Magnetic Field Correlation Imaging of Brain Iron in Attention-Deficit/Hyperactivity Disorder

Vitria Adisetiyo[1,2], Rachael L. Deardorff[3], Ali Tabesh[3], Els Fieremans[2], Amanda Allen[3], Rebecca Grzadzinski[4], Adriana Di Martino[4], Francisco X. Castellanos[4], Jens H. Jensen[3], and Joseph A. Helpern[3]

[1]Neuroscience & Physiology, NYU School of Medicine, New York, NY, United States, [2]Radiology, NYU School of Medicine, New York, NY, United States, [3]Radiology, Medical University of South Carolina, Charleston, SC, United States, [4]NYU Child Study Center, NYU School of Medicine, New York, NY, United States

Introduction

Several groups have found significantly lower serum iron (ferritin) in attention-deficit/hyperactivity disorder (ADHD) that correlated with higher symptom severity [1-3]. Since the extent to which serum ferritin correlates with brain iron remains unclear, we are interested in examining brain iron in ADHD due to its role in myelin development and dopamine metabolism in the fronto-striatal pathway, both of which are implicated in this disorder [4, 5]. The purpose of this study is to quantify brain iron in ADHD compared to typically developing controls (TDC) using a recently developed imaging method called magnetic field correlation (MFC) imaging together with the more conventional iron measures of R2 and R2*. 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 either R2 or R2*, in part because it is independent of dipolar relaxation mechanisms [6, 7]. The globus pallidus (GP), caudate nucleus (CN), putamen (PUT), nucleus accumbens (ACC) and thalamus (THL) were chosen as bi-hemispheric regions of interest (ROIs) because of their suspected role in ADHD in addition to having high iron content [8]. Serum measures of iron were also collected in the same study visit.

Materials & Methods

This study involved a total of 49 participants: 22 individuals with ADHD (15 males) with a mean age of 12.6 ± 2.8 years (range: 8.3-18.2 years) and 27 typically developing children (TDC; 12 males) with a mean age of 13.3 ± 2.6 years (range: 8.6-18.1 years). ADHD subjects were recruited from the NYU Child Study Center, were either drug naïve (n=12) or off medication on the scan day and met either current DSM-IV criteria for Combined Type ADHD (n=14) or Predominantly Inattentive type ADHD. Serum measures collected after at least 4 hours of fasting include: complete blood count, serum iron, ferritin, transferrin, transferrin saturation and total iron binding capacity. Imaging was conducted on a 3T MR system (Siemens Trio). Imaging parameters for each sequence are: MFC asymmetric spin echo images: TR/TE = 5550/40 ms, voxel = 1.7 × 1.7 × 1.7 mm³, slices = 78, averages = 4, flip angle = 90°, EPI factor = 33, bandwidth = 1346 Hz/pixel. Refocusing pulse time shifts of 0, -4 and -16 ms where the negative sign indicates a reduction of the interval between the initial 90° excitation pulse and 180° refocusing pulse from the usual spin echo value of TE/2, and acquisition time = 6 min, 40 sec. T2 spin echo images: TR/5TEs = 6450/15, 30, 45, 60, 75 ms, voxel = 1.7 × 1.7 × 3.4 mm³, slices = 36, average = 1, flip angle = 180°, turbo factor = 2, bandwidth = 292 Hz/pixel, and acquisition time = 3 min, 59 sec. T2* gradient echo images: TR/10TEs = 60/7, 11.99, 16.87, 21.75, 26.63, 31.51, 36.39, 41.27, 46.15, 51.03 ms, voxel = 1.7 × 1.7 × 1.7 mm³, slices = 72, average = 1, flip angle = 20°, bandwidth = 210 Hz/pixel, and acquisition time = 5 min, 20 sec. MFC, T2 and T2* images are all whole brain, without gaps, with FOV = 220 × 220 mm², matrix = 128 × 128. T1-weighted MPRAGE images: TR/TE = 2200/2.26 ms, matrix = 256 × 256 × 160, voxel = 1 × 1 × 1 mm³, and acquisition time = 3 min, 29 sec. The MFC [6, 7], R2 and R2* parametric maps were calculated with in-house software as previously described [9]. 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 [10, 11] 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 49 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 (Figure1). Student's two sample t-test was used to test for group differences (2-tailed, unequal variances assumed).

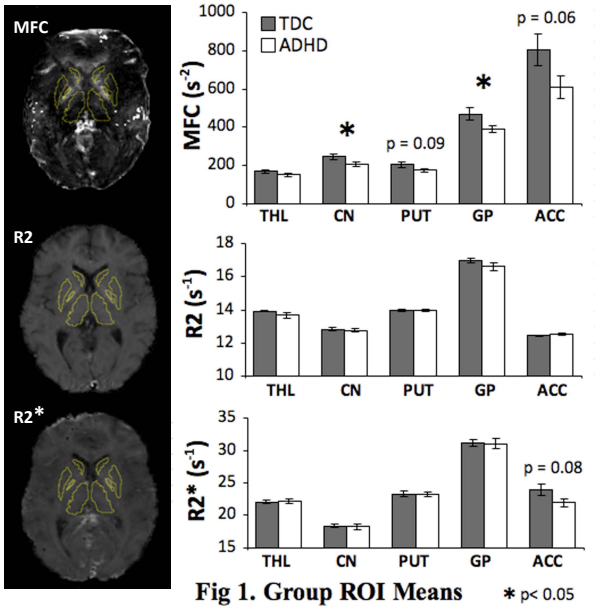

Fig 1. Group ROI Means * p< 0.05

Results

ADHD and TDC groups did not significantly differ in age (p = 0.40) or in any of the serum iron measures. However, MFC means were significantly lower in the ADHD group for the CN (TDC mean ± SEM: 248.4 ± 14.7, ADHD: 208.4 ± 10.7, p = 0.033) and for the GP (TDC: 470.2 ± 31.1, ADHD: 390.7 ± 19.7, p = 0.036) while no significant group differences were detected in either R2 or R2* (Figure 1). Trends of lower MFC in ADHD were found in the PUT (TDC: 204.9 ± 13.2, ADHD: 176.0 ± 9.8, p = 0.085) and ACC (TDC: 806.6 ± 83.1, ADHD: 610.9 ± 58.1, p = 0.060) and with R2* in the ACC (TDC: 23.9 ± 0.9, ADHD: 21.9 ± 0.6, p = 0.075).

Discussion

Consistent with another study of brain iron in ADHD, these results suggest that brain iron in basal ganglia regions is reduced in ADHD [12]. In particular, we found significantly lower levels in the CN and GP compared to age-matched TDC. These regions are likely targets of ADHD stimulant medications that function, in part, by indirectly increasing dopamine concentrations [13]. As iron plays a role in dopamine metabolism, we speculate the reduction in brain iron may be associated with aberrant levels of dopamine in ADHD. We note only MFC measures were able to detect these group differences, supporting the advantage of acquiring this sequence along with conventional R2 and R2* data. Despite significant group differences on an index of brain iron, there were no such differences detected in serum iron measures. This suggests that mechanisms for iron absorption into the brain maybe aberrant in ADHD even when serum iron levels are normal.

References

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