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Microstructure of Temporo-Parietal White Matter as a Basis for Reading Ability: Evidence from Diffusion Tensor Magnetic Resonance Imaging

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Summary

Diffusion tensor magnetic resonance imaging (MRI) was used to study the microstructural integrity of white matter in adults with poor or normal reading ability. Subjects with reading difficulty exhibited decreased diffusion anisotropy bilaterally in temporo-parietal white matter. Axons in these regions were predominantly anterior–posterior in direction. No differences in T1-weighted MRI signal were found between poor readers and control subjects, demonstrating specificity of the group difference to the microstructural characteristics measured by diffusion tensor imaging (DTI). White matter diffusion anisotropy in the temporo-parietal region of the left hemisphere was significantly correlated with reading scores within the reading-impaired adults and within the control group. The anisotropy reflects microstructure of white matter tracts, which may contribute to reading ability by determining the strength of communication between cortical areas involved in visual, auditory, and language processing.

Introduction

Reading is a complex cognitive skill that requires multimodal processing of visual symbols, speech sounds (known as phonology), and linguistic entities such as words and sentences (Adams, 1990). Neuroimaging studies demonstrating that a widespread set of brain regions are engaged during reading tasks (Fiez and Petersen, 1998; Demb et al., 2000) highlight the need for communication between these regions in skilled readers. About 5%–10% of children, however, exhibit developmental dyslexia, an impairment in learning to read despite adequate instruction and normal intelligence (Shaywitz, 1998). Dyslexia is associated with deficits in language processing beyond reading, particularly in the processing of phonology (e.g., Pennington et al., 1990). In addition, dyslexic individuals exhibit deficits in nonlinguistic perceptual processing, particularly on tasks requiring the processing of rapidly changing acoustic (Tallal, 1980; Farmer and Klein, 1995) and visual (Eden et al., 1996b; Stein and Walsh, 1997) signals.

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A growing body of evidence suggests that dyslexia is a neurological disorder. A genetic basis for dyslexia has also been suggested (e.g., Pennington et al., 1991). Postmortem studies of dyslexic brains have discovered a consistent pattern of pathological changes (cortical microlesions and glial scars) throughout the left perisylvian cortices, along with reduced left–right asymmetry of the planum temporale (Galaburda et al., 1985; Humphreys et al., 1990). Functional magnetic resonance imaging (fMRI) and positron emission tomography (PET) studies have found atypical activation patterns in the temporo-parietal cortex of adult dyslexics during reading tasks, particularly on tasks involving the recoding of written symbols into their phonological counterparts (Rumsey et al., 1992, 1997; Paulesu et al., 1996; Shaywitz et al., 1998). Studies using magnetoencephalography (MEG) have also found differences in the time course of cortical processing in poor readers compared to normal readers (Salmelin et al., 1996; Nagarajan et al., 1999). Each of these findings is consistent with a neural basis for dyslexia, but the underlying cause of these differences in neural processing is not currently known.

Two studies have suggested that developmental dyslexia may represent a disconnection syndrome in which communication is impaired between cortical areas involved in reading. In particular, dyslexic individuals have exhibited decreased correlations of cortical activity between the angular gyrus and inferior frontal, extrastriate occipital, and temporal areas (Horwitz et al., 1998). Another study has suggested such an impairment based on the basis of abnormal patterns of activation in the temporo-parietal, frontal, and insular cortices in dyslexic adults (Paulesu et al., 1996). This proposal is consistent with behavioral evidence that dyslexic individuals are impaired at the cross-modal mapping of visual and auditory information (Snowling, 1980). This impaired communication could be the result of a structural disturbance, but the nature and cause of a putative structural impairment is currently unknown.

A plausible locus for such a disruption in communication is the white matter tracts connecting temporo-parietal and frontal cortices, but to date there is no consistent evidence of white matter disturbance in reading disorders. A number of previous studies have examined the differences in neuroanatomical structure between dyslexic individuals and normal readers. These studies have focused primarily on hemispheric asymmetry of the planum temporale and on differences in corpus callosum size, and found mixed results in each of those areas (reviewed by Beaton, 1997). None of these studies has demonstrated specific differences in white matter morphology, but the imaging techniques used in these studies (such as T1-weighted structural MR imaging) can only image macrostructural features of white matter. One postmortem case study found abnormalities in the width of one single dyslexic brain, possibly indicating a white matter abnormality (Galaburda and Kemper, 1979). Other postmortem studies of brains from dyslexic subjects have focused on gray matter abnormalities and

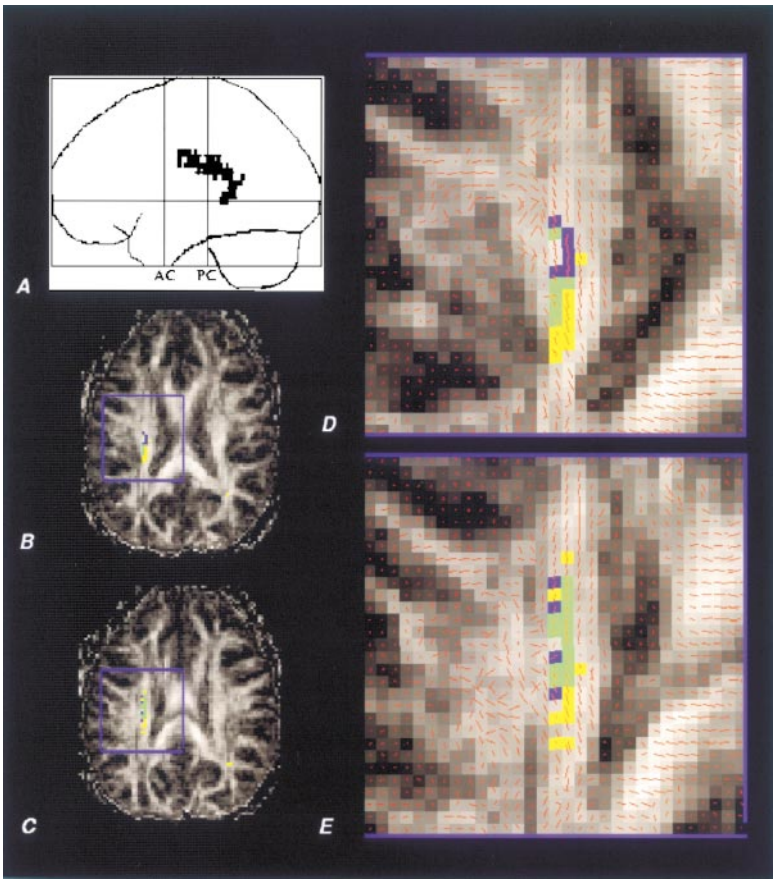

Figure 1. Anisotropy: Regions with Group Differences and Correlations with Reading Scores

(A) Sagittal projection of the left hemisphere VOI where there was a significant difference in anisotropy between the poor readers and the control group. The contour and the superimposed grid represents the standard anatomical space (Talairach and Tournoux, 1988). Abbreviations: AC, anterior commissure; PC, posterior commissure. The VOI had a volume of 960 mm^3, and was located within $x = -36$ to -26, $y = -50$ to -10, and $z = 0$ to 32 mm relative the to anterior commissure.

(B and C) Axial slices from an anisotropy image of one control subject. Left hemisphere is to the left in the image; $z = 20$ mm (B) and $z = 24$ mm (C) above the anterior–posterior commissure line. For the gray scale, lighter colors represent higher anisotropy. Green indicates voxels significant in both the between-group analysis and the Word ID correlation analysis; yellow indicates voxels significant only in the between-group analysis; and blue indicates voxels significant only in the correlation analysis. The cluster from the correlation analysis had a volume of 670 mm^3, of which 52% overlapped with the cluster from the between-group comparison.

(D and E) Part of the image in Figures 1B and 1C shown at higher magnification. Shown in red is a two-dimensional representation of the primary eigenvector of diffusion within each voxel (after Makris et al., 1997), which is the main direction of diffusivity and thus can be interpreted as representing the main direction of the axons within a voxel.

have not reported any white matter abnormalities (Galaburda et al., 1985, 1994; Humphreys et al., 1990; Livingstone et al., 1991; Jenner et al., 1999).

Progress in understanding the cellular basis of reading disorders has been greatly limited by dependence upon informative, but very rare, postmortem studies. There is now, however, a novel magnetic resonance (MR) imaging technique called diffusion tensor imaging (DTI) that provides information about white matter microstructure in vivo. Unlike standard structural MR imaging techniques, DTI allows measurement of the microstructural features of white matter. The DTI technique is based on sensitizing the MR signal to the movement of water on the order of micrometers and determining the magnitude and direction of the water diffusion in three dimensions (Basser et al., 1994). In white matter of the brain, diffusion of water perpendicular to the direction of the axons is restricted by the myelin sheath and cell membrane such that diffusion will be greater along the length of the axon than perpendicular to the axon (Moseley et al., 1990). Anisotropy is a measure that quantifies the degree to which diffusion differs in the three dimensions (van Gelderen et al., 1994; Basser, 1995; Basser and Pierpaoli, 1996; Conturo et al., 1996).

Anisotropy in myelinated white matter is likely to be determined by a number of microstructural features: the integrity of axonal cell membranes, the amount and integrity of myelin around the axons, the coherence of axonal orientation, and the number and size of axons. In particular, anisotropy has been noted to vary directly with myelination: increased myelination is associated with greater anisotropy. Diffusion anisotropy in white matter correlates with histological markers of myelination (Wimberger et al., 1995), with the developmental course of myelination in newborns (Hüppi et al., 1998; Neil et al., 1998) and young children (Klingberg et al., 1999), and with demyelination in multiple sclerosis (Werring et al., 1999).

If the reading deficit in dyslexia is related to a structural disturbance of the white matter tracts connecting anterior and posterior cortical regions, this disturbance may be reflected in lower anisotropy values. To test this hypothesis, six adults with poor reading skills and a history of developmental reading disorders and eleven control adults with no history of reading problems were studied with DTI. The inclusion criteria for the subjects in the poor reading group were a previous diagnosis of developmental dyslexia and a current complaint about reading ability. All subjects in this group scored below the population mean on a standard test of reading ability (Word Identification [ID] test; Woodcock, 1987). Not all subjects, however, scored more than one standard deviation below the population mean, suggesting that they may have partially compensated for their developmental reading problems. This group, therefore is described as one composed of "poor readers," because it is unclear how to relate their current reading impairment to formal definitions of developmental dyslexia created primarily to classify children.

Anisotropy of diffusion was measured in the entire

brain of each individual, the images were normalized to a standard anatomical space, and the anisotropy of the group of poor readers was compared to that of the control group. We also collected high-resolution T1-weighted anatomical images, which reveal anatomical structure but are not sensitive to diffusion anisotropy. With these measures, both the location and the nature of any white matter disturbance associated with poor reading ability could be evaluated for the first time.

Results

Between-Group Comparison

The poor readers showed significantly lower anisotropy in only two regions of the brain, located bilaterally in the white matter of the temporo-parietal region ($p < 0.05$, one-tailed, corrected for multiple comparisons) (Figure 1). This statistical difference was not, however, apparent by visual inspection of the individual anisotopy images. An identical statistical comparison of the high-resolution T1-weighted anatomical images failed to show any differences between the groups ($p > 0.98$, one-tailed, corrected). Autocorrelation (smoothness) between voxels within images was slightly lower in the T1-weighted images than in the anisotropy images, which could possibly have affected the outcome of the statistical analysis. A second analysis was therefore performed after smoothing T1-weighted images with a Gaussian kernel in three dimensions to an autocorrelation that matched the anisotropy images. This reanalysis also failed to show any significant differences in T1 images between the groups ($p > 0.56$, corrected). In addition, T1 signal differences specifically in the two volumes of interest (VOIs) were measured, but no group differences were found (t tests, $p > 0.74$ for both VOIs). Thus, the observed group difference was specific to the tissue properties measured by diffusion rather than to any gross anatomical differences, such as gyral pattern or white matter volume.

The foregoing analysis was performed on anisotropy values that were normalized by scaling to the global image mean. The mean unscaled anisotropy values in the left hemisphere VOI were 0.59 ± 0.02 for the control group and 0.46 ± 0.03 for the poor readers ($p < 0.0002$). The corresponding numbers for the right hemisphere VOI were 0.56 ± 0.01 and 0.38 ± 0.04 for the control and poor reading group, respectively ($p < 0.0001$). Thus, group differences were significant for both the scaled and unscaled values, and in both the left and right temporo-parietal VOIs.

Correlation between Anisotropy and Reading Scores

To test the behavioral relevance of the group difference in anisotropy, each subject performed a standardized measure of reading ability: the Word ID test (Woodcock, 1987). A correlation analysis was performed to find voxels anywhere in the brain with a positive correlation between anisotropy scores and the Word ID score. The correlation analysis revealed one cluster of significantly correlated voxels in the left hemisphere, which overlapped (52% of voxels) with the left temporo-parietal region found in the group comparison analysis ($p < 0.001$ for the entire region, one-tailed, corrected). No overlap was found with the right temporo-parietal region, and the rest of the analysis was therefore restricted to the left VOI. The maximum correlation in the left temporo-parietal region was $r = 0.84$, for the entire group (Figure 2). An additional analysis was performed in which effects of age and gender were removed as confounds prior to correlation between anisotropy and the Word ID score. This analysis gave similar results to the first statistical parametric mapping (SPM) analysis, with maximum correlation in the same voxel ($x = -28$, $y = -20$, $z = 28$; $p < 0.05$, corrected).

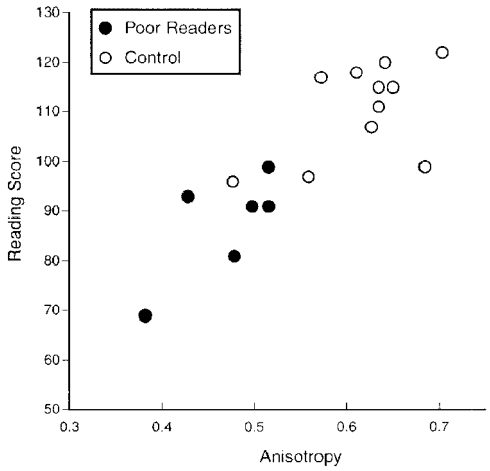

Figure 2. Reading Scores and Anisotropy

Scores from the Word ID test plotted against anisotropy in the voxel with maximum correlation within the left temporo-parietal VOI ($x = -28$, $y = -20$, $z = 28$ mm; $r = +0.84$).

The correlation between reading scores and anisotropy could result from (1) only the difference between reading-impaired and control groups or (2) correlations between reading scores and anisotropy that occur within each group. We therefore examined the correlation between reading scores and anisotropy separately in each group within the VOI determined from the foregoing correlation analysis. Significant correlations were observed in both the poor reading ($r = 0.74$, $p < 0.05$, one-tailed) and control ($r = 0.53$, $p < 0.05$, one-tailed) groups examined separately. Thus, the relationship between white matter microstructure and reading skill reflected a structure–function relationship encompassing both normal and impaired readers. A significant correlation between Word ID score and mean anisotropy within the left temporo-parietal VOI from the correlation analysis was found also using unscaled values ($r = 0.72$, $p < 0.001$). The values obtained from the group comparison analysis showed a significant correlation with reading scores ($r = 0.77$, $p < 0.0003$), and the values obtained from the correlation analysis showed a significant group difference ($p < 0.0001$).

In order to determine the generality of the correlation between anisotropy and reading ability, the correlation was also examined between anisotropy and performance on a pseudoword reading task (Word Attack test; Woodcock, 1987). The anisotropy values that correlated maximally with Word ID scores were also significantly correlated with Word Attack scores ($r = 0.65$, $p < 0.01$, one-tailed).

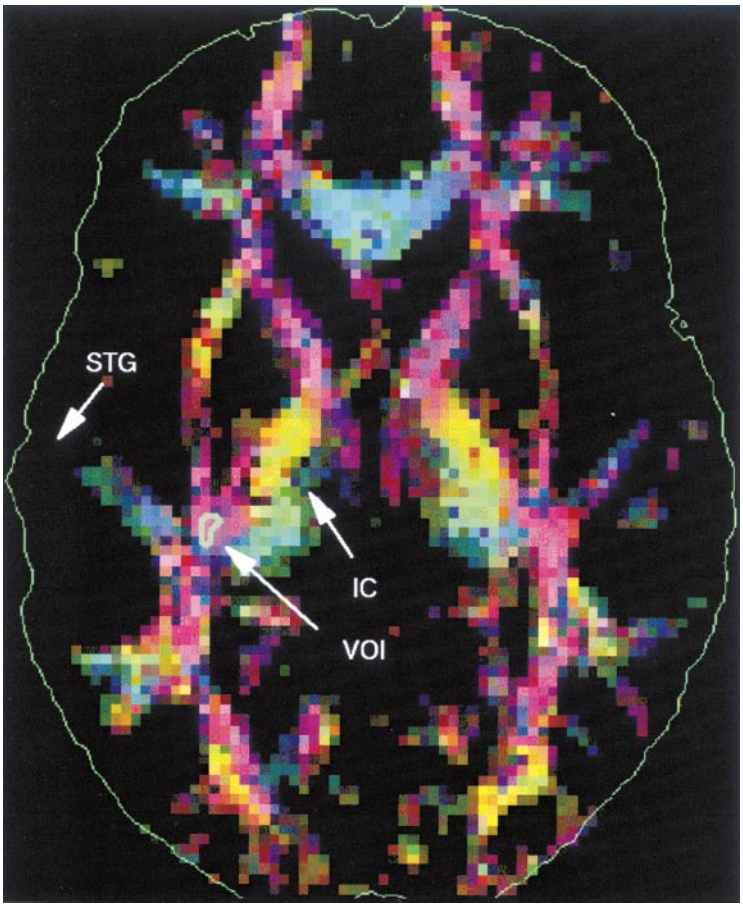

Figure 3. Axonal Directions

Color representation of axonal orientation in a single control subject (after Coremans et al., 1994). Red voxels have a primary eigenvector of diffusion, which is oriented in an anterior–posterior direction; yellow voxels indicate an inferior–superior orientation (as seen in the internal capsule); and blue voxels indicate a left–right orientation (as seen in the genu of the corpus callosum). Left hemisphere is to the left in the image. Abbreviations: IC, internal capsule; VOI, volume of interest for the significant cluster in the between-group analysis; STG, superior temporal gyrus.

Subjects also performed a test of nonverbal intelligence and spatial ability, the Matrix Analogies test (MAT) (Naglieri, 1985). There was a positive correlation between MAT scores and anisotropy scores from the maximally significant focus in the correlation analysis ($r = 0.42$). This correlation was, however, secondary to the correlation between Word ID and MAT scores ($r = 0.562$, $p = 0.02$). When variance in anisotropy due to Word ID scores was removed in a stepwise multiple regression, there was no remaining correlation between MAT scores and anisotropy ($F[1, 14] = 0.2$, $p > 0.65$). In contrast, when variance due to MAT scores was removed, there was still a significant correlation between anisotropy and Word ID ($F[1, 14] = 25$, $p < 0.0002$). Therefore, the correlation between the left temporo-parietal anisotropy and reading ability could not be accounted for by differences in nonverbal ability as measured by the MAT.

Analyses of Coherence and Direction

Anisotropy can be affected by how coherently and regularly oriented the myelinated axons are within each voxel being measured. If a voxel contains crossing axons or branching bundles of axons, the diffusion within the voxel will be more equal in different directions and thus less anisotropic. Coherence can be estimated and quantified as a coherence index (Basser and Pierpaoli, 1996). This index estimates between-voxel coherence, as there is currently no technique for specifically estimating within-voxel coherence. No significant group difference in between-voxel coherence was observed within the left hemisphere VOI ($p > 0.97$). This suggests that differences in anisotropy between the poor reading and control groups likely reflect differences in white matter microstructure rather than differences in the coherence of axonal orientation.

In addition to providing information about anisotropy, DTI also provides information about the orientation of axons in each voxel. A two-dimensional representation of axonal orientation is shown in Figures 2D and 2E, using an illustration method from Makris et al. (1997). In Figure 3, axonal orientation is color coded as described by Coremans et al. (1994). In order to quantitate the orientation of white matter tracts in the left hemisphere VOI, the orientation of diffusion in each subject for each voxel within the VOI was classified as either anterior–posterior, left–right, or inferior–superior. A significant proportion, 56% ($\pm$ 4%), of the voxels in the VOI exhibited anterior–posterior orientation, consistent with the involvement of these white matter tracts in cortico-cortical communication both within the temporo-parietal region and between temporo-parietal and frontal regions. The proportion of anterior–posterior voxels was less than 100%, indicating that the VOI was not confined to anterior–posterior axons, but was significantly more than the 33% that would be expected if orientation was random ($p < 0.001$).

Discussion

Using diffusion tensor MR imaging, differences in white matter microstructure between normal readers and individuals with poor reading ability were found bilaterally in the temporo-parietal white matter underlying perisylvian cortical areas. No differences in T1-weighted MR signal were found in these regions, demonstrating that the differences were specific to the microstructural features measured by diffusion anisotropy. Measurement of between-voxel coherence demonstrated no difference between groups, suggesting that the group difference in anisotropy primarily reflected differences in white matter microstructure. An overlapping region in the left temporo-parietal white matter exhibited significant correlation between white matter microstructure and reading ability across all 17 subjects. This correlation was apparent both within the poor reading group alone and within the control group alone, demonstrating for the first time a structural neural correlate of reading skill in normal readers.

These results indicate that white matter underlying left temporo-parietal cortex plays a critical role in reading ability. Left temporo-parietal cortex has long been associated with reading; lesions in this region can result in different types of acquired dyslexia (Dejerine, 1891; Geschwind, 1965a, 1965b; Marshall and Newcombe, 1966). Previous neuroimaging studies of reading-impaired adults have found abnormally reduced activation in temporo-parietal cortex during reading tasks requiring phonological processing (Paulesu et al., 1996; Rumsey et al., 1997; Shaywitz et al., 1998) and abnormally low correlation of metabolic activity between temporo-parietal cortex and other cortical areas during these same tasks (Horwitz et al., 1998). The location of the white matter disturbance identified by DTI is thus convergent with other forms of evidence that indicate the essential role of this brain region for reading.

The white matter disturbance associated with reading ability discovered using DTI likely affects white matter tracts connecting these temporo-parietal areas with each other and with other brain regions. Case studies of white matter anatomy using postmortem dissection (Dejerine, 1895; Gluhbegovic and Williams, 1980) and DTI (Makris et al., 1997; see also Makris et al., 1999; Meyer et al., 1999) show that this left temporo-parietal region contains sagittally oriented axons in the external capsule and the arcuate fasciculus that project from occipital, inferior parietal, and temporal cortices to frontal cortex. These findings are consistent with our DTI analysis showing that axons in the region of interest were predominantly oriented in the anterior–posterior direction. The present finding thus demonstrates a plausible structural basis for the functional disconnection of temporo-parietal and frontal cortices that has been previously suggested to occur in developmental dyslexia. Variability in the microstructure of the white matter tracts connecting temporo-parietal cortex and other cortices would affect communication between these areas and could thereby impair the coordination of visual and phonological codes that is necessary for skilled reading.

The precise cellular and histological basis for the inter-individual variations in anisotropy is not known. Several histological characteristics could affect the anisotropy, such as differences in the number of axons, the thickness of axons, the amount and integrity of myelin, or structural disruptions of the white matter tracts. It is also unknown as to how these white matter differences relate to potential differences in the soma of the neurons whose axons constitute the temporo-parietal white matter tracts.

It is noteworthy that the group differences were bilateral but that the reading scores correlated only with the left hemisphere anisotropy. The left hemisphere correlation likely reflects the critical role of that hemisphere in language. The significance of the right hemisphere differences, if any, is presently unknown. The bilateral differences, however, possibly suggest a biological etiology that is not related to hemispheric specialization per se.

White Matter and Rapid Perceptual Processing

Although developmental dyslexia is defined as a deficit in reading, there is strong evidence demonstrating impairments of perceptual processing of both verbal and nonverbal stimuli in subjects with poor reading ability, particularly for rapidly changing acoustic stimuli (Farmer and Klein, 1995) and moving visual stimuli (Stein and Walsh, 1997). The processing of rapidly changing acoustic information is particularly important for the perception of phonology, in which differences between phonemes can be determined by differences in frequency changes occuring over tens of milliseconds (Tallal et al., 1993). Deficits in visual motion processing may interfere with other aspects of reading, such as the accurate visual perception of letter position (Cornelissen et al., 1998).

A disturbance of white matter microstructure provides a plausible explanation for multimodal deficits in the processing of rapidly changing sensory stimulation. In particular, intact myelination is important for rapid conduction of action potentials, and a disturbance of myelination would be particularly detrimental for accurate coding and transmission of rapidly changing stimuli. In vision, rapid change is especially associated with the perception of movement, and two fMRI studies have reported diminished activations in area MT, an area specialized for visual motion perception, in reading-impaired individuals (Eden et al., 1996a; Demb et al., 1997). The reduction in MT activation correlated with reading impairment (Demb et al., 1997). The importance of myelination for area MT processing is evident from the exceptional degree of myelination in that area relative to adjacent cortices (Tootell and Taylor, 1995). Furthermore, the particular location of the white matter difference in anisotropy found in the present study, which could contain fibers from both auditory and visual cortices, provides a possible explanation for the correlation that has been observed between deficits in rapid auditory and visual processing (Witton et al., 1998). Thus, the present findings are consistent with findings that dyslexia or poor reading ability is characterized by disproportionate difficulties in processing rapidly changing signals, which may make greater demands upon the conduction speed of white matter.

Structure–Function Relations in Impaired and Normal Readers

The poor reading group in this study had significantly worse reading scores than the control group, but reading impairment was relatively mild (about a standard deviation below the control group). Given their history of reading disorders of and current complaints about reading difficulties, these findings suggest that the poor readers had compensated somewhat for their childhood reading impairment. Prior functional imaging studies that examined language processing in either compensated (Paulesu et al., 1996) or more severly impaired (Rumsey et al., 1997) poor adult readers found similar patterns of abnormal activation. That similarity suggests that the pattern of DTI results in the present study may extend to more overtly dyslexic adults.

The present findings may thus inform the debate over two conceptualizations of dyslexia. One conceptualization emphasizes the differences between normal and dyslexic readers as a discontinuity between intact and impaired reading ability. Prior postmortem and functional neuroimaging studies have focused on these group differences. Another conceptualization emphasizes continuities across normal and dyslexic readers, interpreting dyslexia as the disadvantageous tail end of a normal distribution of reading abilities (Shaywitz et al., 1992). One interpretation of the present results is that the microstructure associated with reading disorders represents one end of a continuous distribution. By this view, reading difficulty becomes apparent when white matter integrity falls below some threshold. The finding of a correlation of white matter microstructure and reading in both poor and normal readers does not exclude the possibility of a discrete neurological insult affecting white or gray matter in dyslexic subjects. However, the present findings show that it is not necessary to presuppose such an insult in order to explain the deficits in reading. Although discrete pathology in dyslexic subjects has been reported in the perisylvian cortices (Galaburda et al., 1985; Humphreys et al., 1990), the finding of quantitative differences in thalamic structure between dyslexic and normal and impaired readers (Livingstone et al., 1991; Galaburda et al., 1994) is more easily reconciled with a continuous relation of structure and function in both normal and impaired readers.

The test scores that correlated with left temporo-parietal anisotropy reflect only a subset of the multiple possible components of reading skill. The Word ID test measures the ability to read (or decode) isolated words accurately, and the Word Attack test is a measure of nonsense word decoding that requires the subject to translate novel visual letter strings to sounds (phonemes). Both tests are untimed measures of decoding and thus do not measure other aspects of reading such as rapid naming or comprehension. The present results, therefore, show a specific relation between decoding processes that are essential for reading and the microstructural properties of the left temporo-parietal anisotropy.

Because of the correlational nature of the present study, it is not possible to determine whether the differences in reading skill are caused by differences in white matter structure or follow from the acquisition of reading skill. Comparisons of literate and illiterate adults have demonstrated that literacy changes the functional anatomy of speaking (Castro-Caldas et al., 1998), and it is plausible that learning to read exerts other powerful changes on brain organization as well. These questions can be most directly addressed by longitudinal studies examining whether white matter structure in preliterate children predicts reading performance and whether white matter exhibits specific changes related to reading acquisition.

The Promise of Diffusion Tensor Imaging

Finally, we note that diffusion tensor imaging offers considerable promise for extending the range of neuroimaging in cognitive neuroscience. Functional neuroimaging techniques, including fMRI and PET, have proven important for identifying gray matter contributions to cognition. The present demonstration of a correlation between reading skill and white matter structure suggests that DTI may provide a complimentary method for imaging white matter contributions to cognition. DTI has been used, for example, to demonstrate separable contributions of axonal structure and directional coherence to brain development and to hemispheric asymmetry (Klingberg et al., 1999) and to follow specific white matter tracts between brain regions (Conturo et al., 1999). DTI is safe and noninvasive, which makes it suitable for a wide range of subjects, including young children and patients.

Structural imaging techniques such as DTI do not require any behavior on the part of the subject during scanning. This contrasts to functional imaging techniques such as fMRI and PET, which measure the gray matter activation associated with performance of a particular task. Differences in functional imaging data between normal and impaired subject groups can be difficult to interpret because the groups will usually differ in their level of performance; in this case, one cannot tell whether the differences in imaging relate to the underlying pathology or the differential performance. Because DTI does not require behavior, group differences are more easily interpreted in terms of underlying pathology. The combination of DTI with functional and structural neuroimaging techniques and postmortem studies should provide novel insights into the neural basis of literacy.

Experimental Procedures

Subjects

Subjects in the poor reading group (five males and one female, age 31.5 $\pm$ 5.3 years [mean $\pm$ SEM]) had a history of developmental dyslexia based on a professional psychological evaluation and reported continued reading difficulties in adulthood. The control group included six males and five females, age 23.1 $\pm$ 1.4 years. None of the subjects had any history of neurological disease. Subjects were right handed, except for one person in the poor reading group, as determined by the Annett handedness inventory (Annett, 1967). All subjects were given two standardized and widely used tests of reading skill. One was the Word ID test (Woodcock, 1987), in which single words of increasing complexity are visually presented and subjects are asked to pronounce them. The score is based on the subject's ability to pronounce the words and is converted into a standardized score with a population mean of 100 (SD 15). Mean reading score on the Word ID test was 87.3 ($\pm$ 4.4) for the poor reading group and 111 ($\pm$ 2.6) for the control group, with a significant difference between the groups ($p < 0.0003$). Of the subjects with a

history of dyslexia, four subjects exhibited reading scores below, but within 1 SD, of the standardized mean; two were more than 1 SD below the mean. All subjects also performed the Word Attack test (Woodcock, 1987), in which subjects are asked to pronounce pseudo-words. The mean group scores on the Word Attack test were 93.7 ($\pm$ 5.9) and 111 ($\pm$ 4.3) for the poor reading group and the control groups, respectively, with a significant group difference ($p < 0.05$).

MRI Acquisition

Scanning was performed with the Signa system (1.5T GE Signa Horizon EchoSpeed). Anatomical images were acquired using a T1-weighted, 3D, SPGR volume acquisition (TE/TR = 2.0/11.1 ms, field-of-view [FOV] = 240 $\times$ 240 $\times$ 186 mm, and matrix size = 256 $\times$ 256 $\times$ 124 voxels). DTI was performed using a diffusion-weighted single-shot spin-echo, echo planar imaging sequence (TE/TR = 106 ms/6000 ms, slew rate = 120 mT/m/ms, delta = 32 ms, Δ = 34 ms, maximum diffusion gradient = 14 mT/m, FOV = 360 mm, and matrix size = 128 $\times$ 128 zero-filled to 256 $\times$ 256). Sixteen axial, 5 mm thick slices (no skip) were imaged. Two b values were used, b = 0 and b = $\sim$860 s/mm^2. The high b value was obtained by applying gradients along two axes simultaneously in a total of six noncollinear directions. Eddy current effects were unwarped using inversion recovery echo planar images (TI $\approx$ 2100 ms, b = 0 s/mm^2) (de Crespigny and Moseley, 1998, ISMRM 6th Meeting, abstract). Six apparent diffusion coefficients were calculated, from which the six independent elements of the diffusion tensor were determined (Basser and Pierpaoli, 1996). From the diffusion tensor, three eigenvectors that define the direction of the diffusion system were determined for each voxel. The eigenvalues $\lambda 1$, $\lambda 2$, and $\lambda 3$, which correspond to the three eigenvectors, represent the magnitude of diffusivity in the three principal directions. Based on these three principal diffusivities and the mean diffusivity (λ), the fractional anisotropy (FA) was calculated (Basser, 1995; Basser and Pierpaoli, 1996) to yield values between 0 and 1:

$$FA = \frac{\sqrt{3}}{\sqrt{2}} \frac{\sqrt{(\lambda_1 - \lambda)^2 + (\lambda_2 - \lambda)^2 + (\lambda_3 - \lambda)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

The coherence index for a particular voxel was defined as the mean dot product of the principal eigenvector in that voxel and the principal eigenvector in its eight neighboring voxels in the same slice (Basser and Pierpaoli, 1996; Klingberg et al., 1999). When the eigenvectors are of unit length, the dot product is the cosine of the angle between the vectors.

Data Analysis

Analysis was carried out using Statistical Parametric Mapping software (SPM96, http//www.fil.ion.ucl.ac.uk/spm). Anisotropy images were spatially coregistered to each individual T1-weighted image, and both anisotropy and T1-weighted (SPGR) images were anatomically normalized to the standard stereotactic space of Talairach and Tournoux (1988) using the same parameters. After verifying that there were no group differences in global signal ($p > 0.40$), anisotropy values were scaled to the mean global value. Results were also confirmed using unscaled data. Signal intensities in the T1-weighted images were also normalized. Statistical significance was based on a combination of both Z values in voxels as well as the spatial extent of clusters of voxels having a suprathreshold Z value, providing a significance level of $p < 0.05$, after correction for the large number of comparisons across voxels in the whole brain volume (Friston et al., 1995). Two VOIs were defined as being the clusters of contiguous voxels where there was a significant difference in anisotropy between reading impaired and control subjects. Correlation analysis between reading scores and diffusion anisotropy was also performed with the general linear model implemented in SPM96.

For analysis of direction of axonal orientation, the eigenvector of the diffusion tensor was calculated for each voxel. Orientation along the anterior–posterior axis was defined as a voxel having a principal eigenvector with a $<45^\circ$ deviation from a line passing through the anterior and posterior commisures.

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