Mode of Anisotropy Reveals Global Diffusion Alterations in Attention-Deficit/Hyperactivity Disorder

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Objective: Diffusion tensor imaging (DTI) can identify structural connectivity alterations in attention-deficit/hyperactivity disorder (ADHD). Most ADHD DTI studies have concentrated on regional differences in fractional anisotropy (FA) despite its limited sensitivity to complex white matter architecture and increasing evidence of global brain differences in ADHD. Here, we examine multiple DTI metrics in separate samples of children and adults with and without ADHD with a principal focus on global between-group differences.

Method: Two samples: adults with ADHD (n = 42) and without (n = 65) and children with ADHD (n = 82) and without (n = 80) were separately group matched for age, sex, and head motion. Five DTI metrics (FA, axial diffusivity, radial diffusivity, mean diffusivity, and mode of anisotropy) were analyzed via tract-based spatial statistics. Group analyses tested for diagnostic differences at the global (averaged across the entire white matter skeleton) and regional level for each metric.

Results: Robust global group differences in diffusion indices were found in adults, with the largest effect size for mode of anisotropy (MA; Cohen's $d = 1.45$). Global MA also differed significantly between groups in the pediatric sample ($d = 0.68$). In both samples, global MA increased classification accuracy compared to the model with clinical Conners' ADHD ratings alone. Regional diagnostic differences did not survive familywise correction for multiple comparisons.

Conclusion: Global DTI metrics, particularly the mode of anisotropy, which is sensitive to crossing fibers, capture connectivity abnormalities in ADHD across both pediatric and adult samples. These findings highlight potential diffuse white matter microarchitecture differences in ADHD.

Key words: ADHD, DTI, fractional anisotropy, adults, biomarkers

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Models of the pathophysiology of attention-deficit/hyperactivity disorder (ADHD), a childhood-onset psychiatric disorder, have evolved from concentrating on fronto-striatal-cerebellar circuits to encompassing large-scale distributed networks.[1-3] Diffusion tensor imaging (DTI), which allows quantification of white matter microstructure, can inform the whole-brain substrates of pathologic alterations in structural connectivity. Most DTI studies of ADHD have limited their scope to tracts selected a priori or are pending definitive replication with rigorous control for multiple comparisons[4]; consequently, the localization and significance of particular regional white matter abnormalities in ADHD remain tentative.

In considering the heterogeneity of DTI findings, we note the global structural alterations in ADHD that other imaging modalities have consistently detected. Reliable overall reductions in total brain volume[5-7] and global cortical thickness[8-10] led us to reason that white matter connectivity might also be globally altered in ADHD. Furthermore, although delineating regional DTI differences can isolate particular loci of ADHD-related abnormalities,[11-14] global measures reduce neuroimaging data dimensionality, which is statistically advantageous,[15] providing impetus for a systematic examination of global diffusion indices.

The most ubiquitously reported diffusion parameter is fractional anisotropy (FA).[16] Although FA is often interpreted as indexing white matter "integrity," Jones *et al.*[17] compellingly argued that this is an oversimplification. Moreover, interpreting FA is particularly problematic in areas with complex white matter architecture, e.g., crossing fibers, the proportion of which ranges from 63% to 90% in typical-resolution white matter voxels.[18] As the precise nature of white matter pathology in ADHD is unclear, complementary indices of diffusion tensor geometry warrant investigation.

One candidate tensor shape metric is the mode of anisotropy (MA),[19] not to be confused with the statistical term mode denoting the most frequent item in a set. MA is mathematically orthogonal to FA and quantifies second-order geometric properties,[19,20] notably resolving whether anisotropy is more planar (e.g., due to predominant crossing fibers within a voxel) or more linear (see Figure S1, available online). Investigators have begun to examine MA in brain disorders.[21-23] MA has contributed unique information relevant to clinical neurodegenerative progression,[24] but it has yet to be examined in ADHD.

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The current study investigated global white matter microstructure in individuals with ADHD, assessing a gamut of DTI indices (including MA and conventional FA). Primary analyses were conducted in an adult sample and, to assess generalizability, repeated in a separate, pediatric sample with data acquired using the same scanner and imaging protocol. Within each of the 2 samples, the ADHD group was contrasted with an age-matched neurotypical (NT) comparison group. Tract-based spatial statistics (TBSS)[25] was used to create a white matter skeleton common to all individuals in each sample. First, all global measures, aggregated across all white matter voxels in the TBSS skeleton, were contrasted between ADHD and NT groups. Second, we explored separately in each sample the prediction of ADHD diagnosis by combining global diffusion, demographic measures, and clinical ratings. Finally, to facilitate comparison with prior regional difference reports, we conducted supplementary whole-brain contrasts[26] of ADHD and NT participants within each sample.

METHOD

Participants

We report on 2 samples (1 adult and the other pediatric) obtained as part of separate studies using identical imaging protocols (Table 1). The adult sample, after quality assurance of imaging data, consisted of 42 individuals with ADHD (age range, 18.2–52.9 years, 57% male and 43% female) and 65 neurotypical (NT) comparisons (18.6–51.9 years, 65% male and 35% female). Inclusion in the adult ADHD group required a clinician's *DSM-IV-TR* diagnosis of ADHD based on the Adult ADHD Clinical Diagnostic Scale Version 1.2[27] and the Structured Clinical Interview for *DSM-IV*, Research Version, Non-patient Edition (SCID)[28] to assess Axis I disorders. Most participants with ADHD (38 of 42) met criteria for persistent ADHD diagnosis (i.e., symptoms and impairment in childhood and adulthood), 2 participants for current ADHD only (i.e., meeting criteria only in adulthood), and 2 presented with history of ADHD in remission (i.e., symptoms in only childhood). All but 7 participants completed the self-report Conners' Adult ADHD Rating Scales (CAARS).[29]

The pediatric sample, after imaging data quality assurance, consisted of 82 individuals with ADHD (age range, 5.2–17.2 years, 78% male and 22% female) and 80 NT children (4.9–17.7 years, 69% male and 31% female). Inclusion in the ADHD group required a clinician's *DSM-IV-TR* diagnosis of ADHD supported by review of prior history and results of the Conners' Parent Rating Scale–Revised: Long Version (CPRS-R:LV, obtained for all but 22 participants)[30] and psychiatric interview using the Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version (KSADS-PL),[31] administered separately to child and parent.

Inclusion as NT in both the adult and pediatric samples required absence of current Axis I diagnosis, assessed for the adult sample with SCID, and for pediatric sample with KSADS-PL (administered to both child and parent in 75 instances; in 5 instances, child-only KSADS-PL was supplemented by unstructured clinical interviews of the parent). Exclusion criteria for all participants were current evidence of autism, major depression, suicidality, substance-related disorder, obsessive-compulsive disorder, conduct disorder, post-traumatic stress disorder, panic disorder, Tourette disorder, lifetime history of psychosis or mania, general chronic medical conditions, left-handedness, or estimated full-scale IQ below 80. Comorbid disorders were present in 7 adults and 27 children with ADHD (see Supplement 1, available online). The Wechsler Abbreviated Scale of Intelligence (WASI) provided estimates of full-scale IQ[32] in all adults and all but 20 children (Differential Ability Scales II[33] was used for 1 NT child, and the Kaufman Brief Intelligence Test[34] for 3 NT and 16 children with ADHD). The institutional review boards of the New York University (NYU) School of Medicine and NYU granted ethical approval. All participants provided written informed consent and, for minors, assent.

Data Acquisition

Magnetic resonance imaging (MRI) data were obtained at the NYU Center for Brain Imaging using a 3T Siemens Allegra scanner with a single-channel Nova head coil. Anatomical T1-weighted images were obtained using 3D Magnetization Prepared Rapid Acquisition Gradient Echo sequence (TR = 2,530 milliseconds; TE = 3.25 milliseconds; TI = 1,100 milliseconds; flip angle = 7°). Two DTI scans were acquired using a twice-refocused diffusion-weighted echo-planar image sequence with parameters TR = 5,200 milliseconds; TE = 78 milliseconds; 50 slices; acquisition matrix 64 × 64; field of view = 92 mm; acquisition voxel size = 3 × 3 × 3 mm; 64 non-collinear diffusion directions, uniformly distributed around a unit sphere with a b-value of 1000 s/mm^2; 1 image with no diffusion weighting. A gradient echo field map was collected (TR = 834 milliseconds; TEs = 5.23 and 7.69 milliseconds) with slice position and resolution identical to those of the diffusion-weighted images.

DTI Preprocessing and Quality Assurance

Diffusion-weighted data were pre-processed using FMRIB Software Library version 5.[35] Motion correction (linear registration) was followed by correction of image distortions from eddy currents and B0-field inhomogeneities. Absolute intervolume displacement[36] of each image with respect to the first image in the run was computed. For participants with maximum displacement within 1.5 × voxel size (grand total = 410 participants), individual maps were visually inspected for signal dropout, brain coverage, artifacts, and additional motion. Based on quality control criteria, data from 5 ADHD (11% of initial sample of adults with ADHD) and 12 NT (13%) adults, and 67 ADHD (45%) and 57 NT (42%) children, were discarded. Mean absolute intervolume displacement served as the primary head motion index for subsequent analyses. Analyses were repeated with mean volume-by-volume translation and mean volume-by-volume rotation as supplementary motion indices.[36,37] Diffusion gradients were rotated to improve consistency with the motion parameters, and data for each of the two 64-direction scans were used to fit the tensor parameters, thus improving signal-to-noise ratio. Following fitting of diffusion tensors at each voxel, fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), mean diffusivity (MD), and mode of anisotropy (MA) values were generated. Three additional shape measures (linear c_L, planar c_P, and spherical c_S tensor components[38]) were computed to characterize post hoc differences in diffusion tensor geometry.[19] All analyses detailed below (global and voxelwise) were performed separately for the pediatric and adult samples, unless noted otherwise.

Tract-Based Spatial Statistics (TBSS)

Further data processing was performed using tract-based spatial statistics (TBSS),[25] which calculates a white matter "skeleton" to represent the center of each white-matter tract common to all participants, thus ameliorating the impact of imperfect alignment, registration, and arbitrarily thresholded spatial smoothing. TBSS is commonly preferred when contrasting patients with NT individuals