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Diffusion tensor imaging correlates of reading ability in dysfluent and non-impaired readers

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ABSTRACT

Many children and adults have specific reading disabilities; insight into the brain structure underlying these difficulties is evolving from imaging. Previous research highlights the left temporal-parietal white matter as important in reading, yet the degree of involvement of other areas remains unclear. Diffusion tensor imaging (DTI) and voxel-based analysis were used to examine correlations between reading ability and tissue structure in healthy adolescents and young adults ($n = 136$) with a range of reading ability. Three complementary reading scores (word reading, decoding, and reading fluency) yielded positive correlations with fractional anisotropy (FA) that spanned bilateral brain regions, particularly in the frontal lobes, but also included the thalamus and parietal and temporal areas. An analysis of the unique effects of each reading assessment revealed that most of the variance in FA values could be attributed to sight word reading ability.

1. Introduction

Many children and adults struggle with reading despite otherwise normal intelligence, opportunity, and motivation. Dyslexia is a specific reading disability thought to result from phonological processing deficits that affects between 5% and 17% of the population (Demonet, Taylor, & Chaix, 2004; Ramus, 2003; Shaywitz & Shaywitz, 2005). Reflecting the language basis for reading and dyslexia, three neural systems critical in reading and dyslexia are localized in the left hemisphere: two posterior systems in the parieto-temporal and occipito-temporal regions, and an anterior system around the inferior frontal gyrus (Broca's area) (Brambati et al., 2006; Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Kronbichler et al., 2006; Nakamura et al., 2006; Paulesu et al., 2001; Shaywitz et al., 2002, 2003, 1998).

In addition to these key cortical regions, white matter connections may contribute to functional differences in reading ability. Diffusion tensor imaging (DTI) is an insightful MRI technique that yields quantitative metrics for the assessment of brain white matter. Fractional anisotropy (FA) is one of the most commonly measured DTI parameters, with higher FA values often interpreted to indicate more consistent ordering of axons, greater myelination, and/or denser axon packing (for review, see (Beaulieu, 2002)). The first published DTI study of reading reported significant positive correlations between reading ability (Woodcock–Johnson Word ID) and FA in 17 adults in a region of left temporal-parietal white matter (Klingberg et al., 2000). Since then, additional studies have confirmed this left temporal-parietal relationship in children (Beaulieu et al., 2005; Carter et al., 2009; Deutsch et al., 2005; Nagy, Westerberg, & Klingberg, 2004; Niogi & McCandliss, 2006; Odegard, Farris, Ring, McColl, & Black, 2009; Qiu, Tan, Zhou, & Khong, 2008; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010). Tractography studies have also demonstrated relationships between the arcuate fasciculus, a frontal-parietal-temporal white matter pathway, and cognitive scores reflective of reading ability, particularly emphasizing the role of the left arcuate fasciculus (Lebel & Beaulieu, 2009; Qiu, Tan, Siok, Zhou, & Khong, 2011; Vandermosten et al., 2012; Yeatman et al., 2011). However, other studies have failed to find significant relationships between DTI parameters and reading ability in this left temporal-parietal region (Andrews et al., 2009; Dougherty et al., 2007; Rollins et al., 2009). Correlations between diffusion parameters and reading ability have been observed beyond this area, including in the corpus callosum (Andrews et al., 2009; Dougherty et al., 2007; Odegard et al., 2009), but the results have not always been consistent (Odegard et al., 2009; Qiu et al., 2008; Rimrodt et al., 2010). Several interesting reports suggest a link between white matter status and remediation, including relationships between diffusion changes in the left anterior centrum semiovale and reading remediation in

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children (Keller & Just, 2009), white matter connectivity and children's response to reading intervention (Davis et al., 2010), and a longitudinal relationship between right arcuate fasciculus FA and future reading gains in children (Hoeft et al., 2011).

Since the original paper on dyslexic adults (Klingberg et al., 2000), most DTI reading studies have focused on children and adolescents, with a few exceptions. One group measured FA in the corpus callosum of 28 young adults, and observed negative correlations between splenium FA and word reading (Frye et al., 2008). Another study examined 16 German-speaking adults and found positive correlations between pseudo-word reading and FA in several left hemisphere regions including the inferior frontal gyrus, external capsule, superior temporal gyrus and medial occipital gyrus (Steinbrink et al., 2008). Group differences have been observed in 14 adult dyslexic males that show significantly lower FA than 7 non-dyslexic males in multiple, bilateral brain regions (Richards et al., 2008).

Most previous DTI studies have used measures of word or pseudoword reading to assess reading ability in healthy and/or dyslexic subjects (for a recent review of DTI reading studies, see (Vandermosten, Boets, Wouters, & Ghesquiere, 2012)). Over the past decade, researchers have become increasingly interested in how reading progresses from the identification of single words to the rapid, fluent identification of connected text, and measures of reading fluency are now included in the identification of reading disabilities (Lyon, Shaywitz, & Shaywitz, 2003; Meisinger, Bloom, & Hynd, 2010). Several studies have examined relationships between fluency and diffusion parameters, finding significant correlations in healthy children (Gordon et al., 2011) and adults (Sullivan, Zahr, Rohlfing, & Pfefferbaum, 2010), as well as in subjects with dyslexia (Rimrodt et al., 2010), periventricular nodular heterotopia (Chang et al., 2007), Alzheimer's disease (Chen et al., 2009) and Parkinson's disease (Rae et al., 2012). These structure–function relationships identified several brain regions, but most commonly highlighted the frontal lobes. Interventions targeted at word identification in dyslexic readers are well established, but progress continues to be slow in developing interventions to improve fluency. Thus, while the current study uses measures of word and pseudoword reading to compare to previous work, the focus here is on subjects who have particular fluency difficulties. The goal of this study was to determine the extent of correlations between three different reading measures (word reading, nonword reading, and fluency) and white matter structure (as measured by the diffusion parameter FA) in a large sample of healthy adolescents and young adults ($n = 136$) with a wide range of reading ability.

2. Methods

2.1. Subjects

Healthy adolescent and young adult volunteers ($N = 136$, mean age ± standard deviation: 20.1 ± 3.1 years, range 15–28 years; 73 male/63 female; all right-handed), who had participated previously as young children in investigations of reading and learning disabilities at the Yale Center for the Study of Learning and Attention were recruited on the basis of their reading fluency and decoding ability, and were selected for a range of scores. Subjects were originally recruited from a number of sources, including referrals from pediatricians, nurses, psychologists, educators, and family physicians, as well as through notices in parent–teacher association bulletins, public libraries, scouting groups, children's toy stores, and community organizations. Children with sensory disorders, brain injury, and children where the cause of the reading problem was likely attributable to emotional disturbance, clinically apparent neurogenetic disorders, or social, cultural, or economic disadvantage were excluded from the study. The Institutional Review Board at Yale University approved this study and written informed consent was obtained from all subjects. Volunteers received a battery of cognitive tests including the Gray Oral Reading Test (GORT) that yielded fluency scores, as well as the Woodcock–Johnson Word Identification and Word Attack tests; one subject was missing a score for the Word ID test, and a different subject was missing a score for the GORT Fluency. The GORT Fluency score is a composite score for speed and accuracy of reading text passages. The Woodcock–Johnson Word ID is an untimed measure of word reading, and the Word Attack is an untimed measure of pseudoword reading or decoding. All reported measures are age-adjusted standard scores. Table 1 provides subject demographic information including age, reading test scores, and the Wechsler Abbreviated Scale of Intelligence (WASI) full scale IQ score.

2.2. Image acquisition

All subjects underwent MRI scanning on a 1.5T Siemens Sonata scanner at Yale University. The scanning protocol included structural T1-weighted imaging, functional MRI, and DTI; note that T1 and fMRI data are not presented here. DTI was acquired using spin echo echo-planar imaging with 28 5 mm slices (no gap), image matrix of 64×64, field of view = 240×240 mm^2, TE = 85 ms, TR = 9000 ms, $b = 1000$ s/mm^2, six diffusion-encoding directions, and six averages. Note that the DTI resolution is much lower than what is typical and had been chosen to match the fMRI acquisition (although this low spatial resolution is not recommended for DTI). Total DTI acquisition time was 7:24 min, yielding very high signal-to-noise ratio ($\sim$70) given the averages and voxel volume.

2.3. Statistical analysis

Non-diffusion weighted images ($b = 0$ s/mm^2) were normalized to the ICBM EPI template using non-affine transformations in SPM8 (Wellcome Trust Centre for Neuroimaging, London), and interpolated to a resolution of $2 \times 2 \times 2$ mm^3. Fractional anisotropy (FA) maps were calculated for each subject, then normalized to the ICBM template using the same parameters as the $b = 0$ images and smoothed using a 4 mm kernel, which approximates the original voxel size. Voxel-based tests for correlations of FA with standardized GORT Fluency, Woodcock–Johnson Word Attack and Word ID scores were conducted in SPM8. Initially, statistical analyses were conducted separately for each variable. Following this, all three reading measures were included in the same model to test for the unique effects of each reading skill. As FA is known to increase over this age span (Lebel & Beaulieu, 2011), age was corrected in all analyses by regressing it out of both dependent and independent variables using linear regression. To minimize comparisons with cortical gray matter or cerebrospinal fluid, only voxels with FA $\geqslant 0.2$ in all individuals were included in the analysis (note that this threshold leaves white matter and some deep gray matter structures such as the thalamus). In total, 37,099 voxels were analyzed in the whole brain FA maps. Due to the unique shape of this search area and the fact that large clusters are less likely to occur in long, narrow white matter regions, Monte Carlo simulations were conducted in AlphaSim (B. Ward, http://afni.nimh.nih.gov/afni/doc/manual/AlphaSim) to determine the probability that clusters of various sizes would randomly occur for this exact search region. These simulations showed that a p-value of 0.01 and a cluster size of 32 contiguous voxels produced an overall, family-wise alpha of 0.009 for each cognitive measure. Thus, an F-test with $p < 0.01$ per voxel and cluster size $\geqslant 32$ was used to determine significant clusters.