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A dual DTI approach to analyzing white matter in children with dyslexia

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Abstract

Using voxel-based (VBA) and region-of-interest (ROI) diffusion tensor imaging (DTI) analyses, we examined white matter (WM) organization in 7 children with dyslexia and 6 age-matched controls. Both methods demonstrated reduced fractional anisotropy (FA) in the left superior longitudinal fasciculus (SLF) and abnormal orientation in the right SLF in dyslexics. Application of this complementary dual DTI approach to dyslexia, which included novel analyses of fiber orientation, demonstrates its usefulness for analyzing mild and complex WM abnormalities.

Keywords

reading disability; anisotropy; superior longitudinal fasciculus

1. Introduction

Diffusion tensor imaging (DTI) is a technique that provides information on organization, orientation, and other features of WM bundles (Mori and Zhang, 2006). Most DTI studies of neuropsychiatric disorders have relied primarily on automated voxel-based analyses (VBA) of standardized images (Kanaan et al., 2005). As in other areas of neuroimaging research, co-

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application of automated and manual methods, the latter delineating regions-of-interest (ROIs) in native space, is becoming more common in DTI (Seok et al., 2007; Ng et al., 2007). This dual approach, which overcomes the limitations of each methodology, has been particularly recommended for the study of the complex changes affecting WM development (Snook et al., 2007).

Dyslexia or reading disability, a learning disorder characterized by selective difficulties in decoding and recognizing single words (Lyon, 1995), is uniquely suited for the aforementioned dual DTI analyses. Dyslexia has been linked to relatively mild developmental abnormalities (i.e., microdysgeneses, abnormal symmetry of the planum temporale) and dysfunction of cortical regions surrounding the Sylvian fissure, by both postmortem and MRI studies (Galaburda, 1993; Pugh et al., 2000; Eckert, 2004). These data suggest mild and complex disturbances in WM bundles coursing through the temporo-parietal region, as the result of focal disruption or topographic changes. Supporting this hypothesis, earlier DTI studies of dyslexia have revealed decreased fractional anisotropy (FA) in the area of the left superior longitudinal fasciculus (SLF) (Klingberg et al., 2000; Beaulieu et al., 2005; Deutsch et al., 2005). However, they have also demonstrated a more diffuse cerebral WM involvement (e.g., corona radiata, internal capsule) (Beaulieu et al., 2005; Deutsch et al., 2005; Niogi and McCandliss, 2006). With the exception of the report by Niogi and McCandliss (2006), these studies have mainly used VBA and no concurrent evidence has been presented for any particular finding. In this study, VBA and ROI approaches, including novel analyses of fiber orientation, were complementarily used to examine key cortical WM tracts in children with dyslexia. We also explored relationships between DTI measures and reading ability.

2. Methods

2.1 Subjects

Participants were children, between 10–14 years, who had received a classification of either dyslexic (n=7; 6M, 1F) or control (n=6; 2M, 4F) from a previous research study and were recruited for the present one. In order to confirm current group classification, children were re-administered various reading measures widely used to differentiate dyslexic subjects (Pugh et al., 2001), including Word-Level Accuracy (Woodcock, 1998; Newcomer, 2001) and Word-Level Efficiency (Torgesen et al., 1999). Children with dyslexia scored significantly lower than controls on both measures ($P=0.0034$; Wilcoxon rank sum test); group means and standard deviations (reported in percentiles) were: *Word-Level Accuracy*: dyslexic = 20.6 $\pm$ 13.2, control = 72.7 $\pm$ 11.8; *Word-Level Efficiency*: dyslexic = 7.1 $\pm$ 6.4, control = 63.3 $\pm$ 31.2. Additional reading constructs included Naming Speed (Wolf and Denckla, 2005) and Reading Comprehension (Woodcock, 1998; Newcomer, 2001). Other measures included IQ scores (Wechsler, 1991), handedness, (Oldfield, 1971), and socioeconomic status (Hollingshead, 1985). Symptoms of attention-deficit-hyperactivity disorder (ADHD) were evaluated through a variety of parent questionnaires (Reynolds and Kamphaus, 1992; Conners et al., 1997; Gioia et al., 2000; Achenbach and Rescorla, 2001). Four children (3 dyslexics; 1 control) had a history of treatment for ADHD; 3 were receiving stimulant medication. All protocols were approved by the Johns Hopkins Medical Institutional Review Board.

2.2 Image acquisition and processing

Fifty 2.5-mm-thick contiguous slices were acquired on a 1.5 Tesla unit (Gyrosan NT, Philips Medical Systems, Andover, Massachusetts) using single-shot axial echo-planar imaging with sensitivity encoding (SENSE). Acquisition and post-acquisition processing were performed as described previously (Wakana et al. 2004); specifically, diffusion weighting was applied along 30 independent axes (Jones et al., 2002) at $b=800$ s/mm², in addition to 5 images with $b=0$ s/mm². Three eigenvectors and three eigenvalues were obtained from each voxel after

diagonalization of the diffusion tensor. Fiber orientation was assessed using the absolute value of the eigenvector associated with the largest eigenvalue and color-coded according to the red (medial-lateral), green (anterior-posterior), blue (superior-inferior) convention (Pajevic and Pierpaoli, 1999). This approach is essentially a simplified version of the Watson test for principal diffusion direction described by Schwartzman and colleagues (2005). It should be noted that in taking the absolute value of the eigenvector (principal diffusion direction), our approach is insensitive to fiber directionality (e.g., right-to-left vs. left-to-right), and thus fiber orientation is expressed with both planar components (i.e., medial-lateral, superior-inferior, anterior-posterior).

2.3 Voxel-based analyses (VBA)

Images corresponding to FA, apparent diffusion coefficient (ADC) and each color (orientation) map, in order to facilitate imaging processing, were converted to *Analyze* format using an algorithm developed by one of the authors (X.C.), and analyzed using Statistical Parametric Mapping software (SPM2) (Wellcome Department of Imaging Neuroscience, London, England). Prior to VBA, non-diffusion weighted images (i.e., $b=0$ s/mm²) were spatially normalized to stereotactic space using the Montreal Neurological Institute (MNI) EPI template, and the resultant parameters were applied to FA, ADC, and color maps. Spatially transformed images were subsequently re-sampled into 2 mm³ isometric voxels and smoothed using a Gaussian kernel of $8 \times 8 \times 8$ mm³. Between-group statistical significance was based on a combination of voxel Z-scores and the spatial distribution of local maxima, after correcting for multiple comparisons across the whole-brain volume using a family-wise error correction scheme.

2.4 Region of interest (ROI) analyses

Using DTI-Studio software (H. Jiang, S. Mori, Johns Hopkins University), the following ROIs were outlined bilaterally in native space: (1) frontal deep WM (axially); (2) SLF (axially and coronally), further segmented into anterior-posterior, arcuate posterior, and projecting temporo-parietal segments. Finally, the anterior and posterior segments of the inferior longitudinal fasciculus (ILF), at similar locations to those for the SLF, were examined as a putative “negative control.” Figure 1 schematically depicts the location of ROIs. ROIs were selected based on evidence-based hypotheses and outlined according to the human WM atlas published by Wakana and colleagues (2004) and operationally defined parameters which included FA (≥ 0.3 , on a scale of 0–1) and orientation (color intensity ≥ 100 , on a scale of 0–255) thresholds. These criteria conform to the conventional definition of WM (Basser & Pierpaoli, 2004) and were adopted in order to ensure consistency and accuracy in isolating tracts of interest from surrounding WM, and also reduce tract overlap. As such, only the “cores” of tracts of interest were delineated; branching or potential orientational changes were not considered for this purpose. Measures for each ROI included cross-sectional area, FA, ADC, and fiber orientation (color). Recognizing that ROIs comprised areas of heterogeneous content (i.e., principal fiber orientation was not uniformly distributed), we examined the distribution of fibers (voxels) of a given orientation (diffusion direction) *within* ROIs. ROI drawings were performed by raters blind to the subject group membership. Intra- and inter-rater reliability (*Cohen’s kappa*) ranged from >0.6 – 0.9 for axial ROIs to >0.5 – 0.8 for coronal ROIs. Contentious ROIs were resolved through post-tracing editing.

2.5 Statistical methods

Wilcoxon rank sum exact tests were performed on all ROI-based DTI and reading (i.e., Naming Speed, Word-Level Accuracy, Word-Level Efficiency, Reading Comprehension) measures to detect between-group differences. DTI regions demonstrating significant group differences were then used for imaging-behavior correlations (Spearman’s rho). *P*-values in VBA were

corrected using SPM's native family-wise error correction scheme. *P*-values in ROI-based imaging and behavioral analyses were Bonferroni-corrected for multiple comparisons/tests and are reported as such.

3. Results

3.1 Demographic and behavioral characteristics

Preliminary analyses revealed no sex differences; consequently, all analyses were conducted with boys and girls together. Between-group analyses demonstrated no significant differences in age, handedness, or socioeconomic status. As expected, children with dyslexia scored significantly lower than controls on all reading constructs (i.e., Naming Speed [Objects subtest: $P=0.023$; Letters subtest: $P=0.0047$], Word-Level Accuracy [$P=0.0012$], Word-Level Efficiency [$P=0.0012$] and Reading Comprehension [Passage Comprehension: $P=0.0221$]; Wilcoxon rank sum tests), as well as on verbal IQ ($P=0.025$; Wilcoxon rank sum test). The dyslexic group also demonstrated increased inattentive symptoms ($P=0.048$; Wilcoxon rank sum test).

3.2 VBA analyses

VBA revealed no between-group differences in ADC. Dyslexic subjects had significantly lower FA in the left SLF region ($P=0.0012$; Wilcoxon rank sum test), left middle/superior frontal gyrus (Brodmann area 8) ($P=0.0012$; Wilcoxon rank sum test), and left precuneus (Brodmann area 7) ($P=0.0012$; Wilcoxon rank sum test). Dyslexics also showed significantly smaller proportions of medial-lateral-oriented fibers in the left SLF ($P=0.0027$; Wilcoxon rank sum test) and anterior-posterior-oriented fibers ($P=0.0012$; Wilcoxon rank sum test) in the right SLF, as well as a trend-level increase in superior-inferior-oriented fibers ($P=0.087$; Wilcoxon rank sum test) in the right SLF.

3.3 ROI analyses

ROI-based analyses showed no significant between-group differences in ADC for any ROI, or in FA or fiber orientation in frontal WM. There were trend-level differences in cross-sectional area of the right posterior SLF (Control>Dyslexia; $P=0.078$; Wilcoxon rank sum test), but no differences in FA. ROIs corresponding to the right SLF's temporo-parietal projection showed a significantly greater proportion of superior-inferior-oriented fibers in dyslexics ($P=0.014$; Wilcoxon rank sum test), whereas controls tended to show a predominance of anterior-posterior and medial-lateral fibers. ROIs along the ILF showed significant differences only in the left posterior portions of the tract, specifically an increase in the relative proportion of medial-lateral fibers ($P=0.014$; Wilcoxon rank sum test) and a decrease in superior-inferior fibers ($P=0.022$; Wilcoxon rank sum test) in dyslexics. The anterior ILF was comparable between dyslexics and controls.

Although ROI analyses did not show FA changes in the left posterior SLF, because of the widely reported findings in this region and our VBA data, we re-examined this ROI under the premise that an FA-based delineation criterion ($FA \geq 0.3$) could have biased ROI outlining to include only central portions and exclude bifurcating or overlapping regions. Systematic sampling of voxels comprising the periphery of the left posterior SLF showed that dyslexics had significantly lower FA ($P=0.002$; Wilcoxon rank sum test), particularly along the ventral aspect (Supplementary Figure).

Given the increase in superior-inferior fibers, normally the smallest component, of the right temporo-parietal SLF observed by both VBA and ROIs, we further assessed this abnormal profile by studying the *within*-ROI distribution of "high intensity" blue fibers (i.e., voxels with a degree of superior-inferior orientation greater than two standard-deviations above the mean).

The latter were localized in the medial aspect of the SLF ROI in controls, but diffusely distributed in dyslexics. Moreover, a substantially greater proportion of the ROI in dyslexics was occupied by “high intensity” blue fibers (32%) than in controls (14%).

Figure 2 illustrates the findings demonstrated by both VBA and ROIs: a dyslexia-associated decrease in FA in the left posterior SLF and an abnormal preponderance of superior-inferior fibers in the temporo-parietal right SLF, as well as the abovementioned within-ROI right SLF analysis.

3.4 Imaging-reading ability correlations

Exploratory correlations of imaging and reading variables showed that FA in the left SLF and its periphery was positively correlated with most reading measures, whereas the proportion of superior-inferior fibers in the right SLF was negatively correlated only with Word-Level Accuracy and Letter Naming Speed ($P < 0.05$; Spearman's rho, corrected for multiple comparisons). These relationships remained significant even after controlling for ADHD status.

4. Discussion

This study is the first to our knowledge to use two complementary DTI approaches to characterize WM abnormalities in children with dyslexia (Klingberg et al., 2000; Beaulieu et al., 2005; Deutsch et al., 2005; Niogi and McCandliss, 2006). Both VBA and ROI analyses revealed that in dyslexia there is a decrease in FA in the left posterior SLF, apparently driven by the ventral peripheral portion of the tract, and an abnormal orientation of the right SLF in dyslexics, specifically an increase in superior-inferior oriented fibers in its temporo-parietal projection that ordinarily runs anterior-laterally. The detailed ROI sampling technique of the periphery of the left SLF undertaken in this study emphasizes the importance of VBA-guided ROI analyses in identifying areas of subtle or diffuse abnormality. Not surprisingly, VBA also demonstrated reductions in FA in areas only partially (i.e., left prefrontal) or not (i.e., left precuneus) covered by ROIs. On the other hand, ROI but not VBA analyses of the ILF, a “control” fiber bundle, suggested that the bilateral SLF changes are part of a more global disturbance of the temporo-parietal WM that also affects the posterior ILF. Complementary application of VBA and ROI individual color map (orientational distribution) analyses, an innovation in this study, not only provided concurrent evidence of fiber orientation changes in the right SLF but also demonstrated an atypical and disorganized WM pattern in dyslexic subjects in line with neurobiological studies of dyslexia and connectivity abnormalities in rodent models of microdysgenesis (Galaburda, 1993; Rosen et al., 2001; Eckert, 2004).

Our observations extend the current understanding of the neuroanatomical and neurobehavioral features of dyslexia. Both VBA and ROI approaches demonstrated FA decreases in the left perisylvian WM of dyslexic subjects, a finding which accords with a substantial body of existing literature on the neuroanatomy of dyslexia (Galaburda et al., 1985; Humphreys et al., 1990; Galaburda et al., 1994; Jenner et al., 1999), and may represent focal disruptions in fiber tracts subserving reading ability, relatively independent of other cognitive operations. Moreover, our finding of increases in the proportion of superior-inferior oriented fibers in the right SLF of subjects with dyslexia, ordinarily an anterior-posterior/medial-lateral-oriented portion of the tract, may illustrate an aberration of tract geography, possibly a displacement of normal curvature resulting from disrupted axonal connectivity due to enlargement of the planum temporale in dyslexia (Eckert & Leonard, 2000). Although exploratory due to the relatively small number of subjects, imaging-behavioral correlations supported the functional implications of these DTI findings.

In conclusion, a dual automated and manual DTI approach, particularly if it includes detailed and integrated analyses of key DTI parameters, is able to provide concurrent and expanded evidence on subtle and complex WM abnormalities such as those present in dyslexia. We support previous statements about the need of applying this multi-DTI strategy to normal and disordered WM development (Kanaan et al., 2005; Snook et al., 2007).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Schematic representation of ROIs in the SLF (green outlines) and ILF (blue outlines). ROIs in the SLF correspond to anterior (A) and posterior (B) segments where the tract's principal orientation is anterior-posterior, the arcuate component (C), and the projecting parietal-temporal component (D). ROIs in the ILF correspond to anterior (E) and posterior (F) segments of the tract. Underlay image adapted from Wakana and colleagues (2004).

Figure 2.

Concordant VBA (top row) and ROI (bottom row) findings for FA in the left posterior SLF (**Panel A**) and superior-inferior fiber orientation in the right temporo-parietal component of the SLF (**Panel B**); the regions are denoted by blue cross-hairs on the sagittal, axial, and coronal planes. Panel C shows the relative distribution of superior-inferior-oriented (“blue”) fibers in the SLF; light blue represents fibers with orientations within two standard deviations of the mean, whereas dark blue represents fibers with superior-inferior vector components greater than two standard deviations above the mean. Note the wide and inhomogeneous distribution of superior-inferior oriented fibers in dyslexia.