Title
White Matter Morphometric Changes Uniquely Predict Children's Reading Acquisition

Journal
Psychological Science, 25(10)

ISSN
0956-7976

Authors
Myers, Chelsea A
Vandermosten, Maaike
Farris, Emily A
et al.

Publication Date
2014-10-01

DOI
10.1177/0956797614544511

Peer reviewed

Structural changes in white matter are uniquely related to children's reading development

Journal:	*Psychological Science*
Manuscript ID:	PSCI-13-2303.R2
Manuscript Type:	Research article
Date Submitted by the Author:	11-Jun-2014
Complete List of Authors:	Myers, Chelsea; University of California, San Francisco, Psychiatry Vandermosten, Maaike; KU Leuven, Parenting and Special Education Research Unit Farris, Emily; University of Texas of the Permian Basin, Psychology Hancock, Roeland; University of California, San Francisco, Psychiatry Gimenez, Paul; University of California, San Francisco, Psychiatry Black, Jessica; Boston College, Graduate School of Social Work; University of California, San Francisco, Psychiatry Casto, Brandi; Palo Alto University, Pacific Graduate School of Psychology Drahos, Miroslav; University of California, San Francisco, Psychiatry Tumber, Mandeep; Palo Alto University, Pacific Graduate School of Psychology Hendren, Robert; University of California, San Francisco, Psychiatry Hulme, Charles; University College London, Psychology Hoeft, Fumiko; University of California, San Francisco, Psychiatry
Keywords:	Brain, Reading, Literacy, Cognitive Development, Childhood Development

Structural changes in white matter are uniquely related to children's reading development

Running Title: White matter development in beginning readers

Authors:

Chelsea A. Myers[1], Maaike Vandermosten[2], Emily A. Farris[1,3], Roeland Hancock[1], Paul Gimenez[1], Jessica M. Black[1,4], Brandi Casto[1,5], Miroslav Drahos[1], Mandeep Tumber[1,5], Robert L. Hendren[1], Charles Hulme[6], Fumiko Hoeft[1,7,8*]

Affiliations:

[1]Division of Child and Adolescent Psychiatry, Department of Psychiatry, University of California, San Francisco, 401 Parnassus Ave., San Francisco, CA 94143, USA

[2]Parenting and Special Education Research Unit, KU Leuven, Leopold Vanderkelenstraat 32, PO Box 3765, 3000 Leuven, Belgium

[3]Department of Psychology, University of Texas of the Permian Basin, 4901 E. University Blvd., Odessa, TX 79762, USA

[4]Graduate School of Social Work, Boston College, 140 Commonwealth Ave., Chestnut Hill, MA 02467, USA

[5]Pacific Graduate School of Psychology, Palo Alto University, 1791 Arastradero Rd., Palo Alto, CA 94304, USA

[6]Division of Psychology and Language Sciences, Department of Psychology, University College London, Gower Street, London, WC1E 6BT, United Kingdom

[7]Haskins Laboratories, Yale University, 300 George St., Suite 900, New Haven, CT 06511, USA

[8]Department of Neuropsychiatry, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, 160-8582, Japan

*Corresponding author: Fumiko Hoeft, 401 Parnassus Ave., San Francisco, CA 94143, 415-476-9861, Fumiko.Hoeft@ucsf.edu

ABSTRACT

This study examined whether variations in brain development between kindergarten and Grade 3 predicted individual differences in reading ability at the latter time point. Structural MRI measurements indicated that increases in volume of two left temporo-parietal white matter clusters are unique predictors of reading outcome at Grade 3. Using diffusion MRI, the larger of these two clusters was identified as a location where fibers of the long segment of arcuate fasciculus and superior corona radiata intersect, and the smaller cluster as the posterior arcuate fasciculus. Bias-free regression analyses using regions-of-interest from prior literature revealed white matter volume changes in temporo-parietal white matter, together with preliteracy measures, predicted 56% of the variance in reading outcomes. Our findings demonstrate the important contribution of developmental differences in areas of left dorsal white matter, often implicated in phonological processing, as a sensitive early biomarker for later reading abilities, and by extension, reading difficulties.

INTRODUCTION

Learning to read is critical for educational success and has an enduring influence on career opportunities and psychosocial wellbeing. Difficulties in learning to decode print (developmental dyslexia) are relatively common, affecting somewhere between 3-7% of the population (Peterson & Pennington, 2012). To explain the decoding difficulties seen in children with dyslexia, we must understand the cognitive mechanisms that are causally linked to variations in decoding skills. Robust evidence indicates that there are three main early behavioral predictors of individual differences in learning to decode in alphabetic languages: letter knowledge, phonological awareness (PA), and rapid naming (Caravolas et al., 2012; Lervåg, Bråten, & Hulme, 2009). Further, family history and socio-economic status have been shown to be strong predictors (e.g. Bowey, 1995; Lefly & Pennington, 2000). Here, we examine whether variations in structural brain development (from kindergarten to Grade 3) are additional, sensitive, and early predictors of variations in reading ability.

The development of PA and related skills are believed to involve temporo-parietal and caudal inferior frontal / precentral regions that are major nodes of the dorsal pathway (Hoeft et al., 2006; Hoeft, Meyler, et al., 2007; Yamada et al., 2011). Specifically, key white matter tracts are important for the development of reading including those in left temporo-parietal regions. For example, evidence suggests that the arcuate fasciculus (and/or superior longitudinal fasciculus) plays a role in language, speech-sound processing (Dick & Tremblay, 2012), word learning (López-Barroso et al., 2013) and phonological processing (Saygin et al., 2013; Thiebaut de Schotten, Cohen, Amemiya, Braga, & Dehaene, 2012; Vandermosten et al., 2012; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012). The nearby corona radiata is also thought to be

related to variations in reading skill (Beaulieu et al., 2005; Niogi & McCandliss, 2006; Odegard, Farris, Ring, McColl, & Black, 2009).

Recently, several studies have explored whether neuroimaging measures are effective predictors of later reading abilities. These studies showed that (1) functional and structural neuroimaging measures in children were effective in predicting future reading after relevant cognitive and earlier reading skills had been accounted for (Hoeft, Ueno, et al., 2007), (2) developmental changes in reading correlated with activation of dorsal and ventral pathways that changed with age (McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011), (3) reading skills of children with reading disabilities (RD) with compensatory skills were predicted by functional activation and white matter integrity (Hoeft et al., 2011), and (4) ERP and fMRI measures in preliterate children correlated with reading outcome (Bach, Richardson, Brandeis, Martin, & Brem, 2013). These studies utilized imaging data from one time-point to predict reading outcomes. However, there is ample evidence suggesting longitudinal studies measuring developmental changes are more sensitive than static measures in detecting abnormalities (e.g. Giedd & Rapoport, 2010).

Therefore, the aim of the current study was to examine whether developmental structural changes in neural circuits predict variations in reading outcomes in Grade 3. We measured changes in white matter in children, as its development appears critical for reading. We examined the degree to which white matter development uniquely predicted reading outcome after controlling for the influence of other potentially important predictors. We hypothesized that left temporo-parietal dorsal white matter pathway development, considered critical for phonological tasks, would be an early predictor of reading outcome.

METHODS

Participants. As outlined in NIH K23HD054720 which was the main source of funding for the project, sample size was determined using power calculation based on ours and related papers that examined how neuroimaging predicts reading ability and future reading outcome. Also as outlined in the same grant, we recruited children in 2008 and 2009 and all children that qualified after screening were included. Thirty-eight healthy, native English-speaking children, with varying degrees of preliteracy skills and family history of reading difficulty, participated in our study at ages five or six (Time 1) and again three school years later (Time 2; **Table 1**). These children are a subset of an original 51 participants. Among the original 51, six were excluded because of participant dropout or insufficient follow-up data (N=45) and seven were excluded due to movement during their scans at one or both time-points (N=38). Excluded participants (N=13) did not statistically differ from included participants in demographic and behavioral measures at Time 1 & 2 (all p's > 0.1), with the exception of the Time 1 Comprehensive Test of Phonological Processing (CTOPP) Blending Words subtest ($t_{(15.79)}$=2.19, p=0.044), on which the excluded participants performed better than those included. Of the 38 participants, using an Adult Reading History Questionnaire (ARHQ) cut-off score of > 0.4 (for at least one parent) as specified in Black et al., 2012, 18 participants met the criterion for a family history of reading difficulty. Participants had no neurological or psychiatric disorders including attention deficit hyperactivity disorder (ADHD), were not on any medication, and had no contraindications to MRI. The Stanford University Panel on Human Subjects in Medical Research and the University of California, San Francisco Human Research Protection Program approved the study and informed assent and consent were obtained.

Table 1. Demographics

Measure	Mean (SD)	Range (Min, Max)
Time 1		
Age (years)	5.52(0.38)	1.82(5.03,6.85)
Gender	24 males/14 females	
Handedness	33 right-/5 left-handed	
Parental education	16.92(1.75)	8.50(12.50,21.00)
Home literacy environment	6.91(2.01)	11.00 (3.00,14.00)
Maternal family history (mARHQ)	0.31(0.15)	0.60(0.07,0.67)
Paternal family history (pARHQ)	0.35(0.13)	0.52(0.09,0.61)
CTOPP Blending	12.03(1.62)	7(8,15)
CTOPP Elision	11.68(2.75)	12(7,19)
WRMT Letter ID	108.76(10.52)	51(80,131)
PPVT4 Vocab	121.84(9.87)	51(97,148)
RAN Objects	101.53(15.73)	78(57,135)
RAN Colors	98.47(15.58)	82(55,137)
IQ (BIA)	119.61(10.62)	47(92,139)
Preliteracy Index 1*	0(1.00)	4.26(-2.29,1.98)
Preliteracy Index 2*	0(1.00)	4.81(-2.78,2.02)
Receptive language (CELFrec)	118.66(11.85)	43(94,137)
Expressive language (CELFexpr)	117.29(11.97)	53(91,144)
Total gray matter volume (cc)	782.62(68.40)	275.52(621.42,896.94)
Total white matter volume (cc)	419.44(49.95)	215.69(347.28,562.97)
Time 2		
Age (years)	8.24(0.40)	1.57(7.51,9.08)
TOWRE Word Reading	111.34(12.98)	52(86,138)
WRMT Word ID	116.89(10.71)	42(97,139)
WRMT Word Attack	114.66(13.61)	54(92,146)
WRMT Passage Comprehension	114.82(9.99)	42(99,141)
WJ-III Reading Fluency	113.26(16.64)	71(91,162)
WJ-III Spelling	105.92(17.83)	74(74,148)
TOWRE Decoding	106.66(13.91)	67(77,144)
RAN Objects	97.71(16.96)	70(62,132)
RAN Colors	97.39(15.65)	63(60,123)

RAN Numbers	100.21(12.58)	53(76,129)
RAN Letters	103.47(11.47)	56(78,134)
RAS 2-Set	103.82(14.19)	69(72,141)
RAS 3-Set	101.58(15.13)	79(64,143)
CTOPP Blending	12.68(2.29)	10(6,16)
CTOPP Elision	10.24(2.17)	9(7,16)
CTOPP Memory for Digits	10.21(2.59)	10(5,15)
CTOPP Non-word Repetition	13.13(2.92)	10(7.17)
Reading-related Index 1**	0(1.00)	4.31(-1.89,2.42)
Reading-related Index 2**	0(1.00)	4.57(-2.44,2.13)
Reading-related Index 3**	0(1.00)	4.71(-2.75,1.95)
Total gray matter volume (cc)	776.02(74.77)	379.78(552.14,931.92)
Total white matter volume (cc)	445.31(56.04)	246.39(361.84,608.23)

Handedness: Evaluated with the Edinburgh Handedness Questionnaire; ***Parental education:*** Average of parents education years starting in 1st grade; ***Home Literacy Environment (HLI):*** Measured using an average of non-print activities and reading activities; ***Family History (mARHQ; pARHQ):*** Adult Reading History Questionnaire (ARHQ); ***CTOPP Blending***- Comprehensive Test of Phonological Processing (CTOPP) Blending Words subtest; ***CTOPP Elision***- CTOPP Elision Words subtest; ***WRMT Letter ID***- Woodcock Reading Mastery Tests-- Revised Normative Update (WRMT-R/NU) Letter Identification; ***PPVT4 Vocab***- Peabody Picture Vocabulary Test 4 (PPVT4); ***RAN Objects***- Rapid Automatized Naming (RAN) Objects subtest; ***RAN Colors***- RAN Colors subtest; ***IQ:*** Woodcock Johnson III Cognitive Battery Brief Intellectual Ability (BIA) commonly used as a proxy for IQ; ***Pre-literacy Index 1:*** 1st factor that loads heavily on phonological awareness, vocabulary, letter identification skills; ***Pre-literacy Index 2:*** 2nd factor that loads heavily on rapid naming of colors and objects; ***CELFexpr:*** Clinical Evaluation of Language Fundamentals 4 (CELF4) Expressive Language Index, which consists of Word Structure, Recalling Sentences, and Formulated Sentences; ***CELFrec:*** CELF4 Receptive Language Index, which consists of Concepts and Following Directions, Word Classes 2-Receptive, and Sentence Structure; ***TOWRE Word Reading***- Test of Word Reading Efficiency (TOWRE) Sight Word Efficiency; ***WRMT Word ID***- (WRMT-R/NU) Word Identification; ***WRMT Word Attack***- (WRMT-R/NU) Word Attack; ***WRMT Passage Comprehension*** (WRMT-R/NU) Passage Comprehension; ***WJ-III Reading Fluency***- Woodcock-Johnson III (WJ-III) Tests of Achievement Reading Fluency; ***WJ-III Spelling***- WJ-III Spelling subtest; ***TOWRE Decoding***- TOWRE Phonemic Decoding Efficiency; ***RAN Objects, Colors, Numbers, Letters***- Rapid Automatized Naming Objects, Colors, Numbers, Letters subtests; ***RAS 2-Set, 3-Set***- Rapid Alternative Stimulus (RAS) tests of Letters and Numbers (2-set) and Letters, Numbers and Colors (3-set); ***CTOPP Memory for Digits***- CTOPP Memory for Digits subtest, ***CTOPP Non-word Repetition***- CTOPP Non-word Repetition subtest. ***Reading-Related Index 1:*** 1st factor that loads heavily on decoding, single word reading, reading comprehension, writing and reading fluency, and spelling; ; ***Reading-Related Index 2:*** 2nd factor that loads heavily on rapid naming of objects and colors; ***Reading-Related Index 3:*** 3rd factor that loads heavily on phonological awareness.

Non-imaging measures. Participants completed a test battery of standardized neuropsychological assessments at both time points. Reading assessments at Time 1 included a letter identification measure, Woodcock Reading Mastery Tests-- Revised Normative Update (WRMT-R/NU) Letter Identification subtest, a vocabulary measure, Peabody Picture Vocabulary Test 4 (PPVT4), rapid naming measures, Rapid Automatized Naming (RAN) Objects and Colors subtests, and PA measures of Elision and Blending Words from the Comprehensive Test of Phonological Processing (CTOPP), which were included to calculate Preliteracy Indices.

At Time 1, factor analysis using standard scores from tests related to reading identified two Preliteracy Indices, which combined explained 70.3% (46.6% and 23.7, respectively) of the total variance in pre-reading skills. Letter knowledge, PA and vocabulary measures loaded

heavily to the first factor, Preliteracy Index 1. Rapid naming measures loaded heavily on the second factor, Preliteracy Index 2.

Other measures included Woodcock Johnson-III (WJ-III) Tests of Cognitive Abilities-Revised Normative Update Brief Intellectual Ability composite score, which consists of Verbal Comprehension, Concept Formation, and Visual Matching subtests and was used as a short and reliable proxy for IQ. Receptive and expressive language were assessed using the Clinical Evaluation of Language Fundamentals 4 (CELF4) Receptive and Expressive Language Indices. The Receptive Language Index consists of Concepts and Following Directions, Word Classes 2-Receptive, and Sentence Structure subtests, and the Expressive Language Index consists of Word Structure, Recalling Sentences, and Formulated Sentences subtests. These tests were used as indicators of early language abilities.

Measures representative of environment included socio-economic status (SES) and home literacy environment. At Time 1, an average of maternal and paternal years of education was used as a marker of SES because education has been demonstrated to be strongly representative of SES (e.g. Smith & Graham, 1995). The average of non-print activities (e.g., singing songs and rhymes, watching television programs or videos) and reading activities completed at home as assessed by the Home Literacy Inventory (Marvin & Ogden, 2002) were used to measure the home reading environment.

Finally, family history of reading difficulty was assessed using the Adult Reading History Questionnaire responses from both biological parents (ARHQ; Lefly & Pennington, 2000). The ARHQ is a widely used self-report assessment, with good reliability and validity. In the current study, we treat ARHQ scores as a continuous variable and maintain separate scores for each

parent to represent varying degrees of maternal and paternal risk. The correlations between the behavioral, environmental, and familial risk measures are shown in **Table S1**.

Tests at Time 2 included rapid naming measures, RAN Objects, Colors, Numbers, and Letters subtests, and the Rapid Alternative Stimulus (RAS) tests of Letters and Numbers (2-set), and Letters, Numbers and Colors (3-set). Single-word reading measures included WRMT-R/NU Word ID and Test of Word Reading Efficiency (TOWRE) Sight Word Efficiency. Pseudoword decoding measures WRMT-R/NU Word Attack and TOWRE Phonemic Decoding Efficiency were also used. Additionally, a reading comprehension measure, Woodcock Reading Mastery Tests-- Revised Normative Update Passage Comprehension, a reading fluency measure, Woodcock-Johnson III Tests of Achievement Reading Fluency, and a spelling measure, WJ-III Spelling, were collected. Finally, Time 2 tests also included measures of phonological memory (the CTOPP Memory for Digits and Non-word Repetition) and PA (CTOPP Elision and Blending Words).

All of these standardized measures collected at Time 2 are related to reading and were entered into a factor analysis. This analysis revealed three correlated factors: Reading-related index 1 (decoding, single word reading, reading fluency, spelling, and reading comprehension) explained 53.4% of the total variance in reading skills. Reading-related Index 2 was defined by measures of rapid naming and explained 16.2% of the variance; whereas, Reading-related Index 3, explaining 6.6% of the variance, was defined by measures of PA and phonological memory. Reading-related index 1 was selected as the primary measurement of reading outcome for the remainder of the study, as it was most representative of reading ability and explained the most variance.

MRI data acquisition and preprocessing. Imaging data were collected at the Richard M. Lucas Center for Imaging at Stanford University in the summer and fall of 2008 and 2009 and again in 2011 and 2012. Prior to the scanning session, families received a packet of materials, including a CD of scanner noises and a DVD of a child going into a scanner, designed to prepare him/her for the scanner sounds and environment. Children also participated in simulated MRI sessions at the center to further minimize movement (http://cibsr.stanford.edu/participating/Simulator.html). MRI data were acquired using a GE Healthcare 3.0 Tesla 750 scanner 20.x software revision and an 8-channel phased array head coil (GE Healthcare, Waukesha, WI). Images acquired included an axial-oblique 3D T1-weighted sequence with fast spoiled gradient recalled echo (FSPGR) pulse sequence (inversion recovery preparation pulse (TI) = 400 ms; repetition time (TR) = 8.5 ms; echo-time (TE) = 3.4 ms; flip angle = 15°; Receiver bandwidth + 32 kHz; slice thickness = 1.2 mm; 128 slices; NEX= 1; field-of-view (FOV) = 22 cm; Phase FOV = 0.75; acquisition matrix = 256 × 192). Scans were inspected by three experienced imaging researchers without the knowledge of the purpose of the study for the presence of excessive motion and excluded when agreed upon by the researchers.

In addition, at Time 2, high-angular resolution diffusion-imaging (HARDI) scans were collected in a subset of the children to examine the likelihood that the results from T1 structural MRI are spatially proximal to a certain white matter tract. The total of 150 diffusion-encoding gradient directions with the diffusion sensitivity of b=2500 s/mm^2 were sampled using repetition time (TR)=5000ms, echo time (TE) = 82.6ms, matrix size 128x128, spatial in-plane resolution 2.0x2.0mm and slice thickness 3.0mm.

The Statistical Parametric Mapping 8 (SPM8) statistical package (SPM8; http://www.fil.ion.ucl.ac.uk/spm) including the voxel based morphometry (VBM8) and

Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra (DARTEL) toolboxes (Ashburner, 2007) was used in the preprocessing of the structural MR images. Images were bias-field corrected and segmented to gray matter, white matter, and cerebro-spinal fluid. Non-linear registration was used to normalize segmented images to Montreal Neurological Institute (MNI) space and modulated. Visual inspection of each participant's data was performed to check for usability of data. An 8-mm FWHM isotropic Gaussian kernel was applied for smoothing.

Visual inspection of HARDI images was first performed to check for possible artifacts. All additional preprocessing was conducted in Explore DTI (Leemans & Jones, 2009). CATNAP was used for correction of eddy current and motion-induced artifacts with the accepted reorientation of the *b*-matrix (Leemans and Jones, 2009). No participants were excluded due to motion in HARDI scans. The root-mean square of estimated translational movement was 1.23mm with a standard deviation of 0.73mm. Of note, six subjects had a motion of greater than 1.5mm. A diffusion tensor model was estimated using non-linear least square fitting. A whole-brain tractography was constructed for each participant's data using a seed point [2 2 2] with additional parameters of an angle threshold of 40 degrees and fiber length range of 50-500mm.

Statistical significance threshold. The statistical significance threshold for whole-brain analyses was determined by Monte Carlo simulations using 3dClustSim in AFNI (Cox, 1996). All reported clusters were significant at $p = 0.05$ corrected for multiple comparisons, which dictated that results were limited to voxel height of $p < 0.005$ and cluster-size of at least 257 contiguous voxels by volume. All reported coordinates are in Montreal Neurological Institute (MNI) space.

Whole-brain analyses of white matter volume. To examine the relationship between white matter development and reading outcome, correlations were computed between measures of white matter development and reading outcome (Reading-related Index 1, defined as a composite reading measure based on factor analysis of reading measures from Time 2). White matter development was measured by the difference in volume between Time 1 and Time 2 images. Further, this basic analysis was repeated to examine the effect of white matter development after controlling for other factors commonly associated with reading outcome, including Time 1 measures of preliteracy (Preliteracy Index 1 and 2, determined by factor analysis of Time 1 preliteracy measures), family history (maternal and paternal), environmental measures (home literacy and SES) and cognitive and linguistic capacities (measures of IQ, receptive and expressive language). Similar analyses were repeated for gray matter and Time 1 gray and white matter, but are not reported as there were no regions that showed specific effects predicting reading outcome above and beyond other measures such as environment, cognition, preliteracy, and family history at thresholds corrected for multiple comparisons reported above. We chose to analyze the relationship between change in white matter volume and reading outcome by regressing out each nuisance variable (i.e., environment, preliteracy, family history, cognitive capacities) separately. This was done so that we could observe the influence of each nuisance variable independently. However, we also examined the relationship between change in white matter volume and reading outcome when all nuisance variables were entered into one model. These results can be found in **Figure S1**.

Analyses based on *a priori* regions of interest (ROIs) from the past literature. We next investigated how brain-imaging measures fared against measures commonly used to identify risk for developing RD and/or poor reading. Stepwise multiple regression analysis was

performed with Reading-Related Index 1 as the dependent variable and several behavioral and imaging independent variables. Behavioral independent variables included Preliteracy Index 1 and 2, maternal and paternal history, home literacy environment, SES, IQ, and receptive and expressive language all acquired at Time 1. Neuroimaging independent variables included change in volumes from Time 1 to Time 2 in white matter ROIs identified from past diffusion imaging literature that reported coordinates of locations that had shown significant association with reading in children (**Table 2**). In the second stepwise regression analysis, we entered all ROIs into one model in order to determine how much of the variance was explained by developmental neuroimaging measures (i.e., Time 2 minus Time 1) alone. In the final stepwise regression analysis, Time 1 white matter volumes of ROIs listed in Table 2 were entered in place of developmental measures (i.e., change in white matter volume from Time 1 to 2).

Table 2. *A priori* regions of interest (ROIs) based on previous voxel-based studies

ROI #	Peak (x,y,z) in MNI	Location	Reference	MNI Coordinates (x,y,z)
ROI 1	-29, -42, 28	Left temporo-parietal white matter	Deutsch *et al.*, 2005	-28, -24, 27
				-28, -30, 22
				-32, -18, 22
			Niogi & McCandliss, 2006	-28, -11, 24
		Posterior limb of the internal capsule	Beaulieu *et al.*, 2005	-28, -14,24
ROI 2	-14, -9, 42	Left superior corona radiata	Odegard *et al.*, 2009	-14, -9, 42
ROI 3	-4, -33, 19	Left posterior corpus callosum	Odegard *et al.*, 2009	-4, -33, 19
ROI 4	-21, 0, 27	Left superior corona radiata (inferior to ROI 2)	Odegard *et al.*, 2009	-21, 0, 27
ROI 5	-11, 24, 37	Left anterior centrum semiovale	Keller & Just, 2009	-10, 20, 38
				-12, 28, 36
ROI 6	28, -42, 28	Right temporo-parietal white matter	Deutsch *et al.,* 2005	28, -42, 28
ROI 7	-27, -29, 5	Left temporal white matter	Nagy *et al.*, 2004	-27, -29, 5
ROI 8	-42, -54 28	Left temporo-parietal white matter near arcuate fasciculus	Saygin *et al.,* 2013	-42, -54, 28

Locations above are based on those reported by the authors that the coordinates correspond with.

In this analysis, ROIs were defined as spheres with a 5mm radius from the peak coordinates of white matter regions reported in previous literature as being important for reading (Beaulieu et al., 2005; Deutsch et al., 2005; Keller & Just, 2009; Nagy, Westerberg, & Klingberg,

2004; Niogi & McCandliss, 2006; Odegard et al., 2009; Saygin et al., 2013). ROIs were combined if overlapping in spatial location (**Table 2**). Studies with coordinates focusing on samples of English-speaking children were included. Since most studies of ventral pathways were in native space, there is a noted bias towards coordinates of the dorsal rather than ventral pathway. For example, studies such as Vandermosten et al., 2012 and Yeatman et al., 2012 were excluded even though these papers found a significant effect of reading in the ventral pathway. Mean white matter volumes of the eight ROIs were extracted for each participant at each time-point and volume differences were calculated.

Fiber tracking. We performed fiber-tracking analyses to examine white matter fibers using the participants' Time 2 HARDI images from whom such data was available (N=28) following the procedure used in Vandermosten et al., 2012. Tractography was performed in native space. The two clusters from analyses of white matter development that predict reading above and beyond preliteracy, cognitive, environmental, and family history measures were used as two independent seed ROIs on each subject's HARDI images. Due to the proximity of our clusters to left temporo-parietal white matter, we suspected the clusters to contain the arcuate fasciculus and potentially the corona radiata. To confirm this, we performed fiber tracking of the arcuate fasciculus and corona radiata in five subjects (see below for details). Once confirmed, resultant tracts from our whole-brain cluster seeds were assessed visually in each and all participants to determine which tract(s) was most probable in accounting for volumetric changes.

To track the corona radiata and arcuate fasciculus to confirm the presence of the two tracts, atlas-based definition was performed for each of the five subjects in native space by manually placing ROIs, based on prior anatomical knowledge of the white matter tracts' trajectory. SEED-ROIs and AND-ROIs represent brain regions that all fibers of the tract must

pass through, whereas NOT-ROIs exclude fibers running through this region. **Figure S2** depicts where the different ROIs (SEED, AND, NOT) were placed for the corona radiata and the three segments of the arcuate fasciculus. To delineate the segments of the arcuate fasciculus (Catani, Jones, & Ffytche, 2005), we adapted the protocol of Wakana et al., 2007, since the original protocol provides ROIs to delineate the long segment, but not to separate the anterior and posterior segment of the arcuate fasciculus (for a similar approach see Vandermosten et al., 2012). With regard to tracking the corona radiata, there is no generally accepted practice, as the corona radiata is a large fiber bundle, which spans between the cortical surface, basal ganglia, and thalamus. First, we selected a ROI based on the study of Niogi & McCandliss, 2006), which included the blue voxels at an axial slice at the level of the body of the corpus callosum. This ROI was used as a seed region for fiber tracking. Next, interhemispheric fibers or fibers that belonged to the arcuate fasciculus were excluded by placing a NOT-ROI.

RESULTS

White matter development and reading outcome. Whole-brain analysis of voxel-by-voxel white matter volume yielded a significant positive correlation between Reading-Related Index 1 and increase in regional white matter volume between Time 1 and 2 in a number of white matter regions encompassing bilateral dorsal fronto-parieto-temporal and left ventral occipito-temporal regions (**Figure 1; Table S2**) ($p < 0.05$ corrected).

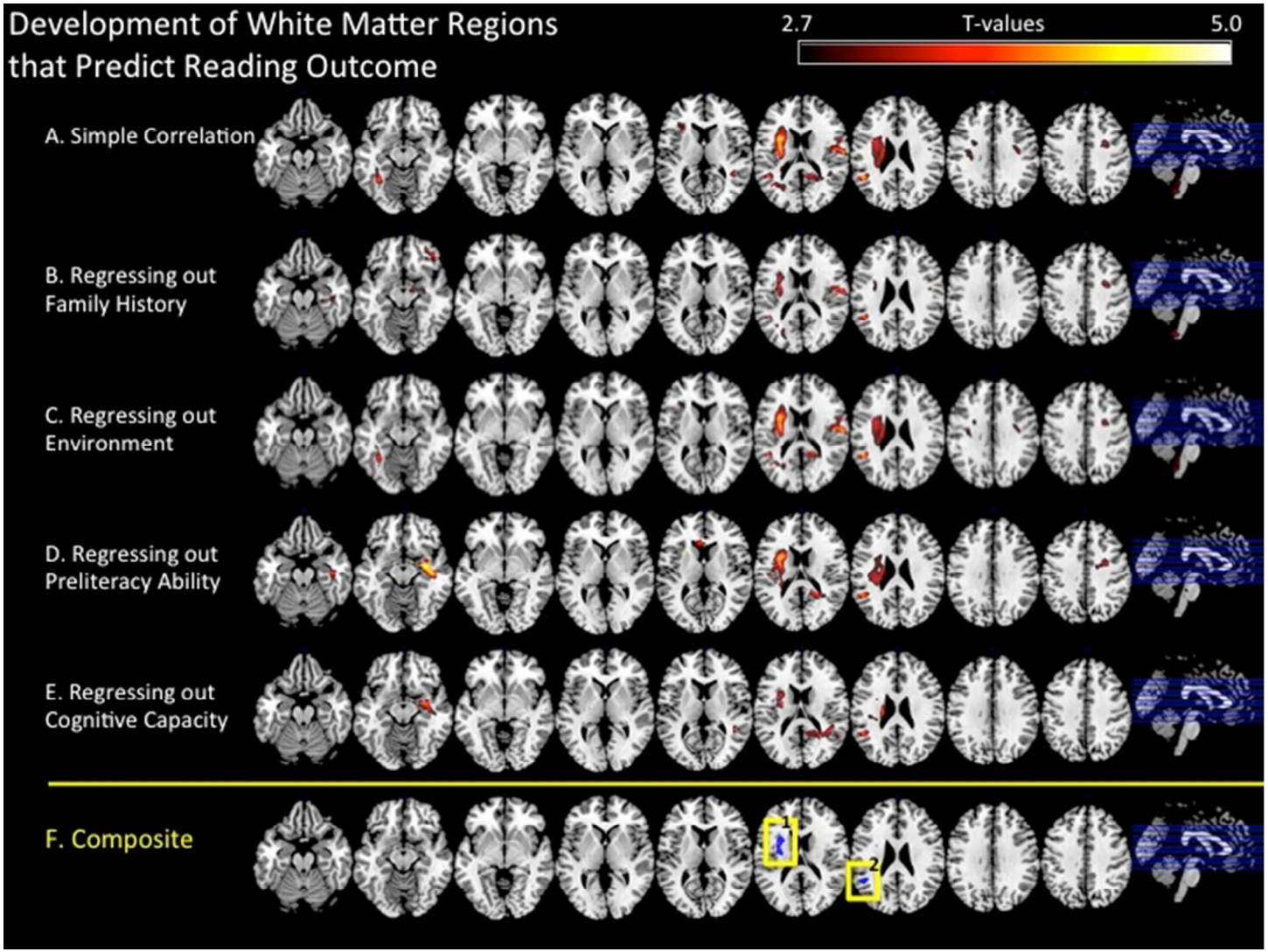

Figure 1. Development of white matter regions that predict reading outcome. Positive correlation between change in white matter volume (Time 2 - 1) and a composite measure of reading at Time 2 without inclusion of any nuisance variables (A), regressing out family history, which included maternal and

paternal Adult Reading History Questionnaire scores (B), regressing out environment, which included Home Literacy Inventory exposure to print and non-print average and maternal and paternal education (C), regressing out preliteracy ability, which included two composite measures of commonly used preliteracy indicators, including measures of PA, letter knowledge, rapid naming, and vocabulary (D), and regressing out cognitive capacity, which included measures of IQ and expressive and receptive language (E). The composite of A-E, determining overlapping regions (F). Cluster 1 and 2 (in blue and enclosed by yellow box) labeling the significant regions corresponding to the regions designated as 1 and 2 on Table S2. All thresholds at P = 0.05 corrected. Results examining the relationship between change in white matter volume and reading outcome when all nuisance variables were entered into one model are reported in Figure S1.

To control for family history, environmental and behavioral variables, we ran a series of whole-brain partial correlation analyses. Nuisance variables included family history, environment, preliteracy, and cognition/early language constructs (**Figure 1B-E; Table S2**). We regressed out each of these key constructs in independent generalized linear models to investigate the influence of each factor separately. A number of white matter regions showed significant positive correlations with white matter volume and a composite measure of reading outcome in both left and right white matter, including many that overlapped with results from simple correlation analysis (**Table S2**).

Conjunction analyses, including all key control variables mentioned above, revealed two left temporo-parietal regions that were significantly and positively associated with increase in white matter volume and reading outcome. In other words, left temporo-parietal white matter development predicted reading outcome above and beyond familial risk, environment, preliteracy ability and cognitive capacity (**Figure 1F, Table S2**). The larger left temporo-parietal white matter region (Cluster 1, 2,633 voxels) overlapped with the most highly replicated findings from previous diffusion imaging studies of reading (**Figure 1F, 2**). A second region (Cluster 2, 1,037 voxels) was proximal to the supramarginal and angular gyri and overlapped with a region reported recently in Saygin et al. (2013) (**Figure 1F, 2;** see also ROI 8). **Figure S1** represents clusters that survived when all nuisance variables were entered into one model. These clusters included two left temporo-parietal clusters as well as clusters in the right hemisphere. Finally, **Figure 3** displays the relationship between reading outcome and change in white matter volume. The figure demonstrates that there is considerable variability in changes of white matter volume over time, with some participants increasing, some remaining stable, and some even decreasing.

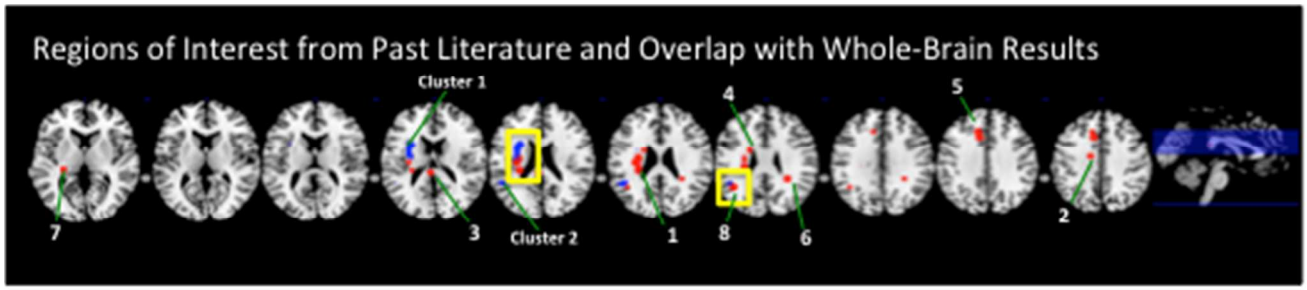

Figure 2. ***A priori*** **regions of interest (ROIs) based on previous voxel-based studies.** Axial view of overlay of selected ROIs (red and labeled according to **Table 2**) and volumetric regions that predict reading above and beyond family history, environment, preliteracy ability, and cognitive factors (blue, and as seen in **Figure 1**). The indicated region (yellow box) points to where there is overlap of the two in the left temporo-parietal regions. Lack of ROIs from ventral pathways is due to the fact that the majority of past studies that report the ventral pathway have performed tractography and/or analyses in native space.

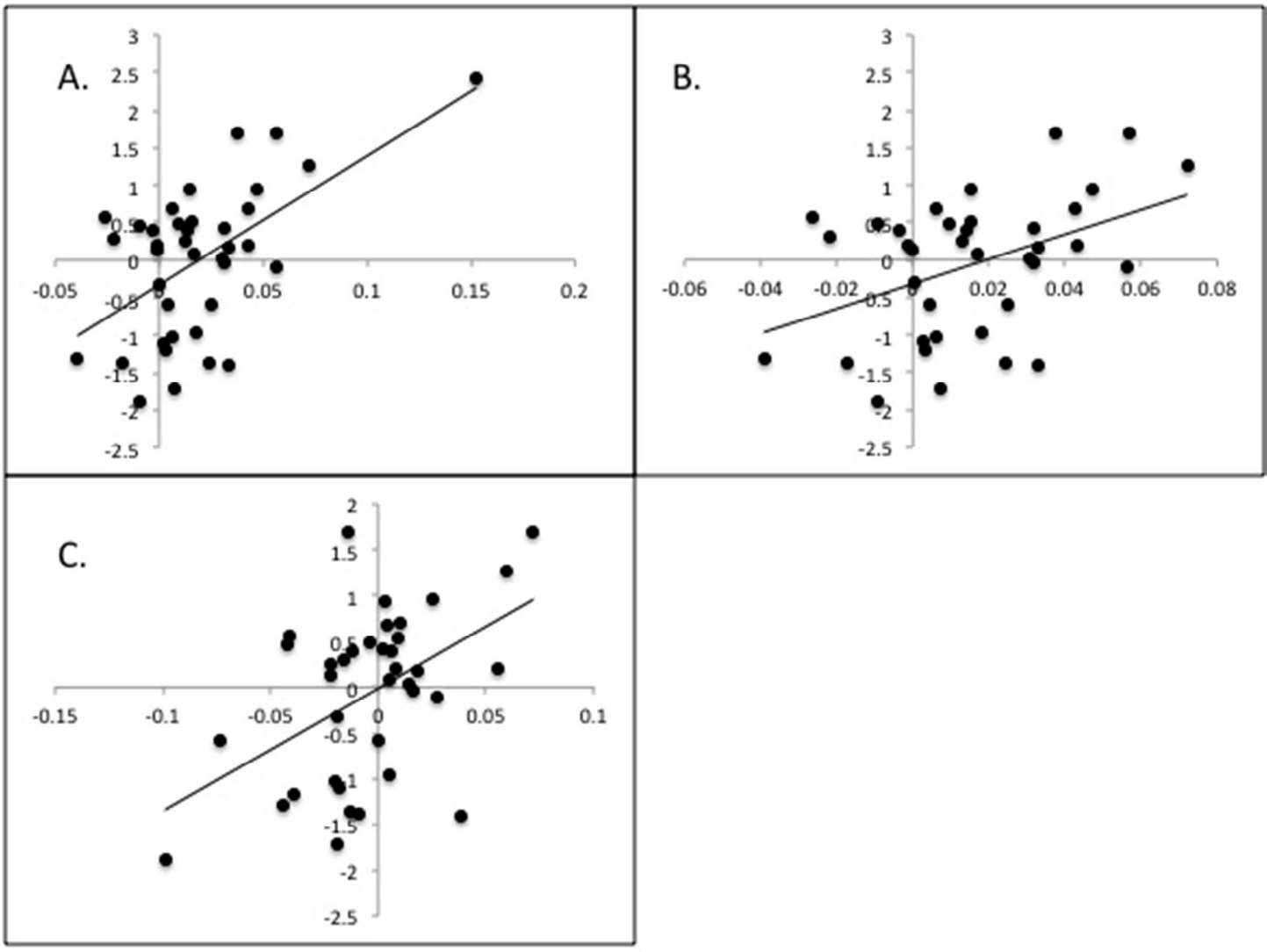

Figure 3. Relationship between development of white matter (Time 2- Time 1) and Time 2 reading outcome. **Clusters 1 and 2** (as seen in Figure 1F), white matter volume changes are represented on the x-axis and Reading-Related Index 1 at Time 2 is represented on the y-axis (A). Cluster 1 with all participants (N=38). (B) Cluster 1 with the omission of an outlier (N=37). This outlier was not considered an outlier from any other measures (demographic, behavioral, Time 1 or Time 2 white matter volume in Cluster 1, and change in volume in other clusters) and thus remains in the remaining analyses. The results remain significant without this participant. (C) Cluster 2 with all participants (N=38). The participant omitted in B is not an outlier for Cluster 2.

A priori ROI-based approaches. Multiple regression analyses examined whether developmental changes in white matter volume of brain regions identified in previous diffusion

imaging studies as being associated with reading, would be as predictive as non-imaging measures that are known to predict reading outcome. ROIs identified in previous studies (summarized in **Table 2;** Beaulieu et al., 2005; Deutsch et al., 2005; Keller & Just, 2009; Nagy et al., 2004; Niogi & McCandliss, 2006; Odegard et al., 2009; Saygin et al., 2013) and measures of preliteracy (Preliteracy Indices 1 & 2), environment, cognition, and family history were entered into the stepwise regression model. Explanatory variables that were retained in the final model included Preliteracy Index 1 explaining 34.2% of the variance ($F_{(1,36)}$=20.20 p<0.001), ROI 1 (as labeled in Table 1 and Figure 2) ($F_{(1,35)}$=11.66 p=0.002), and ROI 2 (as labeled in Table 1 and Figure 2) ($F_{(1,34)}$=6.21 p=0.018), both regions located in left temporo-parietal white matter, which explained an additional 21.6% of the variance (**Table 3**). The inclusion of the remaining candidate variables did not increase the variance accounted for in the model including ROI 8 that overlapped with Cluster 2 in whole brain analysis. Variables were retained on the forward step at an R^2 change at p<0.05 and removed on backward step at an R^2 change of p>0.1. In the second analysis, when the neuroimaging developmental measures were entered into a model without the behavioral measures, ROI 1 accounted for 20.6% of the variance in reading outcome and combined with ROI 2 explained 27.4% of the variance. The remaining ROIs were not significant predictors.

In the final ROI-based regression analysis in which Time 1 white matter volume of ROIs listed in Table 2 were entered instead of developmental measures (i.e., Time 2 minus Time 1), the neuroimaging measures were not statistically significant predictors and so were not included in the final model. When Time 1 neuroimaging measures were used, instead, a model which included Preliteracy Index 1 ($F_{(1,36)}$=20.20 p<0.001), CELF Expressive Language ($F_{(1,35)}$=5.27

p=0.028), and maternal family history ($F_{(1,35)}$=7.01 p=0.012) provided the best prediction of reading outcome, explaining 50% of the variance.

Table 3. Stepwise multiple regression predicting reading outcome

Model	R	Adjusted R^2 Change	β	t	Significance
1					
PLI1	0.599	0.342	0.599	4.494	<0.001
2					
PLI1	0.721	0.150	0.545	4.613	<0.001
ROI 1			0.404	3.415	0.002
3					
PLI1	0.770	0.066	0.535	4.846	<0.001
ROI1			0.817	4.101	<0.001
ROI2			-0.494	-2.491	0.018

PLI1= Preliteracy Index 1, a composite of phonological awareness (PA), letter knowledge, and vocab.

Diffusion imaging correlates. At Time 2, HARDI scans in a subset of the children were used to examine the likelihood that the results from T1 structural MRI are spatially proximal to a particular white matter tract. The fibers running through the larger cluster (Cluster 1) were difficult to determine due to the proximity of this region to many crossing fibers. Nevertheless, in all 28 subjects, superior-inferior fibers were observed, which denotes the superior corona radiata in this region. In 24 of the subjects fibers of the long segment of the arcuate fasciculus ran through this cluster-based seed (Note: The four out of the 28 subjects that we were unable to delineate the arcuate fasciculus for, had more than 1.5 mm movement. The excessive motion could have impeded our ability to find the arcuate fasciculus, and hence the importance of the arcuate fasciculus may be underestimated by these analyses). In 11 subjects, there were some fibers of the anterior segment of the arcuate fasciculus. Cluster 2 revealed a presence in 27 of the 28 subjects of fibers of the posterior segment of the arcuate fasciculus (in one subject, no fibers were found). Additionally, in 10 of 28 of the subjects, the anterior or long segment of the arcuate fasciculus was present **(Figure 4**).

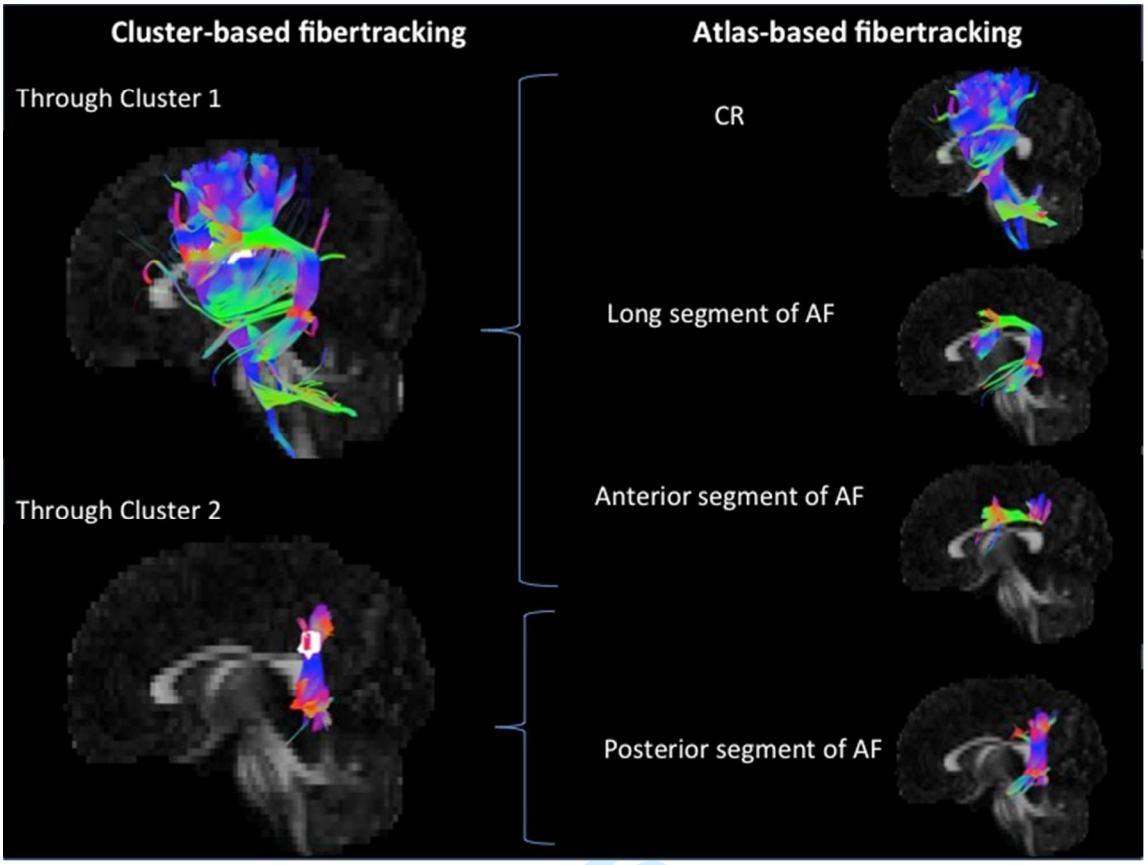

Figure 4. Seed tracking for a representative subject for which cluster-based and atlas-based fibers are delineated. In the left panel the upper figure represents the fibers running through Cluster 1 and the lower figure represents the fibers running through Cluster 2 (both clusters shown in white). In order to determine to which anatomical validated white matter tracts these cluster-based fibers belong, we delineated for this subject the corona radiata (CR) and arcuate fasciculus (AF), split up in its three segments based on an atlas-based protocol (see **Methods** and **Figure S2** for more details). Comparison of the cluster-based tracking to the atlas-based results indicate that Cluster 1 contains predominantly fibers of the corona radiata and of the long segment of the arcuate fasciculus as well as a few fibers of the anterior segment of the arcuate fasciculus. Cluster 2 contains only fibers of the posterior segment of the arcuate fasciculus.

DISCUSSION

We have presented evidence that developmental increases in left dorsal white matter volume uniquely contribute to the prediction of reading outcome at a time when children have typically become proficient readers. Two left temporo-parietal white matter regions predicted reading outcome after controlling for a range of predictors generally considered important for literacy development (**Figure 1F**). These predictors included maternal and paternal familial history of reading difficulty, SES, home literacy environment, general linguistic and cognitive capacities and preliteracy measures such as PA, letter knowledge, vocabulary and rapid naming. The larger cluster identified as critical for the prediction of reading development in this study is the most replicated white matter location associated with reading from previous cross-sectional neuroimaging studies (**Figure 2**; i.e., Beaulieu et al., 2005; Deutsch et al., 2005; Klingberg et al., 2000; Nagy et al., 2004; Niogi & McCandliss, 2006). In a complementary ROI-based analysis where ROIs were derived from previous reading-related diffusion imaging studies, increases in volume in two ROIs located in left dorsal white matter explained 21.6% of unique variance in addition to kindergarten preliteracy abilities, which on its own explained 34.2% of the variance of reading outcome at Grade 3 (**Table 3**).

Phonological processing—in particular, PA—is crucial to the development of reading skills, enabling beginning readers to associate basic component sounds of words with visual representations (Liberman, Shankweiler, Fischer, & Carter, 1974). The development of PA skills is believed to involve the dorsal pathway that connects temporo-parietal and caudal inferior frontal / precentral regions (Hoeft et al., 2006; Hoeft, Meyler, et al., 2007; Yamada et al., 2011) and is also believed to be heavily involved in earlier stages of reading acquisition (Yamada et al., 2011). More specifically, the arcuate fasciculus is considered crucial for phonological skills (Thiebaut de Schotten et al., 2012; Vandermosten et al., 2012; Yeatman et al., 2012), as well as

other skills important to literacy acquisition such as speech-sound processing (Dick & Tremblay, 2012) and word learning (López-Barroso et al., 2013). While most of these neuroimaging studies have employed a cross-sectional design, a recent study by Yeatman et al. (2012) demonstrated that the rate at which fractional anisotropy (a measure calculated in diffusion imaging that reflects the degree of diffusion anisotropy of water through biological tissue; Pierpaoli & Basser, 1996) changed over time in both the arcuate fasciculus and inferior longitudinal fasciculus predicted reading outcome measures in an accelerated longitudinal design. Our findings compliment and add to our understanding of the development of white matter and reading abilities by utilizing a different imaging modality (T1-weighted MRI) and a longitudinal design beginning at a younger age (~4 years on average younger) before the start of formal reading instruction.

One possible interpretation of our data is that structural brain differences causally influence early variations in reading development. However, we measured *changes* in the volume of critical left hemisphere fiber tracts during a time when children were making large strides in learning to read. Changes in volume in the structures we have identified may in part reflect changes in the amount of myelin present (Fjell et al., 2008). The degree of myelination is related to the electrical activity of a particular axon (Ishibashi et al., 2006) and may reflect differences in experience that drive differences in brain development. Thus, changes in volume in our left hemisphere fiber tracts that relate to reading acquisition in the same time window may reflect differences in brain growth that are at least partly the product of experiential influences. There may, however, be genetic influences that serve to constrain the degree of plasticity seen in these brain areas due to different environmental influences. Further studies are required to examine these complex issues of cause and effect. It would be interesting, for instance, to

examine in a randomized trial the extent to which intensive reading practice is associated with changes in the volume of brain areas identified in this study.

Using diffusion MRI from Time 2, we were able to identify the probable fiber/s underlying the clusters identified in whole-brain analyses. In Cluster 1, the mixed probability of the volumetric differences residing in the arcuate fasciculus and the superior corona radiata reflect the difficulty in differentiating fiber tracts in the left temporo-parietal region of white matter due to close proximity. In almost all subjects, our larger cluster contained fibers of the long segment of the arcuate fasciculus, and in one-third of our subjects this cluster also contained fibers from the anterior segment of the arcuate fasciculus. The long segment represents the traditional arcuate fasciculus connection between Broca's and Wernicke's area which is strongly associated with language processing (Wernicke, 1908); whereas, the anterior segment connects Broca's region to the inferior parietal region. Catani, Jones, & Ffytche (2005) speculate that a lesion proximal to Broca's region, such as Cluster 1, may include both anterior and long segments of the arcuate fasciculus and result in Broca-like aphasia symptoms, such as an impairment in language fluency. Lesions to the long segment of the arcuate fasciculus are often reported to result in conduction aphasia, which is marked by poor speech repetition and phonemic paraphasic errors (Dick & Tremblay, 2012).

Cluster 2 from the whole-brain analysis appears to contain the posterior segment of the arcuate fasciculus. A recent study in adults found that increased fractional anisotropy in the posterior segment of the arcuate fasciculus was related to better reading scores, independent of early schooling experience (Thiebaut de Schotten et al., 2012). This posterior segment appears to connect the temporal lobe with temporo-parietal regions. Remarkably, ROI 8 (**Table 2),** reported in a recent study, overlaps with Cluster 2 (Saygin et al., 2013). They found a correlation between

PA and the volume and microstructure of the posterior arcuate fasiculus in preliterate children. Our results provide additional evidence that this region may be important for the development of reading skills between kindergarten and Grade 3.

While our study is novel in several ways, there are some potential limitations such as having access to diffusion MRI data only at Time 2. Future studies may limit the sample to preliterate children, and examine how developmental changes in white matter (e.g. grade K-1) predict reading outcome (e.g. Grade 3), making these imaging metrics more applicable to reading diagnosis and assessment. Additionally, despite 18 of our participants beginning the study with a family history of reading difficulty, only one participant had a formal diagnosis of reading difficulty at Time 2. Finally, we have a noted bias in our ROI analysis of not including ventral pathways due to reports of these findings being in native space. For example, studies such as Vandermosten et al., 2012 and Yeatman et al., 2012 were excluded, though these papers found a significant and unique effect of the ventral pathway (Yeatman et al., 2012).

Nevertheless, our finding that developmental change in left dorsal temporo-parietal white matter predicts reading achievement is unique. We have shown for the first time, that this relationship is (1) independent of associated behavioral, demographic, and environmental measures and (2) with structural developmental predictors beginning in early kindergarten readers. The study emphasizes the importance of multimodal longitudinal neuroimaging to gain a comprehensive understanding of the brain bases of reading, especially as developmental measures were sensitive predictors of reading outcome while cross-sectional measures were not. The predictive relationships we observed are unlikely to be a widespread means of diagnosis in developmental studies due to cost and time constraints; however; they do point to the critical nature of this time period for reading development. We believe that differences in the rates of

structural brain development may have important implications for understanding variations in reading development, and the nature and causes of a range of other developmental disorders as well (e.g. Shaw et al., 2007 in relation to ADHD; Yeatman et al., 2012 in relation to reading disorder). Finally, our findings call for a need to investigate what may be influencing the brain during this critical period of reading development with the hope of constructing more targeted and time-appropriate methods of intervention.

AUTHOR CONRTIBUTIONS

F. Hoeft developed the study design. J.M. Black, B. Casto, and M. Tumber contributed to study design. C.A. Myers, M. Vandermosten, M. Drahos and E.A. Farris analyzed data. C.A. Myers drafted the manuscript with contributions by F. Hoeft, C. Hulme, R. Hancock and R. Hendren.

ACKNOWLEDGMENTS

This research was supported by the Eunice Kennedy Shriver National Institute of Child Health and Human Development Grants K23HD054720, R01HD067254, R01HD065794, P01HD001994, Flora Family Foundation, UCSF Catalyst Award, UCSF Resource Allocation Program, Brain & Behavior Research Foundation Young Investigator Award, Stanford University Lucile Packard Foundation for Children's Health, Spectrum Child Health & Clinical and Translational Science Award, and the Dyslexia Foundation to FH. Thanks to Teresa Soriano, Rociel Martinez, Alexandra Thurston, Leanne Stanley, Hiroko Tanaka, Emily Kutner, and Nicolle Bugescu for data collection.

REFERENCES

Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, *38*(1), 95–113. doi:10.1016/j.neuroimage.2007.07.007

Bach, S., Richardson, U., Brandeis, D., Martin, E., & Brem, S. (2013). Print-specific multimodal brain activation in kindergarten improves prediction of reading skills in second grade. *NeuroImage*, *82*, 605–615. doi:10.1016/j.neuroimage.2013.05.062

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*(4), 1266–1271. doi:10.1016/j.neuroimage.2004.12.053

Black, J. M., Tanaka, H., Stanley, L., Nagamine, M., Zakerani, N., Thurston, A., … Hoeft, F. (2012). Maternal history of reading difficulty is associated with reduced language-related gray matter in beginning readers. *NeuroImage*, *59*(3), 3021–3032. doi:10.1016/j.neuroimage.2011.10.024

Bowey, J. A. (1995). Socioeconomic status differences in preschool phonological sensitivity and first-grade reading achievement. *Journal of Educational Psychology*, *87*(3), 476–487. doi:10.1037/0022-0663.87.3.476

Caravolas, M., Lervåg, A., Mousikou, P., Efrim, C., Litavský, M., Onochie-Quintanilla, E., … Hulme, C. (2012). Common Patterns of Prediction of Literacy Development in Different Alphabetic Orthographies. *Psychological Science*, *23*(6), 678–686. doi:10.1177/0956797611434536

Catani, M., Jones, D. K., & ffytche, D. H. (2005). Perisylvian language networks of the human brain. *Annals of Neurology*, *57*(1), 8–16. doi:10.1002/ana.20319

Cox, R. W. (1996). AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Computers and Biomedical Research, an International Journal*, *29*(3), 162–173.

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*(3), 354–363.

Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: consensus and controversy in the connectional anatomy of language. *Brain*. doi:10.1093/brain/aws222

Fjell, A. M., Westlye, L. T., Greve, D. N., Fischl, B., Benner, T., van der Kouwe, A. J. W., … Walhovd, K. B. (2008). The relationship between diffusion tensor imaging and volumetry as measures of white matter properties. *NeuroImage*, *42*(4), 1654–1668. doi:10.1016/j.neuroimage.2008.06.005

Giedd, J. N., & Rapoport, J. L. (2010). Structural MRI of pediatric brain development: what have we learned and where are we going? *Neuron*, *67*(5), 728–734. doi:10.1016/j.neuron.2010.08.040

Hoeft, F., Hernandez, A., McMillon, G., Taylor-Hill, H., Martindale, J. L., Meyler, A., … Gabrieli, J. D. E. (2006). Neural basis of dyslexia: a comparison between dyslexic and nondyslexic children equated for reading ability. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *26*(42), 10700–10708. doi:10.1523/JNEUROSCI.4931-05.2006

Hoeft, F., McCandliss, B. D., Black, J. M., Gantman, A., Zakerani, N., Hulme, C., … Gabrieli, J. D. E. (2011). Neural systems predicting long-term outcome in dyslexia. *Proceedings of*

the National Academy of Sciences of the United States of America, *108*(1), 361–366. doi:10.1073/pnas.1008950108

Hoeft, F., Meyler, A., Hernandez, A., Juel, C., Taylor-Hill, H., Martindale, J. L., … Gabrieli, J. D. E. (2007). Functional and morphometric brain dissociation between dyslexia and reading ability. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(10), 4234–4239. doi:10.1073/pnas.0609399104

Hoeft, F., Ueno, T., Reiss, A. L., Meyler, A., Whitfield-Gabrieli, S., Glover, G. H., … Gabrieli, J. D. E. (2007). Prediction of children's reading skills using behavioral, functional, and structural neuroimaging measures. *Behavioral Neuroscience*, *121*(3), 602–613. doi:10.1037/0735-7044.121.3.602

Ishibashi, T., Dakin, K. A., Stevens, B., Lee, P. R., Kozlov, S. V., Stewart, C. L., & Fields, R. D. (2006). Astrocytes promote myelination in response to electrical impulses. *Neuron*, *49*(6), 823–832. doi:10.1016/j.neuron.2006.02.006

Keller, T. A., & Just, M. A. (2009). Altering cortical connectivity: remediation-induced changes in the white matter of poor readers. *Neuron*, *64*(5), 624–631. doi:10.1016/j.neuron.2009.10.018

Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J. D., 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*(2), 493–500.

Leemans, A., & Jones, D. K. (2009). The B-matrix must be rotated when correcting for subject motion in DTI data. *Magnetic Resonance in Medicine: Official Journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine*, *61*(6), 1336–1349. doi:10.1002/mrm.21890

Lefly, D. L., & Pennington, B. F. (2000). Reliability and validity of the adult reading history questionnaire. *Journal of Learning Disabilities*, *33*(3), 286–296.

Lervåg, A., Bråten, I., & Hulme, C. (2009). The cognitive and linguistic foundations of early reading development: A Norwegian latent variable longitudinal study. *Developmental Psychology*, *45*(3), 764–781. doi:10.1037/a0014132

Liberman, I. Y., Shankweiler, D., Fischer, F. W., & Carter, B. (1974). Explicit syllable and phoneme segmentation in the young child. *Journal of Experimental Child Psychology*, *18*(2), 201–212. doi:10.1016/0022-0965(74)90101-5

López-Barroso, D., Catani, M., Ripollés, P., Dell'Acqua, F., Rodríguez-Fornells, A., & Diego-Balaguer, R. de. (2013). Word learning is mediated by the left arcuate fasciculus. *Proceedings of the National Academy of Sciences*, *110*(32), 13168–13173. doi:10.1073/pnas.1301696110

Marvin, C. A., & Ogden, N. J. (2002). A Home Literacy Inventory: Assessing Young Children's Contexts for Emergent Literacy. *Young Exceptional Children*, *5*(2), 2–10.

McNorgan, C., Alvarez, A., Bhullar, A., Gayda, J., & Booth, J. R. (2011). Prediction of reading skill several years later depends on age and brain region: implications for developmental models of reading. *The Journal of Neuroscience: The Official Journal of the Society for Neuroscience*, *31*(26), 9641–9648. doi:10.1523/JNEUROSCI.0334-11.2011

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*(7), 1227–1233. doi: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*(11), 2178–2188. doi:10.1016/j.neuropsychologia.2006.01.011

Odegard, T. N., Farris, E. A., Ring, J., McColl, R., & Black, J. (2009). Brain connectivity in non-reading impaired children and children diagnosed with developmental dyslexia. *Neuropsychologia*, *47*(8-9), 1972–1977. doi:10.1016/j.neuropsychologia.2009.03.009

Peterson, R. L., & Pennington, B. F. (2012). Developmental dyslexia. *The Lancet*, *379*(9830), 1997–2007. doi:10.1016/S0140-6736(12)60198-6

Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance in Medicine*, *36*(6), 893–906. doi:10.1002/mrm.1910360612

Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., … Gabrieli, J. D. E. (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: The Official Journal of the Society for Neuroscience*, *33*(33), 13251–13258. doi:10.1523/JNEUROSCI.4383-12.2013

Shaw, P., Eckstrand, K., Sharp, W., Blumenthal, J., Lerch, J. P., Greenstein, D., … Rapoport, J. L. (2007). Attention-deficit/hyperactivity disorder is characterized by a delay in cortical maturation. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(49), 19649–19654. doi:10.1073/pnas.0707741104

Smith, T. E., & Graham, P. B. (1995). Socioeconomic Stratification in Family Research. *Journal of Marriage and Family*, *57*(4), 930–940. doi:10.2307/353413

Thiebaut de Schotten, M., Cohen, L., Amemiya, E., Braga, L. W., & Dehaene, S. (2012). Learning to Read Improves the Structure of the Arcuate Fasciculus. *Cerebral Cortex (New York, N.Y.: 1991)*. doi:10.1093/cercor/bhs383

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*, *135*(3), 935–948. doi:10.1093/brain/awr363

Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., … Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, *36*(3), 630–644. doi:10.1016/j.neuroimage.2007.02.049

Wernicke, C. (1908). The symptom complex of aphasia. In E. Church, *Modern Clinical Medicine: Diseases of the Nervous System*. New York: Appleton-Century-Crofts.

Yamada, Y., Stevens, C., Dow, M., Harn, B. A., Chard, D. J., & Neville, H. J. (2011). Emergence of the neural network for reading in five-year-old beginning readers of different levels of pre-literacy abilities: an fMRI study. *NeuroImage*, *57*(3), 704–713. doi:10.1016/j.neuroimage.2010.10.057

Yeatman, J. D., Dougherty, R. F., Ben-Shachar, M., & Wandell, B. A. (2012). Development of white matter and reading skills. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(44), E3045–E3053. doi:10.1073/pnas.1206792109