Neuropsychology
2017, Vol. 31, No. 5, 508–515

0894-4105/17/$12.00 http://dx.doi.org/10.1037/neu0000243

Relation of White-Matter Microstructure to Reading Ability and Disability in Beginning Readers

Joanna A. Christodoulou
Massachusetts Institute of Technology and MGH Institute of Health Professions

Jack Murtagh and Abigail Cyr
Massachusetts Institute of Technology

Tyler K. Perrachione
Massachusetts Institute of Technology and Boston University

Patricia Chang and Kelly Halverson
Massachusetts Institute of Technology

Pamela Hook
MGH Institute of Health Professions

Anastasia Yendiki
Massachusetts General Hospital and Harvard Medical School

Satrajit Ghosh
Massachusetts Institute of Technology and Harvard Medical School

John D. E. Gabrieli
Massachusetts Institute of Technology and Harvard Graduate School of Education

Objective: We examined the white-matter microstructure of the left arcuate fasciculus, which has been associated with reading ability, in beginning readers with or without reading disability. ***Method:*** Groups were typically reading children ($n = 26$) or children with reading disability ($n = 26$), Ages 6–9, and equated on nonverbal cognitive abilities. Diffusion-weighted images were collected and TRACULA was used to extract fractional anisotropy measures from the left arcuate fasciculus. ***Results:*** White-matter microstructure was altered in children with reading disability, who exhibited significantly reduced fractional anisotropy in the left arcuate fasciculus. Among typically reading children, lower fractional anisotropy of the left arcuate fasciculus was associated with superior pseudoword reading performance. Both the group differences and variation in reading scores among the children with reading disability were associated with radial diffusivity (but not axial diffusivity), whereas variation in reading scores among typically reading children was associated with axial diffusivity (but not radial diffusivity). ***Conclusions:*** The paradoxical findings that lower fractional anisotropy was associated both with reading disability and also with better phonological awareness in typical reading development suggest that there are different maturational trajectories of white-matter microstructure in typical readers and children with reading disability, and that this difference is unique to the beginning stages of reading acquisition. The finding that reading disability was associated with radial diffusivity, but that variation in ability among typically developing readers was associated with axial diffusivity, suggests that different neural mechanisms may be associated with reading development in children with or without reading disability.

Keywords: reading, reading disability, dyslexia, DWI, arcuate fasciculus

This article was published Online First March 7, 2016.

Joanna A. Christodoulou, McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, and Department of Communication Science and Disorders, MGH Institute of Health Professions; Jack Murtagh and Abigail Cyr, McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; Tyler K. Perrachione, McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, and Department of Speech, Language and Hearing Sciences, Boston University; Patricia Chang and Kelly Halverson, McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology; Pamela Hook, Department of Communication Science and Disorders, MGH Institute of Health Professions; Anastasia Yendiki, Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital and Harvard Medical School; Satrajit Ghosh, McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, and Massachusetts Eye and Ear and Department of Otology and Laryngology, Harvard Medical School; John D. E. Gabrieli, McGovern Institute for Brain Research and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, and Harvard Graduate School of Education.

We thank the Ellison Medical Foundation and the Halis Family Foundation for funding support to John D. E. Gabrieli. We thank the participants and their families. We thank the Athinoula A. Martinos Imaging Center at the McGovern Institute for Brain Research (MIT) and Atshusi Takahashi, Steve Shannon, and Sheeba Arnold for data collection technical support, and Chunming Lu for advice on analysis. Joanna A. Christodoulou and Jack Murtagh contributed equally to this work.

Correspondence concerning this article should be addressed to Joanna A. Christodoulou, Department of Communication Science and Disorders, MGH Institute of Health Professions, 36 First Avenue, Boston, MA 02129. E-mail: jac765@mail.harvard.edu

Reading disability is the most common learning disability among school-age children. Students with reading disability often meet criteria for developmental dyslexia, a disorder of the ability to acquire and develop word-reading skills (Lyon, Shaywitz, & Shaywitz, 2003). The most prominent underlying deficit of dyslexia is in phonological awareness, the detection and manipulation of language sounds, and, consequently, the ability to link sounds and letters (Bradley & Bryant, 1978). Relative to typically developing readers, children and adults with developmental dyslexia show functional and structural brain differences (reviewed in Gabrieli, 2009). Here, we focused on differences in the microstructural anatomy of white matter, measured by diffusion weighted imaging (DWI), during early stages of reading development in young children with or without reading disability.

Differences in white-matter diffusivity between typical readers and those with reading disability have been noted in several brain regions, but the most consistent difference has been in the left temporoparietal region in or near the left superior longitudinal fasciculus (SLF; Vandermosten, Boets, Wouters, & Ghesquière, 2012). The SLF is comprised of two major components: a direct arcuate fasciculus (AF) pathway connecting posterior (superior temporal gyrus in the region of Wernicke's area) and anterior (in the region of Broca's area) language cortices, and an indirect pathway including the SLFp connecting inferior parietal cortex and anterior language cortices (Catani, Jones, & ffytche, 2005; see Figure 1). Early studies of white-matter microstructure in dyslexia did not distinguish between these pathways, but methodological advances have supported separable analyses of the AF and SLFp components of the SLF (e.g., Yendiki et al., 2011). In particular, definition of the white-matter tracts in native brain spaces using tractography techniques (Beaulieu et al., 2005; Boets et al., 2013; Niogi & McCandliss, 2006; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010; Saygin et al., 2013; Thiebaut de Schotten, Cohen, Amemiya, Braga, & Dehaene, 2014; Vandermosten, Boets, Poelmans, et al., 2012; Welcome & Joanisse, 2014; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012), in contrast to whole-brain averaging (Deutsch et al., 2005; Gold, Powell, Xuan, Jiang, & Hardy, 2007; Klingberg et al., 2000; Nagy, Westerberg, & Klingberg, 2004; Richards et al., 2008; Steinbrink et al., 2008), has improved the precision with which white-matter measures can be associated with specific tracts. These investigations build on a historical foundation of understanding dyslexia as a disconnection syndrome, as advanced by Geschwind (1965a, 1965b) and described as blocked or interrupted information transfer between brain regions, which has been extended by functional neuroimaging investigations (Paulesu et al., 1996).

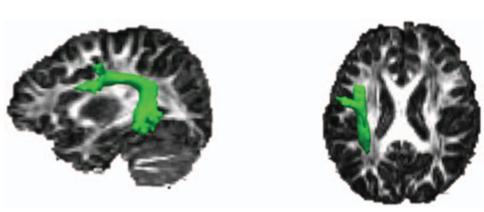

Figure 1. Sample TRACULA reconstruction of the left arcuate fasciculus from probabilistic tractography in sagittal (left) and axial (right) views.

Structural properties of the AF appear to be altered in dyslexia based on multiple measures, including fractional anisotropy (FA) from diffusion tensor imaging (Klingberg et al., 2000). Although the precise location of the difference has varied across studies, in most studies, individuals with dyslexia exhibited reduced FA in or near the AF (Boets et al., 2013; Deutsch et al., 2005; Klingberg et al., 2000; Niogi & McCandliss, 2006; Richards et al., 2008; Rimrodt et al., 2010; Steinbrink et al., 2008; Vandermosten, Boets, Poelmans, et al., 2012). Furthermore, children who had not yet received formal reading instruction exhibited a positive correlation between FA of the left AF and performance on tests of phonological awareness that typically predict success in learning to read (Saygin et al., 2013). This finding suggests that microstructural differences may be a predisposing factor for reading disability rather than being only a consequence of reduced reading experience. Causal evidence for the role of the left AF in learning to read comes from a study in which FA increased in ex-illiterate adults learning to read relative to illiterate adults (Thiebaut de Schotten et al., 2014).

Similar relations between properties of the SLF or AF have been related to individual differences in reading abilities in typically reading children and adults (Beaulieu et al., 2005; Gold et al., 2007; Nagy et al., 2004; Welcome & Joanisse, 2014). The precise location of the left temporoparietal regions in which white-matter microstructure correlated with reading abilities varied. Critically, the studies of variation in typical reading ability aligned with the studies of reading disability by indicating that higher FA in the SLF or AF was associated with superior reading or reading-related language abilities.

A rare longitudinal study of children with a broad range of reading abilities, but without dyslexia, offered a paradoxical finding that children (Ages 7–11) with above-average reading abilities had *lower* FA of the left AF and left inferior longitudinal fasciculus that increased over a 3-year period, whereas children with reading ability in the lower half of the average range had higher initial FA that declined over time (Yeatman et al., 2012). These analyses indicated that when children are beginning to learn to read, lower FA is associated with superior reading ability, and that this pattern reverses in older readers. These findings suggest a dynamic, developmental aspect of white-matter maturation in children that may have been difficult to observe in cross-sectional studies in which most participants, with or without dyslexia, were in the age range (over 10 years old) in which greater FA has consistently been associated with better reading abilities. Thus, there is an apparent paradox that lower FA is associated with both reading disability and also superior reading in typical beginning reading development.

In order to resolve this apparent paradox, we used DWI with children between 6 and 9 years old, in which lower FA of the left AF has been associated with superior reading skills (Yeatman et al., 2012). We included both typical readers and children with reading disability. We used the same measures of reading skill that had shown a negative correlation with FA of the left AF (Yeatman et al., 2012), namely, single-word reading and pseudoword reading measures. This study allowed for the first comparison of a brain difference in white matter between typically developing children versus children with reading disability in the critical early years of reading acquisition before Age 10.

Method

Participants and Assessment Procedures

Participants (Ages 6–9) were native English speakers with no history of neurological or psychiatric diagnoses as indicated by parent questionnaires. Group assignment was based on results from behavioral testing of cognitive and reading skills conducted in a one-on-one setting with a qualified assessor. Nonverbal cognitive ability was measured using the Matrices subtest from the Kaufman Brief Intelligence Test, Second Edition (KBIT-2; Kaufman & Kaufman, 2004). Reading abilities were assessed with four standardized measures of single-word reading. Untimed reading ability was indexed by accuracy for reading real words and pseudowords using the Word Identification and Word Attack subtests, respectively, from the Woodcock Reading Mastery Test-III (WRMT-III; Woodcock, 2011). Timed reading ability was indexed by accuracy for reading real words and pseudowords within time limits using the Sight Word Efficiency and Phonemic Decoding Efficiency subtests, respectively, from the Test of Word Reading Efficiency, Second Edition (TOWRE-2; Torgesen, Wagner, & Rashotte, 2012). Parents of participants completed a background questionnaire concerning developmental history of language and literacy skills, as well as socioeconomic status.

Participants with reading disability ($n = 43$) were struggling readers based on parent report of developmental and clinical history. In addition, participants currently scored below the 25th percentile on at least one of four single-word reading measures, or showed a discrepancy of at least one standard deviation between nonverbal cognitive ability and scores on at least one of four single-word reading measures. Data from four participants were removed from further analysis because of poor data quality (described in the Imaging Procedures and Analysis section, last paragraph). In the reading disability group, 70% of participants had been evaluated by a clinician previously and carried diagnoses of dyslexia or a language-based learning disability. In the typical reader group ($n = 26$), participants performed at or above the 25th percentile on all four single-word reading assessments and carried no reported diagnosis or family history of reading difficulty. A subset of participants with reading disability (reading disability group, $n = 26$) with relatively higher scores on the Matrices subtest was selected so that they were matched to the typical reader group on nonverbal cognitive ability. The participants who had reading difficulty and lower scores on nonverbal cognitive ability were defined as the excluded reading disability group ($n = 13$).

By design, the typical reader group performed significantly better than the reading disability group on standardized measures of untimed and timed single-word reading (Table 1; independent samples t tests, two-tailed, all $ps < .001$). Groups did not differ significantly by gender, $\chi^2(1, N = 52) = .361$, $p = .55$, age, nonverbal cognitive abilities (see Table 1), handedness, socioeconomic status, or ethnicity ($p > .05$).

Analyses were repeated with a subgroup within the reading disability group ($n = 16$) that met stricter criteria consistent with developmental dyslexia. These participants scored below the 25th percentile on Word Identification ($M = 81.00$, $SD = 6.62$) and at least one additional single-word reading measure using WRMT-III Word Attack ($M = 85.56$, $SD = 9.44$), TOWRE-2 Sight Word Efficiency ($M = 80.37$, $SD = 12.36$), and TOWRE-2 Phonemic Decoding Efficiency ($M = 80.00$, $SD = 10.61$). This subgroup did not differ significantly from the typical reader group by gender, age, nonverbal cognitive abilities, handedness, socioeconomic status, or ethnicity ($p > .05$).

Additional analyses were conducted with those with reading disability who were part of the original sample but were excluded when matching for nonverbal cognitive ability. This excluded reading disability group ($n = 13$) did not differ from the typical reader group on gender, age, handedness, socioeconomic status, ethnicity, or motion in the scanner ($p > .05$). Nonverbal cognitive ability, as measured by scores on the Matrices subtest on the KBIT-2, in the excluded reading disability group ($M = 92.31$, $SD = 3.61$) was in the lower half of the average range (standard score range of 87–100), and was significantly lower than those of the reading disability group, $t(37) = 7.28$, $p < .001$, and the typical reader group, $t(37) = 6.05$, $p < .001$.

Imaging Procedures and Analysis

To optimize data quality collected from the young study participants, we employed several strategies to minimize motion and to ensure comfort and understanding of study procedures. Prior to the data collection session, participants were provided a video that offered an overview of the study location, mock scanner room, and scanner room, as well as information on what to wear for the scan (e.g., no metal, comfortable clothing). Upon arrival, participants

Table 1
Standardized Behavioral Test Scores for the Typical Reader Group and the Reading Disability Group

Construct	Behavioral measure	Typical reader group ($n = 26$) ($M \pm SD$)	Reading disability group ($n = 26$) ($M \pm SD$)	p Typical vs. reading disability
Age (months)		94.00 ± 7.66	93.65 ± 7.81	.87
Nonverbal cognitive ability	KBIT-2–Matrices	118.31 ± 15.24	113.35 ± 10.05	.172
Word reading accuracy	WRMT-III–Word Identification	119.00 ± 9.33	86.77 ± 9.46	.000*
	WRMT-III–Word Attack	114.04 ± 9.31	89.27 ± 10.13	.000*
Word reading fluency	TOWRE-2–Sight Word Efficiency	114.48 ± 8.07	84.62 ± 11.70	.000*
	TOWRE-2–Phonemic Decoding Efficiency	112.42 ± 8.31	81.76 ± 9.33	.000*

Note. KBIT-2 = Kaufman Brief Intelligence Test, Second Edition; WRMT-III = Woodcock Reading Mastery Test-III; TOWRE-2 = Test of Word Reading Efficiency, Second Edition.
* $p < .001$, two-tailed t test.

and their families learned about our study as we described the purpose, the value of their contributions, the option to stop participation at any time, and the series of planned activities. We obtained written informed assent and consent for participation in the study, approved by the Massachusetts Institute of Technology Institutional Review Board, from participants and their parent(s). Each participant practiced the scanner tasks and was introduced to the scanner environment in a mock scanner room, which allowed them to preview the look, feel, and sounds associated with MRI. Each participant was also invited to choose from a collection of scanner-safe stuffed animals to bring with them during the scan. Each participant was joined in the scanner room by a "scan buddy," a research team member who remained next to the child for the duration of the scan and was available to offer motion feedback and ensure comfort.

Data were acquired on a 3T Siemens MAGNETOM Trio Tim scanner with a 32-channel phased array head coil. T1 weighted images were acquired with a single shot, interleaved series with TR = 2,530 ms, FoV = 220 mm, flip angle = 7.0°, yielding 176 slices with voxel dimensions 1.0 × 1.0 × 1.0 mm. The high-resolution diffusion sequence was an interleaved series with TR = 9,300 ms, TE = 84 ms, and FoV = 256 mm, for 74 slices with voxel dimensions 2.0 × 2.0 × 2.0 mm. The diffusion scan included 10 non-diffusion-weighted volumes where b = 0 and 30 different gradient directions at b = 700 s/mm^2.

Tract-based analysis using FreeSurfer's TRACULA (Yendiki et al., 2011) defined the tract of interest from each participant's diffusion data. We extracted statistics on FA, axial diffusivity (D_{axial}), and radial diffusivity (D_{radial}) from the temporal branch of the left SLF (SLFt), also known as the AF (see Figure 1). The same statistics were extracted from the right SLF, serving as a control tract. We opted for tract-based analysis rather than whole-brain FA given a priori interest in examining the left SLFt. We hypothesized that there would be significant left SLFt group differences in the FA and correlations between FA and reading measures because of the left hemisphere's role in reading, and we hypothesized that there would be no significant right SLFt findings for these analyses.

TRACULA uses an atlas of white matter tracts, in combination with FreeSurfer segmentations, to derive the prior probability of each tract traveling through or next to each anatomical segmentation label. This information is combined with the participant-specific DWI data and FreeSurfer segmentation in a global probabilistic tractography framework to reconstruct each tract in the participant's native DWI space. This method allows for individual variation while encouraging consistency between participants.

Preprocessing began with DTIPrep's (Liu et al., 2010) automated artifact detection software. Any volume flagged for artifacts was removed from the participant's data, and any participant who had over 20% of his or her gradients removed (six directions out of 30) was removed from analysis altogether. The cleaned data were entered into TRACULA's preprocessing stream, which begins with FSL's eddy_correct tool to adjust for eddy currents and head motion. Next, each participant's b0 diffusion images were registered with his or her T1 scan using bbregister, and then all individual T1 images were registered to the Montreal Neurological Institute 152 template with FSL's flirt. Each participant's DWI mask was then transformed from the individual's diffusion space into the template space with the aid of FreeSurfer's cortical surface models. Dtifit from FSL was then used to estimate the tensor fit at each voxel to generate FA images. The last preprocessing step estimated the prior probability of the tract of interest going through or next to each FreeSurfer segmentation label at every point along the tract's trajectory, based on the TRACULA atlas. Once preprocessing was completed, we used FSL's bedpostx tool to fit a ball-and-stick model of diffusion to each subject's DWIs, which, unlike the tensor fit, can model up to two diffusion directions at each voxel. Finally, TRACULA's pathway reconstruction step generated probability distributions of the trajectory of each major white-matter pathway for each participant. Four participants with reading disability were omitted from further analysis for having more than six directions removed by DTIPrep.

Statistical Methods

A two-tailed Wilcoxon–Mann–Whitney *U* test was run in SPSS to investigate AF FA group differences. Correlations with Word Identification and Word Attack subtests (WRMT-III) were conducted in SPSS using Spearman's rank correlation coefficient. These were run separately for each group to investigate the associated brain–behavior relations. We used nonparametric statistics instead of *t* tests and Pearson correlations because FA is a ratio bounded between 0 and 1, and therefore does not conform to the normality assumption implicit in parametric statistics. Because nonparametric statistics rely on fewer assumptions, they are more robust than their parametric counterparts.

As a further quality control measure, we extracted average motion values for each participant using a tool in TRACULA that measures average translational and rotational movement during the diffusion scan (Yendiki, Koldewyn, Kakunoori, Kanwisher, & Fischl, 2013). There were no significant group differences for motion (average translation, $t[50] = .57$, $p = .57$; average rotation, $t[50] = .86$, $p = .39$). Average translation and average rotation were not significantly correlated with age or gender in full-group or within-group comparisons ($p > .05$).

Results

The typical reader group had significantly higher FA in the left AF than the reading disability group as shown by the Wilcoxon–Mann–Whitney *U* test (reading disability group: $M = .44$, $SD = .03$; typical reader group: $M = .46$, $SD = .03$, $U = 224$, sum of ranks for reading disability group = 575, sum of ranks for typical reader group = 803, $p = .037$; see Figure 2). The groups did not differ on FA in the right AF, the control tract (reading disability group: $M = .43$, $SD = .02$; typical reader group: $M = .44$, $SD = .02$, $U = 254$, sum of ranks for reading disability group = 605, sum of ranks for typical reader group = 773, $p = .124$).

Within the reading disability group, FA in the left AF correlated positively with real-word reading (WRMT-III Word Identification: $r_s = .41$, $p = .035$), but not pseudoword reading (WRMT-III Word Attack: $r_s = .14$, $p = .482$). Within the typical reader group, FA in the left AF correlated negatively with pseudoword reading (WRMT-III Word Attack: $r_s = -.37$, $p = .064$), but not real-word reading (WRMT-III Word Identification: $r_s = -.07$, $p = .75$). By comparison, there were no significant correlations between FA in the right AF with WRMT-III Word Identification or Word Attack in either group ($p > .05$).

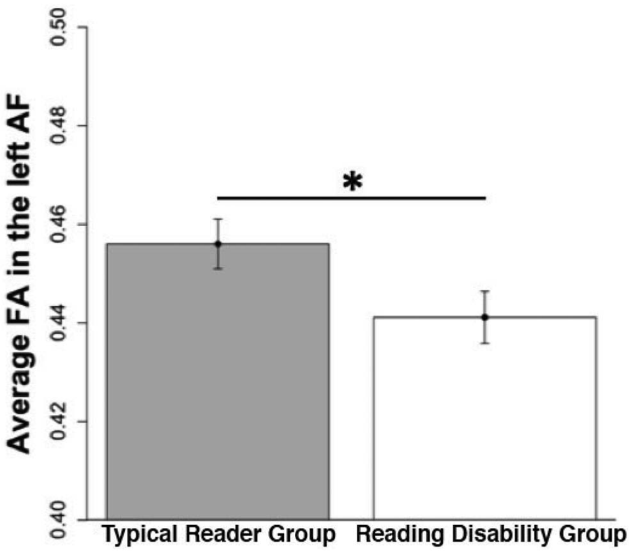

Figure 2. Relative to the typical reading group, the reading disability group had reduced fractional anisotropy (FA) in the left accurate fasciculus (AF). * $p < .05$ (Wilcoxon–Mann–Whitney U test); error bars represent standard error.

To further investigate these effects, axial diffusivity (D_{axial}) and radial diffusivity (D_{radial}), which offer information complementary to FA, were calculated for the left AF. Assuming that there is a single major white-matter tract going through a voxel, D_{axial} measures diffusion occurring along the direction of axons in the tract and D_{radial} measures diffusion perpendicular to the axons, whereas FA measures the asymmetry of diffusion between the parallel and perpendicular directions in that voxel. Group differences were driven by a trend for greater D_{radial} in the reading disability group (D_{radial}: $U = 215$, sum of ranks for reading disability group = 735, sum of ranks for typical reader group = 540, $p = .059$; D_{axial}: $U = 316$, sum of ranks for reading disability group = 667, sum of ranks for typical reader group = 659, $p = .865$). D_{radial} also drove the positive correlation between FA and Word Identification found in the reading disability group (D_{radial}: $r_s = -.46$, $p = .022$; D_{axial}: $r_s = -.09$, $p = .657$), with D_{radial} being inversely related to FA (see Figure 3). The negative correlation between FA and Word Attack in the typical reader group was driven by D_{axial} (D_{radial}: $r_s = .19$, $p = .373$, D_{axial}: $r_s = -.38$, $p = .060$). In the right AF, neither D_{radial} nor D_{axial} had a significant correlation with either behavioral measure ($p > .05$).

We repeated the analyses with only the children in the reading disability group who met the more severe criteria for developmental dyslexia ($n = 16$). Results of this analysis replicated those of the larger reading disability group, with a statistically greater reduction of FA in this more severely affected group ($p = .008$) that was associated with a significant increase in D_{radial} ($p = .008$) and no difference in D_{axial} ($p = .47$). The same findings, however, were not observed when the typical reading group was compared with the Excluded reading disability group who had lower Matrices scores (no group differences in FA or D_{radial}, no correlation with reading scores). This could be related to the lower nonverbal cognitive abilities in the excluded reading disability group, but this group also had some outlier DWI values.

Discussion

In beginning readers Ages 6–9, we found fundamental differences in the relation of the microstructure of the left AF to reading ability between typically developing readers and children with reading disability. By comparison, the right AF tract showed neither significant differences between groups nor any correlations with reading skills. Consistent with prior studies of older readers, we found that young children with reading disability had significantly reduced FA in the left AF. Similar to Yeatman et al. (2012), we also found that there was a negative correlation between FA in the left AF and reading skill among typically developing readers using a measure of pseudoword reading. Thus, there was a developmental dissociation between the relation of left AF white-matter microstructure, such that lower FA was associated with *worse* reading skill in children with reading disability, but *better* reading skill in typically developing children. This dissociation in early reading stands in marked distinction to findings in adolescents and adults in which higher FA has been consistently associated with

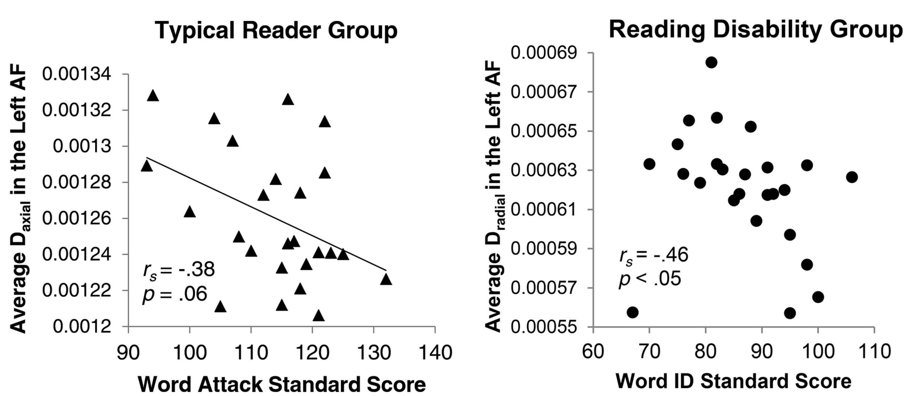

Figure 3. Brain–behavior correlations for typical reader group and reading disability group. The typical reader group had a significantly negative correlation between Word attack scores and axial diffusivity (D_{axial}) in the left AF (left panel). The reading disability group had a significantly negative correlation between word identification (Word ID) scores and radial diffusivity (D_{radial}) in the left arcuate fasciculus (AF) (right panel).

better reading skills in both typical and dyslexic readers. These findings suggest that there is a unique developmental period for learning to read in which different trajectories of white-matter microstructure are established in readers with and without reading disability.

Reduced FA of the left AF in beginning readers with reading disability is consistent with multiple studies reporting such reductions in older children and adults with dyslexia (e.g., Boets et al., 2013; Vandermosten, Boets, Wouters, et al., 2012). The present study of beginning readers bridges prior findings of reduced FA of left AF in prereaders with worse phonological processing skills that typically predict dyslexia (Saygin et al., 2013), and the many studies reporting reduced FA of left AF in older children and adults with dyslexia. In the present study, the relation of reduced FA in the left AF to reading disability was strengthened by the finding that among children with reading disability, lower single-word reading accuracy correlated with lower FA values.

The present study was also consistent with longitudinal evidence that lower FA is associated with better reading skills in typically developing beginning readers (Yeatman et al., 2012). Specifically, lower FA among typical readers was associated with higher scores on a test of pseudoword reading. This replication stands in contrast to studies with typically reading adults in whom higher FA was associated with stronger performance on measures of reading ability (Gold et al., 2007; Welcome & Joanisse, 2014).

The present findings diverged in one way from those of Yeatman et al. (2012), in that the FA values for typical readers correlated significantly with pseudoword reading but not with word reading (whereas Yeatman et al. found such correlations with a score that combined real-word and pseudoword measures). One important difference between the two studies is the reading-ability range of the typically reading children. In the prior study from Yeatman et al., children were recruited to represent a broad spectrum of reading abilities, from the lower half to the upper half of the average range (but not so below average as to represent reading disability or dyslexia). In the present study, so as to exclude reading disability in the typically reading group, the control group did not include below-average readers. Consequently, when considering the standardized reading scores that were used in common across the two studies, the control group in the present study corresponds to the above-average readers from the Yeatman et al. Thus, whereas the correlations in the present study examined variation in a control group that included above-average to superior readers, the correlations in the Yeatman et al. study examined variation in readers who were largely in the average range (with readers referred to as “below average” performing in the lower half of the average range). A future study including the full range of reading ability and disability may resolve the differences between the two studies, but the two studies are convergent in their conclusions that there is a unique early developmental phase of learning to read in which typically reading children exhibit a reversal of the relation between FA and reading ability relative to later development.

In the current study, it is unclear why FA values in the left AF were related significantly and selectively to real-word reading in the reading disability group and with pseudoword reading in the typical reader group. One possibility is that the study lacked measurement power for all correlations. A speculative possibility is that the correlations were most sensitive to differences in learning to read at this age. For typical early readers, the greatest learning could be occurring for mastering generalizable grapheme–phoneme relations that will empower the reading of new and less common words by decoding (i.e., developing broad principles of reading that apply to all possible words). For early readers with dyslexia, the greatest learning could be occurring for a more basic strategy of recognizing words by sight, rather than decoding, and learning to read specific real words that are often encountered in text.

A fundamental question is what neurobiological differences are reflected by the DWI measures that distinguished typical readers from those with reading disability, and that also related to individual differences in reading performance within both groups. Nearly all studies examining the relation of white-matter microstructure to reading have measured FA, a broad measure of such microstructure. Further characterization of white-matter microstructure can examine, more specifically, D_{axial} and D_{radial} associations with reading. There is some evidence suggesting that D_{axial} is more sensitive to changes in axon fibers, whereas D_{radial} is more sensitive to changes in myelin (Song et al., 2002, 2005, but see Wheeler-Kingshott & Cercignani, 2009). We found that reduced FA of the left AF in the reading disability group (although statistically marginally), and the correlation among these individuals between reading skill and FA, was related specifically to D_{radial}. These findings in children are consistent with a specific reduction of D_{radial} in the left AF of adults with dyslexia (Vandermosten, Boets, Poelmans, et al., 2012), and also, in another white-matter region, a specific change in D_{radial} in response to effective remediation (Keller & Just, 2009). Speculatively, reduced FA in reading disability could reflect reduced myelination.

In contrast to the specific relation of D_{radial} to reading disability, we found a specific relation of D_{axial} to the correlation among typically developing readers between reading skill and FA. Lower D_{axial} in early typical reading could reflect delayed pruning of axons. This speculation is constrained by the limited cellular specificity of all DWI measures, and by the complex interplay of axonal and myelin development that is influenced by both genetics and experience (reviewed in Yeatman et al., 2012). The idea, however, that *different* neuronal mechanisms underlie the associations between FA and reading skills in typical reading development versus dyslexia is a potential resolution to what would otherwise be the paradox of higher FA being associated with both better and worse reading skills in early elementary school.

Three issues in participant characterization provide limitations in the present study that may be addressed in future studies, namely, the distinction between dyslexia and reading disability, the characterization of reading education, and the different findings in the children with reading disability who had relatively lower cognitive ability. A challenge in the study of atypical reading acquisition is that there is no clear behavioral boundary between below-average reading and reading so poor that it is categorized as developmental dyslexia. Clinicians and educators must use some sort of boundary for diagnosis that also qualifies children for remedial services, but scores on reading and reading-related language tests are continuous rather than bimodal. Research studies vary considerably in their operational definition of developmental dyslexia or reading disability, in large part because there is no independent evidence that supports an objective demarcation between typical and atypical reading acquisition. Clinically, the term "reading disability" is often used to describe difficulty at the word (accuracy or fluency in decoding or word recognition) or connected text (comprehension, fluency) level, and developmental dyslexia is used specifically for word-level difficulties.

In neuroimaging research, the terms "dyslexia" and "reading disability" have been used largely interchangeably. Prior DWI studies of reading ability have used inclusion criteria for impaired participants ranging from below the third percentile (Vandermosten, Boets, Poelmans, et al., 2012) to below the 30th percentile (Keller & Just, 2009; in addition, studies vary in the specific tests used to characterize participants). In the present study, the same findings were obtained when analyses were performed with a more severely affected group that met conventional criteria for developmental dyslexia, or with the larger reading disability group that also included children with poor, but not as severe, reading difficulties. In regard to the biological measure of left AF white-matter microstructure, there was no apparent distinction between developmental dyslexia and reading disability beyond the greater severity of reading impairment in the dyslexic group.

The formal diagnosis of dyslexia also requires that reading difficulties cannot be accounted for by inadequate educational instruction (American Psychiatric Association, 2013; Lyon et al., 2003), but objective measurement of instructional quality or quantity is notably absent from experimental research in this field. In many studies, including the present study, students are recruited from multiple schools, and it is difficult to collect the requisite data on teaching practices and associated student progress over time to objectively evaluate what constitutes adequate education and progress for each student.

Finally, we observed some differences between groups with reading disability that were and were not matched to typical readers by nonverbal cognitive ability. In older children with reading disability, there is considerable evidence from both behavioral (for review, see Stuebing et al., 2002) and neuroimaging (Simos, Rezaie, Papanicolaou, & Fletcher, 2013; Tanaka et al., 2011) research that core weaknesses in phonological awareness occur independently from IQ. It is unknown whether IQ plays a different role in the initial stages of learning to read. Future studies with larger samples that include a range of IQ scores may clarify this issue.

The present study, however, suggests that there is a meaningful biological boundary between reading disability and typical reading ability. First, the relation of FA to reading skill was the *opposite* in the group with, versus the group without, reading disability. Second, the nature of the diffusivity differences were *opposite* in the two groups, with radial diffusivity selectively related to reading disability and axial diffusivity selectively related to typical reading ability. The present study, in combination with Yeatman et al. (2012), raises the possibility that there are fundamental differences in white-matter development during the initial stages of learning to read, the very stages that separate reading trajectories as early as first grade (Ferrer et al., 2015), that may be distinct in typically reading children compared with children with reading disability including dyslexia.

References

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Arlington, VA: American Psychiatric Publishing.

Beaulieu, C., Plewes, C., Paulson, L. A., Roy, D., Snook, L., Concha, L., & Phillips, L. (2005). Imaging brain connectivity in children with diverse reading ability. *NeuroImage, 25,* 1266–1271. http://dx.doi.org/10.1016/j.neuroimage.2004.12.053

Boets, B., Op de Beeck, H. P., Vandermosten, M., Scott, S. K., Gillebert, C. R., Mantini, D., . . . Ghesquière, P. (2013). Intact but less accessible phonetic representations in adults with dyslexia. *Science, 342,* 1251–1254. http://dx.doi.org/10.1126/science.1244333

Bradley, L., & Bryant, P. E. (1978). Difficulties in auditory organisation as a possible cause of reading backwardness. *Nature, 271,* 746–747. http://dx.doi.org/10.1038/271746a0

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology, 57,* 8–16. http://dx.doi.org/10.1002/ana.20319

Deutsch, G. K., Dougherty, R. F., Bammer, R., Siok, W. T., Gabrieli, J. D. E., & Wandell, B. (2005). Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior, 41,* 354–363. http://dx.doi.org/10.1016/S0010-9452(08)70272-7

Ferrer, E., Shaywitz, B. A., Holahan, J. M., Marchione, K. E., Michaels, R., & Shaywitz, S. E. (2015). Achievement gap in reading is present as early as first grade and persists through adolescence. *The Journal of Pediatrics, 167,* 1121–1125.e2. http://dx.doi.org/10.1016/j.jpeds.2015.07.045

Gabrieli, J. D. (2009). Dyslexia: A new synergy between education and cognitive neuroscience. *Science, 325,* 280–283. http://dx.doi.org/10.1126/science.1171999

Geschwind, N. (1965a). Disconnexion syndromes in animals and man. I. *Brain: A Journal of Neurology, 88,* 237–294. http://dx.doi.org/10.1093/brain/88.2.237

Geschwind, N. (1965b). Disconnexion syndromes in animals and man. II. *Brain: A Journal of Neurology, 88,* 585–644. http://dx.doi.org/10.1093/brain/88.3.585

Gold, B. T., Powell, D. K., Xuan, L., Jiang, Y., & Hardy, P. A. (2007). Speed of lexical decision correlates with diffusion anisotropy in left parietal and frontal white matter: Evidence from diffusion tensor imaging. *Neuropsychologia, 45,* 2439–2446. http://dx.doi.org/10.1016/j.neuropsychologia.2007.04.011

Kaufman, A. S., & Kaufman, N. L. (2004). *Kaufman Brief Intelligence Test* (2nd ed.). Circle Pines, MN: American Guidance Service.

Keller, T. A., & Just, M. A. (2009). Altering cortical connectivity: Remediation-induced changes in the white matter of poor readers. *Neuron, 64,* 624–631. http://dx.doi.org/10.1016/j.neuron.2009.10.018

Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J. D. E., Moseley, M. E., & Poldrack, R. A. (2000). Microstructure of temporo-parietal white matter as a basis for reading ability: Evidence from diffusion tensor magnetic resonance imaging. *Neuron, 25,* 493–500. http://dx.doi.org/10.1016/S0896-6273(00)80911-3

Liu, Z., Wang, Y., Gerig, G., Gouttard, S., Tao, R., Fletcher, T., & Styner, M. (2010). Quality control of diffusion weighted images. *Proceedings of SPIE–The International Society for Optical Engineering, 7628,* 76280J. http://dx.doi.org/10.1117/12.844748

Lyon, G. R., Shaywitz, S., & Shaywitz, B. (2003). A definition of dyslexia. *Annals of Dyslexia, 53,* 1–14. http://dx.doi.org/10.1007/s11881-003-0001-9

Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience, 16,* 1227–1233. http://dx.doi.org/10.1162/0898929041920441

Niogi, S. N., & McCandliss, B. D. (2006). Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. *Neuropsychologia, 44,* 2178–2188. http://dx.doi.org/10.1016/j.neuropsychologia.2006.01.011

Paulesu, E., Frith, U., Snowling, M., Gallagher, A., Morton, J., Frackowiak, R. S. J., & Frith, C. D. (1996). Is developmental dyslexia a disconnection syndrome? Evidence from PET scanning. *Brain: A Journal of Neurology, 119,* 143–157. http://dx.doi.org/10.1093/brain/119.1.143

Richards, T., Stevenson, J., Crouch, J., Johnson, L. C., Maravilla, K., Stock, P., . . . Berninger, V. (2008). Tract-based spatial statistics of diffusion tensor imaging in adults with dyslexia. *AJNR. American Journal of Neuroradiology, 29,* 1134–1139. http://dx.doi.org/10.3174/ajnr.A1007

Rimrodt, S. L., Peterson, D. J., Denckla, M. B., Kaufmann, W. E., & Cutting, L. E. (2010). White matter microstructural differences linked to left perisylvian language network in children with dyslexia. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior, 46,* 739–749. http://dx.doi.org/10.1016/j.cortex.2009.07.008

Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., . . . Gabrieli, J. D. (2013). Tracking the roots of reading ability: White matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *The Journal of Neuroscience, 33,* 13251–13258. http://dx.doi.org/10.1523/JNEUROSCI.4383-12.2013

Simos, P. G., Rezaie, R., Papanicolaou, A. C., & Fletcher, J. M. (2013). Does IQ affect the functional brain network involved in pseudoword reading in students with reading disability? A magnetoencephalography study. *Frontiers in Human Neuroscience, 7,* 932. http://dx.doi.org/10.3389/fnhum.2013.00932

Song, S.-K., Sun, S.-W., Ramsbottom, M. J., Chang, C., Russell, J., & Cross, A. H. (2002). Dysmyelination revealed through MRI as increased radial (but unchanged axial) diffusion of water. *NeuroImage, 17,* 1429–1436. http://dx.doi.org/10.1006/nimg.2002.1267

Song, S.-K., Yoshino, J., Le, T. Q., Lin, S.-J., Sun, S.-W., Cross, A. H., & Armstrong, R. C. (2005). Demyelination increases radial diffusivity in corpus callosum of mouse brain. *NeuroImage, 26,* 132–140. http://dx.doi.org/10.1016/j.neuroimage.2005.01.028

Steinbrink, C., Vogt, K., Kastrup, A., Müller, H.-P., Juengling, F. D., Kassubek, J., & Riecker, A. (2008). The contribution of white and gray matter differences to developmental dyslexia: Insights from DTI and VBM at 3.0 T. *Neuropsychologia, 46,* 3170–3178. http://dx.doi.org/10.1016/j.neuropsychologia.2008.07.015

Stuebing, K. K., Fletcher, J. M., LeDoux, J. M., Lyon, G. R., Shaywitz, S. E., & Shaywitz, B. A. (2002). Validity of IQ-discrepancy classifications of reading disabilities: A meta-analysis. *American Educational Research Journal, 39,* 469–518. http://dx.doi.org/10.3102/00028312039002469

Tanaka, H., Black, J. M., Hulme, C., Stanley, L. M., Kesler, S. R., Whitfield-Gabrieli, S., . . . Hoeft, F. (2011). The brain basis of the phonological deficit in dyslexia is independent of IQ. *Psychological Science, 22,* 1442–1451. http://dx.doi.org/10.1177/0956797611419521

Thiebaut de Schotten, M., Cohen, L., Amemiya, E., Braga, L. W., & Dehaene, S. (2014). Learning to read improves the structure of the arcuate fasciculus. *Cerebral Cortex, 24,* 989–995. http://dx.doi.org/10.1093/cercor/bhs383

Torgesen, J. K., Wagner, R., & Rashotte, C. (2012). *Test of Word Reading Efficiency* (2nd ed.). Austin, TX: Pro-d.

Vandermosten, M., Boets, B., Poelmans, H., Sunaert, S., Wouters, J., & Ghesquière, P. (2012). A tractography study in dyslexia: Neuroanatomic correlates of orthographic, phonological and speech processing. *Brain: A Journal of Neurology, 135,* 935–948. http://dx.doi.org/10.1093/brain/awr363

Vandermosten, M., Boets, B., Wouters, J., & Ghesquière, P. (2012). A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neuroscience and Biobehavioral Reviews, 36,* 1532–1552. http://dx.doi.org/10.1016/j.neubiorev.2012.04.002

Welcome, S. E., & Joanisse, M. F. (2014). Individual differences in white matter anatomy predict dissociable components of reading skill in adults. *NeuroImage, 96,* 261–275. http://dx.doi.org/10.1016/j.neuroimage.2014.03.069

Wheeler-Kingshott, C. A., & Cercignani, M. (2009). About "axial" and "radial" diffusivities. *Magnetic Resonance in Medicine, 61,* 1255–1260. http://dx.doi.org/10.1002/mrm.21965

Woodcock, R. W. (2011). *Woodcock Reading Mastery Tests* (3rd ed.). Bloomington, MN: Pearson.

Yeatman, J. D., Dougherty, R. F., Ben-Shachar, M., & Wandell, B. A. (2012). Development of white matter and reading skills. *PNAS Proceedings of the National Academy of Sciences of the United States of America, 109,* E3045–E3053. http://dx.doi.org/10.1073/pnas.1206792109

Yendiki, A., Koldewyn, K., Kakunoori, S., Kanwisher, N., & Fischl, B. (2013). Spurious group differences due to head motion in a diffusion MRI study. *NeuroImage, 88C,* 79–90.

Yendiki, A., Panneck, P., Srinivasan, P., Stevens, A., Zöllei, L., Augustinack, J., . . . Fischl, B. (2011). Automated probabilistic reconstruction of white-matter pathways in health and disease using an atlas of the underlying anatomy. *Frontiers in Neuroinformatics, 5,* 23. http://dx.doi.org/10.3389/fninf.2011.00023

Received January 13, 2015
Revision received November 23, 2015
Accepted December 29, 2015 ■

Correction to Christodoulou et al. (2016)

In the article "Relation of White-Matter Microstructure to Reading Ability and Disability in Beginning Readers," by Joanna A. Christodoulou, Jack Murtagh, Abigail Cyr, Tyler K. Perrachione, Patricia Chang, Kelly Halverson, Pamela Hook, Anastasia Yendiki, Satrajit Ghosh, and John D. E. Gabrieli (*Neuropsychology*, Advance online publication. March 7, 2016. http://dx.doi.org/10.1037/neu0000243), errors in the dataset owing to two incorrect scores have skewed results. In the second paragraph of the Results section, the second sentence should read as follows: "Within the typical reader group, FA in the left AF correlated negatively with pseudoword reading (WRMT-III Word Attack: $r_s = -.37$, $p = .064$), but not real-word reading (WRMT-III Word Identification: $r_s = -.07$, $p = .75$)." The fourth sentence of the third paragraph should read as follows: "The negative correlation between FA and Word Attack in the typical reader group was driven by D_{axial} (D_{radial}: $r_s = .19$, $p = .373$, D_{axial}: $r_s = -.38$, $p = .060$)." The second sentence of the fourth paragraph should read as follows: "Results of this analysis replicated those of the larger reading disability group, with a statistically greater reduction of FA in this more severely affected group ($p = .008$) that was associated with a significant increase in D_{radial} ($p = .008$) and no difference in D_{axial} ($p = .47$)." In Table 1, for the typical reader group, the resulting values should read as follows: age, 94.00 ± 7.66; KBIT-2–Matrices, 118.31 ± 15.24; WRMT-III–Word Identification, 119.00 ± 9.33; WRMT-III–Word Attack, 114.04 ± 9.31; and TOWRE-2–Sight Word Efficiency, 114.48 ± 8.07. For the reading disability group, the resulting values for age and TOWRE-2–Phonemic Decoding Efficiency should be 93.65 ± 7.81 and 81.76 ± 9.33, respectively. The *p* values for age and KBIT-2–Matrices should be .87 and .172, respectively. In Figure 3, the image for the typical reader group has been replaced. All versions of this article have been corrected.

http://dx.doi.org/10.1037/neu0000388