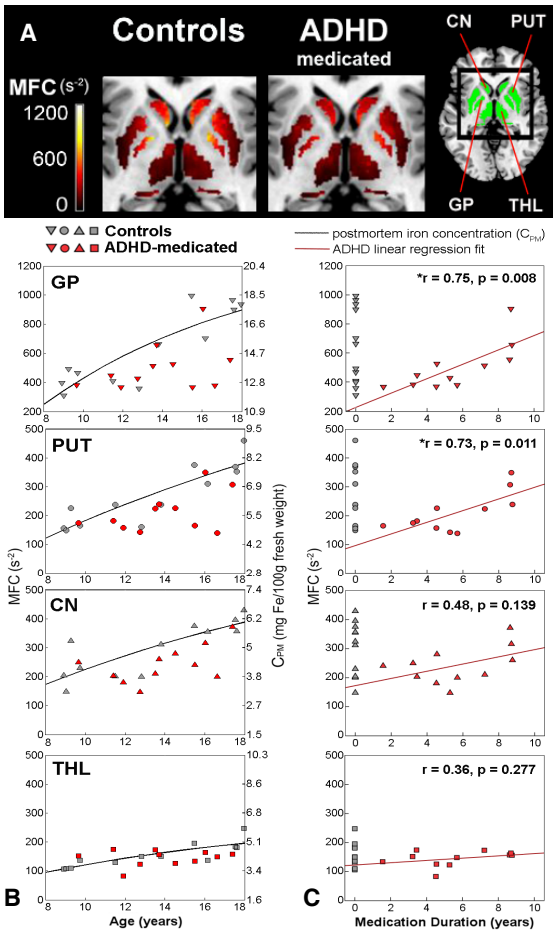

Figure 1. MFC means in ADHD & Controls

Results: The controls and ADHD-medicated groups did not significantly differ in age, IQ and had comparable MFC and R2* indices of brain iron in the GP, PUT, CN and THL ($p > 0.05$; Figure 1A). In controls, MFC in all regions significantly correlated with C_{PM} and significantly increased with increasing age ($r = 0.81 - 0.89$, $p \leq 0.001$); R2* significantly correlated with C_{PM} ($r = 0.79$, $p = 0.002$) and increased with age only in the GP ($r = 0.81$, $p = 0.002$). In the ADHD-medicated group, MFC and R2* in all regions did not significantly correlate with C_{PM} or increase with age ($p > 0.05$). Conversely, MFC in the GP ($r = 0.75$, $p = 0.008$) and PUT ($r = 0.73$, $p = 0.011$) significantly increased with medication duration in the ADHD-medicated group (Figure 1B); R2* detected this only in the GP ($r = 0.077$, $p = 0.006$).

Discussion and Conclusion: Consistent with our previous findings, psychostimulant-medicated ADHD patients had similar brain iron levels to controls. However, unlike controls, the brain iron levels in the medicated ADHD patients did not increase with age. This lack of age-related brain iron increases in ADHD patients may be compensated by psychostimulant medication, with longer treatment duration resulting in normalized brain iron levels comparable to controls. To our knowledge, these results are the first to support that MRI indices of brain iron may be reliable, *non-invasive* biomarkers of DA status sensitive to neuroadaptive changes mediated by psychostimulants. Additionally, MFC exhibits higher sensitivity to variations in brain iron levels compared to R2*.

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