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Converging Evidence for Triple Word Form Theory in Children With Dyslexia

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This article has 3 parts. The 1st part provides an overview of the family genetics, brain imaging, and treatment research in the University of Washington Multidisciplinary Learning Disabilities Center (UWLDC) over the past decade that points to a probable genetic basis for the unusual difficulty that individuals with dyslexia encounter in

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learning to read and spell. Phenotyping studies have found evidence that phonological, orthographic, and morphological word forms and their parts may contribute uniquely to this difficulty. At the same time, reviews of treatment studies in the UWLDC (which focused on children in Grades 4 to 6) and other research centers provide evidence for the plasticity of the brain in individuals with dyslexia. The 2nd part reports 4 sets of results that extend previously published findings based on group analyses to those based on analyses of *individual brains* and that support triple word form awareness and mapping theory: (a) distinct brain signatures for the phonological, morphological, and orthographic word forms; (b) crossover effects between phonological and morphological treatments and functional magentic resonance imaging (fMRI) tasks in response to instruction, suggestive of cross–word form computational and mapping processes; (c) crossover effects between behavioral measures of phonology or morphology and changes in fMRI activation following treatment; and (d) change in the relationship between structural MRI and functional magnetic resonance spectroscopy (fMRS) lactate activation in right and left inferior frontal gyri following treatment emphasizing the phonological, morphological, and orthographic word forms. In the 3rd part we discuss the next steps in this programmatic research to move beyond word form alone.

To establish the importance of a nature–nurture interaction perspective, we first review genetics and brain imaging studies on the biological basis of dyslexia and then studies that used brain imaging to investigate the effects of instruction on the brain.

GENETICS RESEARCH

Multiple lines of evidence have led to the consensus that dyslexia has a genetic basis. Although there are rare families in which dyslexia appears to be transmitted as a single gene defect (Fagerheim et al., 1999; Nopola-Hemmi et al., 2001), studies in the general population show that dyslexia and its component processes are genetically heterogeneous and likely involve the interaction of multiple genes and environmental factors (Fisher & DeFries, 2002; Raskind, 2001). Because of differences in study design and subject pools, the contributions of these etiologic factors may not be equally represented in different study samples. Therefore, preliminary characterization of a particular study population may be helpful in selecting the best phenotypes (observable expression of human traits) for further genetic analyses. The phenotype may be defined as a categorical description (e.g., dyslexic *or* not dyslexic) or characterized as a quantitative variable (e.g., a continuously distributed score on a psychometric test or volume of a specific brain structure).

The study sample at the University of Washington (UW) consisted of families, nuclear and extended, each acquired on the basis of a proband who met the inclusion criteria for the current working definition of *dyslexia* of the International Dyslexia Association (Lyon, Shaywitz, & Shaywitz, 2003). Aggregation studies evaluated the clustering of five continuous trait phenotypes in nuclear family units between parents,

between parents and offspring, and among siblings to determine if a genetic mechanism could account for the observed phenotypes: phonological memory as measured by the nonword repetition (NWR) subtest of the Comprehensive Test of Phonological Processing (Wagner & Torgesen, 1999), short-term and working memory as measured by the digit span (DS) subtest of the Wechsler Intelligence Scale for Children–Third Edition (WISC–III; Wechsler, 1992) or the Wechsler Adult Intelligence Scale–Revised (WAIS–R; Wechsler, 1981), accuracy of phonological decoding as measured by the Word Attack (WA) subtest of the Woodcock Reading Mastery Test–Revised (WRMT–R; Woodcock, 1987), speed of phonological decoding as measured by the Phonemic Decoding Efficiency (PDE) subtest of the Test of Word Reading Efficiency (Torgesen, Wagner, & Rashotte, 1999), and spelling from dictation from the Wide Range Achievement Test–Third Edition (WRAT–III; Wilkinson, 1993). In addition, the Yale Attention Inventory was given as a measure of attention. Findings of single measure aggregation studies in the UW Multidisciplinary Learning Disabilities Center (UWLDC; Hsu, Wijsman, Berninger, Thomson, & Raskind, 2002; Raskind, Hsu, Berninger, Thomson, & Wijsman, 2000) are summarized in Table 1. Aggregation analysis on the same study sample using pairs of correlated measures reciprocally as covariates suggest that (a) NWR and DS might share some genetic factors, but additional factors might contribute to NWR, (b) NWR and spelling from dictation might share some genetic factors, but additional factors might contribute to nonword memory, and (c) phonological-decoding rate and phonological-decoding accuracy might share some genetic factors, but additional factors might contribute to phonological-decoding rate (Hsu et al.).

Although aggregation studies can identify phenotypes that might be good candidates for further genetic studies, they do not evaluate the genetic mechanisms of inher-

TABLE 1
Summary of Selected Aggregation Studies in the University of Washington Learning Disabilities Center

	Significance of Correlations Between Pairs of Relatives[b]		
Phenotype[a] *Analyses of Single Measures*	*Parent–Parent*	*Parent–Offspring*	*Sibling*
Aural nonword repetition	*ns*	$p < .01$	$p < .01$
Rate of nonword reading	*ns*	$p < .01$	$p < .05$
Accuracy of nonword reading	*ns*	$p < .05$	$p < .10$
Inattention rating	*ns*	$p < .05$	$p < .05$
Digit span	*ns*	$p < .05$	$p < .10$
Spelling from dictation	*ns*	$p < .10$	$p < .01$

[a]Results of all aggregation analyses from the University of Washington Learning Disabilities Center are given in Raskind, Hsu, Berninger, Thomson, and Wijsman (2000) and Hsu, Wijsman, Berninger, Thomson, and Raskind (2002). [b]With the exception of the inattention measure, the analyses were done on 409 members of 102 nuclear families. Analysis of the inattention measure was based on 52 nuclear families.

itance of these dyslexia-related phenotypes; segregation analyses are performed for this purpose. Two segregation analysis methods were used to evaluate specific transmission patterns that might explain the observed pattern of phenotypes in 108 to 235 families in the UWLDC subject sample (Chapman Raskind, Thomson, Berninger, & Wijsman, 2003; Raskind et al., 2005; Wijsman et al., 2000); more families have since been obtained since these early analyses. Oligogenic Markov chain Monte Carlo (MCMC) methods allow multiple genes to be modeled at the same time. MCMC analysis estimates the number of quantitative trait loci (QTLs) contributing to a phenotype and can perform segregation and linkage analyses simultaneously. In contrast, complex segregation analysis (CSA) finds the most parsimonious inheritance model of a single gene. Although there is a clear genetic basis for accuracy of phonological decoding, the genetic basis for rate of phonological decoding may be even stronger (Chapman et al., 2003). The combination of aggregation and segregation analyses identified several phenotypes that demonstrate familial patterns most consistent with Mendelian modes of inheritance in our participant set: nonword repetition (a measure of phonological memory), rate of phonological decoding of nonwords, and spelling of real words from dictation.

The strongest evidence for a genetic basis for a trait is the identification of a gene or genes affecting the trait variation in the population. Of the approximately 30,000 human genes, about half are expressed in the brain. In the absence of a priori knowledge about a gene's function, one approach to identify the gene is to map its location on the chromosomes by linkage analyses and then to evaluate systematically the genes in that part of the genome. Although no genes involved in reading ability or dyslexia in the general population have been confirmedmto date, targeted and genome-wide linkage analyses have reported at least eight possible localizations for genes contributing to reading and spelling and a variety of related processes (Figure 1): 15q15-qter (DYX1; Chapman et al., 2004; Grigorenko et al., 1997; Morris et al., 2000; Schulte-Körne et al., 1998; Smith, Kimberling, Pennington, & Lubs, 1983; Smith, Pennington, Kimberling, & Ing, 1990), 6p21.3 (DYX2; Cardon et al., 1994, 1995; Fisher et al., 1999; Gayán et al., 1999; Grigorenko et al., 1997; Grigorenko, Wood, Meyer, & Pauls, 2000), 2p13-16 (DYX3; Fagerheim et al., 1999; Fisher et al., 2002; Grigorenko et al., 2001; Kaminen et al., 2003; Petryshen, Kaplan, Hughes, Tzenova, & Field, 2002; Tzenova, Kaplan, Petryshen, & Field, 2004), 6q13-16.2 (DYX4; Petryshen et al., 2001), 3p12-q13 (DYX5; Nopola-Hemmi et al. 2001), 18p11 (DYX6; Fisher et al. 2002), 11p15.5 (DYX7; Hsiung et al. 2004), and 1p34-36 (DYX8; Morris et al. 2000; Tzenova et al 2004).

The UWLDC chromosome linkage studies, which are informed by the segregation analyses, are best understood in the context of these reported studies. Four localizations previously confirmed by independent studies were evaluated in the UWLDC sample set: DYX1, DYX2, DYX3, and DYX6. We found supportive evidence for the locus on chromosome 15q, one of the two most replicated chromosome loci to date in linkage studies of dyslexia (Stein, 2004), for a measure of ac-

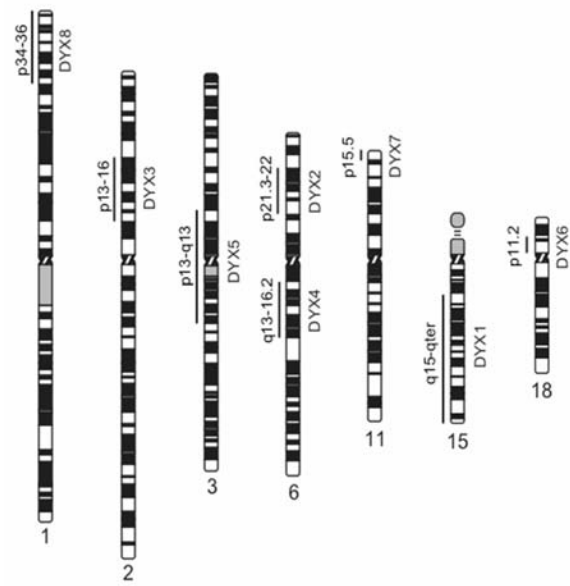

FIGURE 1 Chromosomal loci for which linkage to dyslexia or dyslexia-related phenotypes have been reported.

curacy of real-word reading in isolation (Chapman et al., 2004), consistent with the phenotypes of real-word reading and spelling previously associated with this location. Subphenotyping studies of the UWLDC family set showed unique contributions for phonological, orthographic, and morphological word forms to real-word reading (Berninger et al., 2006; see Figure 2). Recently, in a genome-wide scan, we found significant evidence for a novel locus on chromosome 2q that contributes to speed of phonological decoding (Raskind et al., 2005). For a tutorial explaining current methods for studying the genetics of complex behavioral disorders, see Thomson and Raskind (2003).

Brain-Imaging Research

Genetic mechanisms influence multiple neural substrates contributing to differences between individuals with dyslexia and those who are good readers: structural differences in surface area and volume of neuroanatomical structures, ratio of gray and white matter, myelination; chemical differences in the brain at rest or in the brain performing language tasks; blood oxygen level-dependent (BOLD) response while the brain performs language tasks; and electrophysiological differences in evoked or event-related potentials (Berninger & Richards, 2002). For reviews of the structural studies, see Eckert and Leonard (2000) and Leonard (2001).

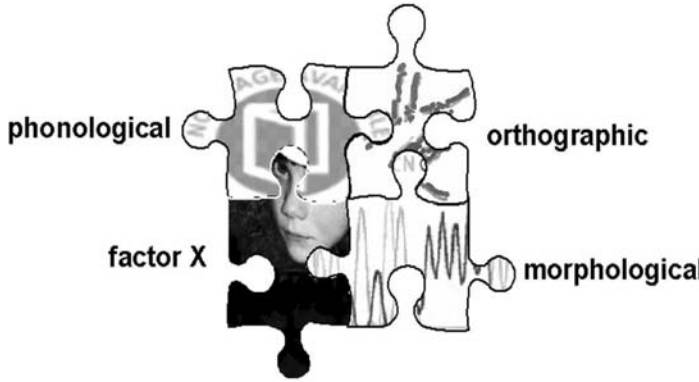

FIGURE 2 Unique predictors of word identification (real-word reading) phenotype: Phonological, orthographic, and morphological word forms and their parts (Berninger et al., 2006).

For reviews of the functional studies, see Berninger (2004b); Berninger and Richards (2002); Papanicolaou et al. (2003); B. Shaywitz, Lyon, & Shaywitz (this issue); S. Shaywitz and Shaywitz (2003); and Simos et al. (this issue). To link the UW family genetics and brain research, all participants with dyslexia for the brain-imaging research were selected from the family genetics study, and beginning in 2003, all controls participants for the brain-imaging research have had to complete the phenotyping battery for the family genetics study. Since 2000 this phenotyping battery has contained measures of phonological, orthographic, and morphological word forms; phonological loop for word learning and maintenance of verbal information in temporary memory; and executive functions for language. In this article we focus on the three word forms.

NATURE–NURTURE INTERACTIONS

Both biological (genetic and neurological) variables and environmental variables influence reading (e.g., Eckert, Lombardino, & Leonard, 2001). Even though genetic and neurological variables explain some of the biological reasons that individuals with dyslexia struggle more than do children without learning disabilities in learning to read, the dyslexic brain is still plastic and responds to instructional interventions; thus, nature and nurture interact and nature alone does not determine the educational outcome for children who have inherited genetic susceptibility to dyslexia. Table 2 summarizes published studies that have combined brain imaging before and after instructional treatment to provide evidence for this brain plasticity in individuals with dyslexia (mostly children). Table 2 is organized by imaging

TABLE 2
Comparison of Studies Combining Brain Imaging and Instructional Treatments

Study	*Imaging Modality*	*Participants*	*Experimental Design*	*Brain-Imaging Tasks*	*Treatment*	*Findings*
Richards et al. (2000)	fMRS (PEPSI)	Ages 10 to 13 years; 8 children with dyslexia; 7 children as the control group (good readers) matched on age and VIQ with those with dyslexia	1. Image participants with dyslexia and those in the control group at Time 1 and Time 2 about 1 year apart 2. Provide treatment for participants with dyslexia after Time 1 imaging and before Time 2 imaging	1. Aural phonological rhyme decision 2. Aural lexical decision 3. Listening to the aural stimuli used in rhyme and lexical decision tasks 4. Aural tone decisions	30 hr, 2 hr a day, over 3 weeks; 5 components: 1. Creating precise phonological representations of words 2. Mapping these onto written words using alphabetic principle and morpheme strategies for Anglo Saxon, Latinate, and Greek words 3. Guided oral reading to improve executive regulation of decoding in context 4. Writing and comprehension activities 5. Science experiments for high intellectual engagement	*Lactate activation changes:* At Time 1, participants with dyslexia and those in the control group differed in lactate activation (an index of efficiency of neural metabolism) in left anterior region during aural phonological judgment but not in aural nonlinguistic tone judgment. At Time 2, following treatment, participants with dyslexia and those in the control group did not differ in lactate activation in left anterior region during phonological or tone judgment. *Behavioral changes:* Significant, relative gains in age-corrected standard scores for WA (+8.7), WI (+3), or *z*-score units for aural nonword repetition (+0.9); GORT 3 accuracy (+0.3); and comprehension (+0.4). No changes in rate of single word or text reading (see Berninger, 2000).

(*continued*)

TABLE 2 (Continued)

Study	*Imaging Modality*	*Participants*	*Experimental Design*	*Brain-Imaging Tasks*	*Treatment*	*Findings*
Richards et al. (2002)	fMRS (PEPSI)	Ages 9 to 12 years; 10 children with dyslexia and 8 boys as the control group matched on age and VIQ with those with dyslexia	1. Image participants with dyslexia and those in the control group at Time 1 and Time 2 about 2 months apart 2. Provide treatment for participants with dyslexia after Time 1 imaging and before Time 2 imaging during summer when no other instructional treatment was provided 3. Randomly assign participants with dyslexia to alternative treatments	Same as Richards et al. (2000)	28 hr, 2 hr a day, over 3 weeks (Berninger et al., 2003) *Alternative treatments* emphasized either phonological or morphological awareness (see Table 3) embedded in an instructional protocol that was otherwise constant and included all components recommended by the National Reading Panel (2000): alphabetic principle and decoding, fluency, and comprehension. Plus, virtual reality for high intellectual engagement	*Lactate activation changes:* Replicated fMRS findings of Richards et al. (2000) for sample as a whole, but morphological treatment was associated with significantly more reduction in lactate activation (improved efficiency in use of energy during neural metabolism; Serafini et al., 2001) than was phonological treatment. *Behavioral changes:* Participants with dyslexia improved significantly in both accuracy and rate/fluency of phonological decoding and morphological decoding. However, the children in the morphological awareness treatment improved significantly more in rate of phonological decoding than those who received only phonological awareness treatment, suggesting that children with dyslexia in upper elementary grades need to learn to coordinate phonological, morphological, and orthographic processes to develop efficient phonological decoding (see Berninger et al., 2003), a major genetic constraint in the family genetics study from which children were selected (Chapman et al., 2003; Hsu et al., 2002; Raskind et al., 2000).

Temple et al. (2000)	fMRI	8 adults with dyslexia and 10 adults with normal reading abilities as the control group; 3 of the participants with dyslexia received treatment	Evaluated pre- and posttreatment change in 3 of the 8 adults with dyslexia	Press button for high but not low pitch for CVC nonspeech analogues that had fast or slow acoustic transitions around a steady state period	Fast Forward (7 computer exercises to improve rapid successive processing of language and nonlanguage stimuli; semantic and syntactic skills) for 100 min a day for 33 days over 5 weeks	*fMRI activation changes:* Previously inactivated inferior frontal gyrus (BA 46, 10, 9) in participants with dyslexia activated in 2 of the participants with dyslexia for rapid nonspeech analogues; no change in the right cerebellum where participants with dyslexia differed from those in the control group before treatment. *Behavioral changes:* Participants with dyslexia improved in oral language (rapid auditory processing and auditory language comprehension) but not reading skills
Temple et al. (2003)	fMRI	Ages 8 to 12 years; 20 children with dyslexia and 12 children with normal reading abilities as the control group matched on Nonverbal IQ (Block Design)	Evaluated changes for participants with dyslexia in regions shown to be reliable across those in the control group from Time 1 to Time 2; no direct test of normalization	Press button if letters rhyme or letters match visually or letters are in the same orientation	8 weeks of Fast Forward (see Temple et al., 2000) for 100 min a day over 5 weeks for an average of 27.9 training days	*Behavioral changes:* After treatment, participants with dyslexia improved in oral language and reading (more in WA than WI or reading comprehension) but not in letter-rhyme judgment. Pre- and posttreatment profiles resemble those for language learning disability more than dyslexia (see Berninger & O'Donnell, 2004).

(*continued*)

TABLE 2 (Continued)

Study	*Imaging Modality*	*Participants*	*Experimental Design*	*Brain-Imaging Tasks*	*Treatment*	*Findings*
						BOLD activation changes (for children with dyslexia): 1. Increased activation in left temporal-parietal cortex and left inferior frontal gyrus bringing activation in these regions closer to that seen in children with normal reading. 2. Increases in left temporal-parietal cortex correlated .41 with improved oral language but not reading. 3. Increases in left inferior frontal gyrus did not correlate with any behavioral improvement. 4. Improvement in CTOPP word blending correlated .43 with increased activity in right inferior frontal gyrus.
Aylward et al. (2003)	fMRI	Ages 9 to 12 years; 10 children with dyslexia and 11 children as the control group matched on age and VIQ with those with dyslexia	Same as Richards et al. (2002)	1. Isolate *phoneme mapping* by comparing *on task*—decide if letters in pink in two pseudowords	Same as Richards et al. (2002)	For *behavioral changes* in accuracy and rate of phonological decoding and morphological decoding, see Berninger et al. (2003) and Richards et al. (2002).

could stand for the same phoneme versus *off task*—decide if letter strings match.		
2. Isolate *morpheme mapping* specific to morphologic al word form apart from semantics alone by comparing *on task*—decide if the top word comes from the bottom word (is meaning related via derivational suffix) versus *off task*—synonym judgment		*BOLD activation changes:* Before treatment, participants with dyslexia were less activated than those in the control group in left inferior frontal gyrus, middle frontal gyrus, middle and inferior frontal gyri, right superior frontal gyri, and bilateral superior parietal regions during *phoneme mapping* and in left middle frontal and right superior parietal and fusiform/occipital region during *morpheme mapping.* Following treatment, the pattern and amount of brain activation of the participants with dyslexia closely resembled that of normal readers. The regions in which the participants with dyslexia showed the most robust changes: during *phoneme mapping,* activation increased in left inferior frontal and middle gyri and in bilateral superior parietal regions (especially right); and during *morpheme mapping,* activation increased in right fusiform and region more superior to the right superior parietal region of original difference.

(*continued*)

TABLE 2 (Continued)

Study	*Imaging Modality*	*Participants*	*Experimental Design*	*Brain-Imaging Tasks*	*Treatment*	*Findings*
Shaywitz et al. (2004)	fMRI	Ages 6 to 9 years (all IQs ≥ 80); word reading and decoding was < 90 (25th percentile) for participants with dyslexia and ≥ 39th percentile for 28 children in the control group	37 participants with dyslexia received experimental treatment and 12 received a control treatment (regular school offerings that did not include explicit phonological instruction)	Letter identification Press button for written letter that matches the aurally presented letter name	8 months of 86 to 115 hr of explicit phonological awareness and alphabetic principle, syllable awareness instruction (5 steps that included review of sound–symbol correspondences, using letter tiles to create new words, timed word reading, oral reading, spelling dictation), independent reading practice	*Behavioral changes:* Experimental treatment group improved significantly on GORT passage score based on accuracy and rate of oral reading *BOLD activation changes:* At end of treatment, increased activation in left inferior frontal gyrus, and left middle temporal gyrus (posterior region). At follow up 1 year later, increased activation in bilateral inferior frontal gyrus and left superior temporal gyrus, and occipital-temporal regions including lingual gyrus and inferior temporal gyrus.
Eden et al. (2004)	fMRI	19 adults (average age = 44 years) with history of dyslexia and current phonological deficits; 19 adults with normal reading abilities as the control group (average age = 41 years)	9 participants with dyslexia received treatment and 10 served as untreated controls	Oral repetition of aural words and sound deletion in aural words	3-hr sessions daily for 8 weeks (average 112.5 hr) sound awareness and articulatory awareness and auditory/visual/ sensorimotor stimulation	*Pretreatment differences:* Compared to those in control groups, participants with dyslexia showed underactivation bilaterally (especially on left) in inferior and superior parietal cortex during phoneme deletion (word repetition as control); also in left and right precuneus, left and right medial frontal gyrus, right occipital-temporal junction, and cingulate.

						Posttreatment behavioral changes: Those with dyslexia who were treated compared to those who went untreated (with IQ covaried) showed significant increases in phonemic awareness, visual imagery, phonological decoding, phonemic transfer, and oral reading accuracy (but not in real-word reading, reading rate, or reading comprehension). *Posttreatment fMRI changes:* Those with dyslexia who were treated compared to those who went untreated showed increased activation in left parietal cortex, left fusiform gyrus, and right superior temporal and parietal cortex.
Simos et al. (2002)	MSI (like MEG, this creates spatio-tempo-ral pro-files)	Ages 8 to 17 years (FIQ ≥ 85); 8 with dyslexia (markedly impaired word reading and phonological problems) of whom 6 had comorbid ADHD—inattentive subtype and were taking stimulant medication;	Participants with dyslexia and those in the control group were imaged twice (second time after those with dyslexia received instructional intervention)	Visual psuedoword matching task—judge whether pairs of written pseudowords rhymed	80 hr of intensive phonologically based instruction over 2 months (6 of the participants in Phono-Graphix and 2 in Lindamood Phoneme Sequencing)	*MSI changes in spatiotemporal profiles:* Prior to treatment, those in the control group activated left superior temporal gyrus (posterior region) and left inferior parietal region (angular and supramarginal gyri), but those with dyslexia had an aberrant profile in which they activated the right homologous regions.

(*continued*)

TABLE 2 (Continued)

Study	*Imaging Modality*	*Participants*	*Experimental Design*	*Brain-Imaging Tasks*	*Treatment*	*Findings*
		8 in the control group (1 with ADHD—inattentive subtype)				After treatment, those with dyslexia increased activation in regions activated by those in the control group at Time 1, consistent with the view that dyslexia is a variation in the functional organization of the brain that is responsive to instruction; but, the peak in left superior temporal gyrus (posterior region) occurred later in time in those with dyslexia than in those in the control group, which is consistent with a residual and persisting rate problem. *Behavioral changes:* Individuals with dyslexia increased in percentiles for reading skills, but increases in left superior temporal-parietal (posterior) and left inferior parietal activation (rather than reduction in right hemisphere activation) was associated with improvement in reading for those with dyslexia.

Note. fMRS (PEPSI) = functional magnetic resonance spectroscopy (proton echoplanar spectroscopic imaging); VIQ = Verbal IQ; WA = word attack; WI = word identification; GORT = Gray Oral Reading Test; fMRI = functional magnetic resonance imaging; CVC = consonant vowel consonant; BA = Brodmann's Area (for anatomical brain region definition); CTOPP = Comprehensive Test of Phonological Processing; BOLD = blood oxygen-level dependent; MSI = magnetic source imaging; MEG = magnetoencephalography; FIQ = full intelligence quotient; ADHD = attention deficit hyperactivity disorder.

modality and, within imaging modality, by year of publication, sample size, and characteristics for those with dyslexia and those in the control groups, experimental design, tasks during scanning, and treatments (one treatment vs. experimental and control treatments vs. alternative treatments) to provide easy comparison of design features across studies. The brief synopsis, which is presented next, of the various findings for brain changes and behavioral changes following treatment in the studies in Table 2 is also organized by imaging modality.

Functional Magnetic Resonance Spectroscopy Studies

Richards et al. (2000) documented changes in lactate activation from Time 1 before treatment, when participants with dyslexia and those in the control group differed in lactate activation—an index of efficiency of neural metabolism—in left anterior region during aural phonological judgment but not in aural nonlinguistic tone judgment, to Time 2, following treatment, when participants with dyslexia and those in the control group did not differ in lactate activation in left anterior region during phonological or tone judgment. On behavioral measures, significant, relative gains were found in age-corrected standard scores for word attack (+8.7), word identification (+3), or *z*-score units for aural NWR (+0.9), Gray Oral Reading Test (GORT) 3 accuracy (+0.3), and comprehension (+0.4), but not in rate of single-word or text reading (Berninger, 2000).

Richards er al. (2002) replicated functional magnetic resonance spectroscopy (fMRS) lactate activation findings of Richards et al. (2000) for sample as a whole, but morphological treatment was associated with significantly more reduction in lactate activation (improved efficiency in use of energy during neural metabolism; Serafini et al., 2001) than was phonological treatment. Participants with dyslexia improved significantly in both accuracy and rate/fluency of phonological decoding and morphological decoding. However, the children in the morphological awareness treatment improved significantly more in rate of phonological decoding than did those who received only phonological awareness treatment, suggesting that children with dyslexia in upper elementary grades need to learn to coordinate phonological, morphological, and orthographic processes to develop efficient phonological decoding (see Berninger et al., 2003), a major genetic constraint in the family genetics study from which children were selected (Chapman et al., 2003; Hsu et al., 2002; Raskind et al., 2000, 2005).

Functional Magentic Resonance Imaging Studies

Temple et al. (2000) noted that in 2 of the study's participants who had dyslexia, previously inactivated inferior frontal gyrus (IFG; Brodmann's Area 46, 10, 9) activated for rapid nonspeech analogues; no change occurred in the right cerebellum where those with dyslexia differed from those in the control before treatment. Par-

ticipants with dyslexia improved in oral language (rapid auditory processing and auditory language comprehension) but not reading skills.

Temple et al. (2002) reported four BOLD activation findings: (a) increased activation in left temporal-parietal cortex and IFG and right frontal and temporal cortex and anterior cingulate as well as in many regions not activated in those in the control group; (b) increased activation in left temporal-parietal cortex correlated .41 with improved oral language but not reading; (c) increased activation in left IFG did not correlate with any behavioral improvement; and (d) improvement in Comprehensive Test of Phonological Processing (CTOPP) word blending correlated .43 with increased activity in right IFG. After treatment, participants with dyslexia improved in oral language and reading (more in word decoding of pseudowords than real words or reading comprehension) but not in letter-rhyme judgment. Pre- and posttreatment profiles resembled those for language learning disability more than for dyslexia (see Berninger & O'Donnell, 2004).

Aylward et al. (2003) found that before treatment those with dyslexia were less activated than those in the control group in left IFG, middle frontal gyrus, middle and inferior frontal gyri, right superior frontal gyri, and bilateral superior parietal regions during *phoneme mapping* and in left middle frontal and right superior parietal and fusiform/occipital region during *morpheme mapping*. Following treatment, the pattern and amount of brain activation of participants with dyslexia closely resembled that of those without a reading disability. During phoneme mapping, participants with dyslexia showed the most robust increased activation in left inferior frontal and middle gyri and in bilateral superior parietal regions (especially right); and during morpheme mapping, their activation increased in right fusiform and a region more superior to the right superior parietal region of the original difference. Accuracy and rate of phonological decoding and morphological decoding improved (Berninger et al., 2003).

B. A. Shaywitz et al. (2004) identified increased activation in (a) left IFG and middle temporal gyrus (posterior region) at the end of treatment, and (b) bilateral IFG and left superior temporal gyrus and occipital-temporal regions including lingual gyrus and inferior temporal gyrus at 1-year follow-up. The experimental treatment group improved significantly on GORT passage score based on accuracy and rate of oral reading (fluency).

Eden et al. (2004) showed that before treatment those with dyslexia, compared to those in the control group, underactivated bilaterally (especially on left) in inferior and superior parietal cortex during phoneme deletion (with word repetition as a control task) and also in precuneus and medial frontal gyrus bilaterally, the right occipital-temporal junction, and cingulate. After treatment, those with dyslexia who were treated, compared to those who were untreated, increased activation in left parietal cortex and fusiform gyrus and right superior temporal and parietal cortex. When those who received treatment were compared to those who did not receive treatment (with IQ covaried), significant increases were observed in phonemic awareness, vi-

sual imagery, phonological decoding, phonemic transfer, and oral-reading accuracy (but not in real-word reading, reading rate, or reading comprehension).

Magnetic Source Imaging

Simos et al. (2002) reported several magnetic source imaging changes in spatiotemporal profiles. Prior to treatment, those in the control group activated left superior temporal gyrus (posterior region) and inferior parietal region (angular and supramarginal gyri) but particpants with dyslexia had an aberrant profile in which they activated the right homologous regions. After treatment, those with dyslexia increased activation in regions activated by controls at Time 1, consistent with the view that dyslexia is a variation in the functional organization of the brain that is responsive to instruction, but the peak in left superior temporal gyrus (posterior region) occurred later in time in those with dyslexia than in those in the control group, consistent with a residual, persisting rate problem. Individuals with dyslexia increased in percentiles for reading skills, but increases in left superior temporal-parietal (posterior) and inferior parietal activation (rather than reduction in right hemisphere activation) was associated with the improvement in reading. See Simos et al. (this issue) for other relevant studies in this line of research.

Although results of imaging studies depend to a large extent on the tasks, imaging modality, and characteristics of the sample (dyslexia is a heterogeneous disorder), a consensus is emerging that individuals with dyslexia differ from typical readers in occipital-temporal, temporal-parietal, and frontal brain systems (S. Shaywitz & Shaywitz, 2003). For example, prior to 2002 we used only aurally presented stimuli, and pretreatment differences and posttreatment changes were identified primarily in parietal and frontal regions. However, pretreatment differences and posttreatment changes were greater in the occipital-temporal regions when tasks were introduced that made greater demands on orthographic processing (Richards et al., 2005, in press). Thus, like other groups (e.g., B. Shaywitz et al., 2002; B. A. Shaywitz et al., 2004; S. E. Shaywitz et al., 2003), the UW studies found differences between individuals with dyslexia and those in the control groups in occipital-temporal, temporal-parietal, and frontal systems. It is clear from the pretreatment results reported in Table 2 that across research laboratories differences between individuals with dyslexia and those in the control groups are found in these three brain systems. Changes in frontal systems are frequently reported following instructional treatment (Aylward, Raskind, Richards, Berninger, & Eden, 2004; Aylward et al., 2003; Richards et al., 2000, 2002; Temple et al., 2000, 2003; B. A. Shaywitz et al., 2004). Likewise, changes in the temporal-parietal regions (Aylward et al., 2003; Eden et al., 2004; B. A. Shaywitz et al., 2004; Simos et al., 2002; Temple et al., 2003) or in occipital-temporal regions (Aylward et al., 2003; B. A. Shaywitz et al., 2004) are often observed. This plasticity in response to instruction is observed across the life span: Previously inactivated regions increase in activation in (a) younger primary grade students in response

to explicit phonological awareness and phonics instruction (Shaywitz et al., 2004; Simos et al., 2002); (b) upper elementary and middle school students in response to all the components of reading instruction recommended by the National Reading Panel (2000; see Aylward et al., 2003; Richards et al., 2000, 2002), including explicit phonological awareness and phonics (Simos et al., 2002); and (c) adults in response to explicit instruction in sound and articulatory awareness and phonics training (Eden et al., 2004). Brain plasticity has also been demonstrated for adults with normal reading ability learning a miniature visual language (McCandliss, Posner, & Givon, 1997).

WORD FORM

Given the well-documented disruption to the posterior word form center (e.g., B. Shaywitz et al., 2002; Temple et al., 2001), one of the goals of our research group has been to disentangle the three word forms—phonological, orthographic, and morphological (see Figure 2)—that contribute to word reading and spelling in reference to subphenotypes (measures of behavioral expression; Berninger et al., 2006), genotypes (Raskind et al., 2005), common and unique fMRI brain activation (Aylward et al., 2003; Richards et al., 2005, in press; also, see Table 3), and instructional treatments (Berninger & Abbott, 2003; Berninger, Abbott, Billingsley, & Nagy, 2001; Berninger et al., 2003; Berninger & Hidi, in press). Although prior research distinguished among phonological, orthographic, and semantic processing of words (e.g., Crosson et al., 1999), we studied the morphological word form (base words plus derivational suffixes that mark part of speech and contribute meaning to the entire lexical unit and its relationship to other words containing the same base). We used synonym judgment as a control task to isolate the processes specific to processing semantic relationships based on derivational suffixes added to the semantic features of the base word rather than to those semantic features alone.

TABLE 3
Unique and Common Circuits in Word Forms[a,b]

Word Forms	*Location of Unique Brain Region*
Phonological	**Left inferior temporal gyrus,** left middle temporal gyrus
Morphological	**Left cerebellum,** bilateral striatal and occipital regions, right posterior parietal
Orthographic	Left superior temporal gyrus
Common regions across all	Left middle frontal gyrus, **left posterior parietal regions,** right lingual

Note. $N = 21$ normal readers (with no reading disability).

[a]Comparisons based on tasks described in Aylward et al. (2003) for phonological and morphological word forms and in Richards et al. (2005,2006) for orthographic word forms. [b]Bolded regions replicated across Aylward et al. (2003) and Richards et al. (2005).

Although understanding word meaning (Pulvermüller, Assadollahi,, & Elbert, 2001) depends to some degree on a network of spreading semantic activation that includes expectancy-based and postlexical access checks (Plaut & Booth, 2000), that network of associated semantic features and underlying word concepts may not contribute directly to the computation of the mental maps among the phonological, morphological, and orthographic word forms and their parts that underlie decoding, word reading, and spelling. Rather, the segmentation of a spoken or written word into a base plus affixes (prefixes and suffixes) may be more directly relevant to the segmentation of words into sound parts (phonemes and syllables) and letter parts (one- or two-letter graphemes or all the constituent letters in a syllable or word unit). The mental maps of written words stored in the lexicon (mental dictionary) may depend to a large degree on the computed interrelationships among the segments within and across phonological, morphological, and orthographic word forms (Berninger, Abbott, Billingsley, & Nagy, 2001; Berninger et al., 2003; Berninger & Richards, 2002).

To investigate how children with dyslexia in the upper elementary grades may construct such mental maps to coordinate the three word forms and their parts, we conducted additional analyses of existing data sets that had been previously analyzed to address other research issues. These additional analyses were theory driven and informed by triple word form awareness and mapping theory. Although this theory has always guided our instructional studies for children with dyslexia in Grades 4 through 6 (Berninger, 2004a, 2004b; Berninger, Abbott, Billingsley, & Nagy, 2001; Berninger & Richards, 2002), the brain-imaging analyses reported in this article provided additional converging evidence for a conceptual framework in which the word form regions of the brain are organized to facilitate the mapping of the interrelationships among words coded in three formats—for sound, word parts conveying meaning and grammar, and letters.

Although fMRI provides precise spatial information about the location of processing during reading and related processes (the where question), the new findings reported here are relevant to future studies that may explore the computational mechanisms underlying the processing in those identified brain regions (the what question). That is, the combination of fMRI and computational modeling may shed light on both where processing is occurring and what the nature of that processing is.

NEW ANALYSES EXTENDING PRIOR PUBLISHED STUDIES

Specific Aims

FMRI may become a useful tool in clinical diagnosis and treatment of dyslexia if techniques can be developed that allow assessment of language activation at the individual subject level. Typically, fMRI results are based on group maps because averaging over brains is thought to improve reliability of conclusions.

However, it is well known in clinical research that results based on a group average may not apply to each individual contributing to that average, especially given that individuals may use unique strategies for performing tasks while their brains are scanned (e.g., Burton, Noll, & Small, 2001). We therefore used an fMRI data analysis technique that draws on results for group maps but allows quantification of fMRI activation data within specific anatomical regions of brain that are important for language processing.

This study was designed to use individual brain fMRI activation data analysis to compare the effect of two different types of instructional treatment—emphasizing either morphological or phonological awareness—on patterns of individual fMRI brain activation during fMRI tasks involving either morpheme mapping or phoneme mapping in children with dyslexia. We hypothesized that the two treatments would show differential changes in fMRI activation patterns in such children. However, we tested which of two possible outcomes would be associated with treatment-specific brain responding. The first possibility was that each kind of language treatment (emphasizing morphological or phonological awareness) would lead to change during a language task performed during scanning or a behavioral measure of language that was theoretically linked to the language treatment. That is, morphological treatment would lead to change in fMRI morphology tasks or behavioral measures of morphology (but not fMRI phonological tasks or behavioral measures of phonology). Conversely, phonological treatment would lead to change in fMRI phonology tasks or behavioral measures of phonology (but not fMRI morphological tasks or behavioral measures of morphology). The second possibility was that cross-language task transfer would occur because the brain is engaged in mapping the interrelationships among the word forms and their parts. That is, morphological treatment would lead to change in fMRI phonology tasks or behavioral measures of phonology, and phonological treatment would lead to change in fMRI morphology tasks or behavioral measures of morphology.

METHOD

Participants

Ten children with dyslexia (4 girls, 6 boys) completed both the treatment and brain imaging. Eleven age-matched control participants were also scanned; group differences between those with dyslexia and those in the control group were previously reported by Aylward et al. (2004) and will not be presented here. The UW Human Subjects Institutional Review Board approved this study, and each participant (as well as parent/guardian) gave written informed consent. The participants with dyslexia were selected from probands in a family genetics study of dyslexia, as described previously (Raskind et al., 2000). These participants were recruited through contacts with schools, other professionals, and widely advertised announcements in newspa-

pers throughout the Seattle area. Entry criteria included (a) Verbal IQ (VIQ) of ≥ 90; (b) evidence of achievement below the population mean on accuracy or rate of single-word, real-word, or pseudoword reading or oral reading of passages; and (c) underachievement on these same skills by at least one standard deviation below VIQ (Berninger, Abbott, Thomson, & Raskind, 2001). All probands in the family genetics study were contacted, and those who were right-handed, had not yet received any intervention through the program, and who did not have nonremovable foreign metal (such as oral braces) were invited to participate in the fMRI study. (It was subsequently determined, however, that one of these participants was predominately left-handed, based on the Edinburgh Handedness Survey).

Of the 14 who agreed to be in the study, 10 had imaging data of sufficient quality (i.e., minimal motion artifact, as described later) on both initial and follow-up scans. At the initial scan, the participants with dyslexia were reading on average about one standard deviation below the population mean for age on the Word Identification (WI; reading real words; $M = 86.0$, $SD = 10.5$) and WA (reading pseudowords; $M = 87.0$, $SD = 7.4$) subtests of the WRMT (Woodcock, 1987) and WRAT–III Spelling subtest (Wilkenson, 1993; $M = 82.7$, $SD = 5.0$). Scores on these tests were significantly below this group's mean VIQ ($M = 112.0$, $SD = 10.7$) and the population mean ($M = 100$, $SD = 15$); thus, these children met both relative criteria (underachievement for verbal ability) and absolute criteria (underachievement for age peers) for dyslexia. The participants with dyslexia were also impaired (below the population mean and significantly different from controls) in the three language markers for dyslexia: (a) phonological coding (CTOPP elision subtest; Wagner et al., 1999), (b) rapid autonomic naming (RAN; Wolf et al., 1986) and/or rapid automatic switching (RAS; Wolf, 1986), and (c) orthographic coding (Berninger, Abbott, Thomson, & Raskind, 2001).

Instructional Treatment

Following the initial scan, the children with dyslexia participated in an instructional treatment program that involved 2 hr of instruction for 14 consecutive weekdays (Berninger et al., 2003). The content of this instructional treatment met the requirements of a national panel of reading experts in the United States that reviewed the research literature to identify the components of reading instruction that are scientifically supported (National Reading Panel, 2000): linguistic awareness, alphabetic principle, fluency, and reading comprehension. None of the participants received any concurrent treatment other than that provided by the current study. The participants with dyslexia were randomly assigned to one of two treatments for the linguistic awareness component, which lasted for 1 hr in each of 14 successive sessions. Treatment emphasized either phonological awareness or morphological awareness. Each treatment had seven comparable activities that were designed to develop awareness of either the phonological word form and its parts or the morphological word form and its parts and how these word forms and parts are interrelated with the

orthographic word form and its parts. Table 4 summarizes the seven comparable components of each treatment. See Berninger et al. (2003) for additional information about the treatment and the larger sample who completed the treatment study. Four of the children in the phonological treatment and 6 of the children in the morphological treatment also completed the brain scanning before and after treatment.

fMRI Tasks

Two fMRI scans were performed, one with a set of tasks to assess brain activation during phoneme mapping (the ability to judge whether one- or two-letter units stand for the same phoneme sound) and the other with a set of tasks to assess brain activation during morpheme mapping (the ability to make correct associations between word parts that signal grammatical information, such as suffixes, and their meaning when affixed to root words).

TABLE 4
Alternative Reading Treatments for Children With Dyslexia in Grades 4 to 6

Treatment	*Description*
Teaching phonological word forms	
Word building	Counting syllables and phonemes in spoken Jabberwocky words (pseudowords)
Word generating	Giving examples of real or Jabberwocky words containing target phonemes
Unit finding	Underlining/writing spelling units and sounding out Jabberwocky words unit by unit
Transferring	Oral reading of a different set of Jabberwocky words than taught in unit finding
Relating units	Deciding if letter(s) in red in Jabberwocky words are twins (i.e., stand for the same sound)
Sorts	Categorizing on basis of alternations (putting words that share a common spelling unit into the category that shares a common phoneme)
Does it fit?	Sorting spelling units into word contexts to spell a real word
Teaching morphological word forms	
Word building	Creating new words from provided bases + affixes
Word generating	Giving new words containing same affixes
Unit finding	Underlining bases and circling affixes
Transferring	Oral reading of a different set of words with the same affixes
Relating units	Deciding if a second word (containing a stem + derivational suffix) comes from (is related in meaning to) the first word
Sorts	Categorizing on basis of spelling units that do and do not share morphemes
Does it fit?	Sorting words with suffixes into sentence contexts

Note. See Berninger et al. (2003).

To assess phoneme mapping, two alternating tasks—*letters–phoneme matching* (target task) and *letters-only matching* (control task) were presented. Letter–phoneme matching required the child to make judgments about correspondences between phonemes and letters in visually presented pseudowords. Letters-only matching required judgments about visually presented letter strings. For the letters–phoneme matching task, only pseudowords were used so that children could not perform the task on the basis of word-specific knowledge and had to rely on sublexical alphabetic principle. In each trial, two pseudowords (three- to five-letter pronounceable monosyllables) were presented, one above the other. Each word had one or two pink letters and the other letters were black. During the letters–phoneme matching task, the child was asked to indicate with a button press whether the pink letters in the top and bottom pseudowords could stand for the same sound (e.g., Could *oa* in *ploat* stand for the same sound as *ow* in *drow*? or Could *kn* in *knop* stand for the same sound as the *k* in *kack*?). The letters-only matching task required the child to decide whether two letter strings (e.g., *szpy* and *sxpy*) matched exactly. Length of the letter strings was comparable to the length of the pseudowords in the letters–phoneme matching task. This control task required attention to all letter positions but did not involve any phonological processing. Comparison of these two tasks isolated phoneme-mapping processes (and the associated brain regions) uniquely involved in assigning phonemes (parts of the phonological word form) to letters apart from letter processing alone. Effects due to visual presentation mode were constant across the target and control tasks and cancelled out.

To assess morpheme mapping, two alternating tasks—*comes from* (target task) and s*ynonym judgment* (control task)—were presented. In neither task did correct judgments depend on ability to read the words because stimuli were presented both visually and auditorally. For both tasks, the child indicated with a button press a "yes" or "no" decision. During the comes-from task, the child heard and saw two words, one presented above the other. In half of the comes-from trials, the top word contained a derivational suffix that rendered it semantically related to the bottom word (e.g., *builder* and *build*).[1] For the other half of the comes-from trials, the top word contained a spelling pattern sometimes used as a derivational suffix (e.g., *er*) but which did not function as a suffix in this particular case; thus the top word was not semantically related to the bottom word (e.g., *corner*, *corn*). During synonym judgment, the child determined whether the top word meant the same as the bottom word (e.g., *small* and *little*). Average word length was the same across tasks. Comparison of activation during these two tasks isolated the process (and associated brain regions) uniquely associated with morpheme mapping, that is, relating morphemes (parts of the morphological word form) to semantic processing of a base

[1]In addition, with one exception, none of the "yes" items in the comes-from task involved the phonological shift in the pronunciation of the affixed word in relation to the unaffixed word (e.g., transforming *nation* to *national* involves a change in the vowel pronunciation of the first syllable).

word apart from semantic processing of the base word alone. Again, effects due to the presentation mode (combined visual and auditory), which was constant across the target and control tasks, cancelled out.

Each of the fMRI scans lasted 5 min and 42 sec. For each scan, the two contrasting tasks were alternated, with four repetitions of each task lasting 30 sec each. A fixation condition (cross-hair) lasting 18 sec was presented at the beginning, in the middle, and at the end of the series to provide a standard baseline. A slide with instructions appeared for 6 sec before each condition. Visual word pairs were presented for 6 sec, with no interstimulus interval. For all tasks, children indicated a "yes" response by pressing a button held in the dominant hand. The button press had to occur during the 6-sec stimulus presentation to be counted as correct. For each task condition, half of the items had "yes" as the correct answer.

Stimuli were presented and responses were recorded using Eprime software (Psychology Software Tools, Pittsburgh, PA). The participant viewed the visual stimuli through a pair of goggles that were connected via high-resolution fiber optic cables to two Infocus projectors, which were, in turn, connected to the Eprime computer.

Scan Acquisition

Structural MRI and fMRI were performed on a 1.5 Tesla MRI system (version 5.8, General Electric Co., Waukesha, WI). Scanning included a 21-slice axial high-resolution set of anatomical images in plane with functional data (TR/TE = 200/2.2 msec; fast-spoiled gradient-echo pulse sequence; 6 mm thick with 1 mm gap; 256 × 256 matrix). These anatomical series were followed by two fMRI series using two-dimensional gradient-echo, echo-planar pulse sequence (TR/TE = 3000/50 msec, 21 slices; 6 mm thick with 1mm gap, 64 × 64 matrix, 114 volumes total; time = 5min 42 sec). The average interval between scans was 3.6 months (*SD* = 0.3). The scan protocol, tasks, and order of tasks were identical across repeated scans for each subject.

Image Processing

FMRI scans were analyzed using MEDx (version 3.4.1, Sensor Systems, Sterling, VA). Scans were considered acceptable for analysis if at least two of the four alternating cycles within the scan had less than 3mm of movement. The data were motion corrected and linear detrended. A *t* test was performed to evaluate whether the two conditions within each scan, expressed as a *z* score, were significantly different. Each participant's activation *z*-map was spatially smoothed with a 4-mm Gaussian filter and converted to standard stereotaxic space of Talairach (Talairach & Tournoux, 1988) using FLIRT (www.fmrib.ox.ac.uk/fsl/).

Parcellation Procedures

Thirteen regions of interest that had shown significant activation on the group maps were analyzed for the individual brains: both right and left for anterior cingulate; insula; parietal; cerebellum; fusiform; inferior frontal; inferior temporal; lingual; middle frontal; middle temporal; parietal; prefrontal; superior frontal; and superior temporal. These 13 regions were outlined using a graphics software program, MEASURE (see Aylward, Augustine, Li, Barta, & Pearlson, 1997; Buchanan, Vladar, Barta, & Pearlson, 1998) on a three-dimensional standardized brain (chosen as a typical brain from one of the children in the control group for this study) that was converted to Talairach space. A mask for each region of interest (ROI) was created using the export function in MEASURE. Software was developed in our laboratory to apply the same anatomical mask to all participants' brain *z*-maps and automatically count the number of voxels with *z* scores above the threshold of 3.0, as well as calculate the mean *z* score of all the voxels within each ROI.

Statistics for Evaluating Treatment Effects

Because of the variability in brain activation measures, change in level of activation for each participant for each region was coded as either increased or not (no change or decrease), based on average *z*- score in the region at initial versus follow-up scan. A nonparametric test, Barnard's unconditional test of superiority (Mehta & Patel, 2004), was used to compare the changes in activation level for the two treatments.

Behavioral Testing

Participants completed a battery of language and reading tests before and after treatment (see Berninger et al., 2003). Phonological processing was assessed using the WA subtest of the Woodcock–Johnson Psycho-Educational Battery–Revised (Woodcock & Johnson, 1990). Morphological processing was assessed using the UW Morphological Signals Test, developed by our group (Nagy, Berninger, Abbott, Vaughan, & Vermeulen, 2003). Posttreatment performance on these tests was correlated with posttreatment activation in specific brain regions.

FOUR NEW FINDINGS

1. Distinct Neural Signatures for Phonological, Morphological, and Orthographic Word Forms

Unique and common regions of fMRI brain activation were observed for the three different language-mapping processes that involve phonological, morphological, and orthographic word forms. Table 3 summarizes the common and unique acti-

vated regions for the three word forms. The pattern of results indicates that each word form has a unique neural signature over and above the general neural activation involved in coding and processing words in memory. Figure 3 (see insert) shows examples of two brain slices where unique and common brain activation can be observed for phoneme mapping and morpheme mapping (Aylward et al., 2003) and orthographic mapping (Richards et al., 2005, in press).

2. Cross-Mapping of the Word Forms Related to Treatment

Behavioral changes. Both treatment groups in the larger treatment study improved significantly from pretreatment to posttreatment on standardized measures of accuracy and rate of phonological decoding, morphological awareness, accuracy of decoding words with morphological units, and silent reading comprehension, but the morphology treatment group improved significantly more in speed of phonological decoding than did the phonological treatment group on a psychometric measure of efficiency or rate of phonological decoding of single pseudowords (Berninger et al., 2003), a source of genetic constraint (Raskind et al., 2000) linked to chromsome 2 (Raskind et al., 2005). Thus, morphological awareness treatment improved efficiency in phonological decoding of written words at the behavioral level, an example of a crossover effect from one language process (morphology) to another language process (phonology).

Brain changes associated with alternative treatments. Previously, Richards et al. (2002) showed that following morphological treatment, children demonstrated increased efficiency in energy utilization during neural metabolism, as reflected by significant decreases in lacate activation in *individual* brains (see Serafini et al., 2001) while they made phonological judgments. The new findings based on individual fMRI BOLD activation, which are reported next, suggest that this increased neural efficiency may have resulted from cross-word form mapping.

Treatment groups were compared for the number of children showing an increase in BOLD activation in each specific brain region (z score higher at Time 2 than at Time 1) on each fMRI on–off task comparison for phoneme mapping and morpheme mapping. (For average z scores for individual BOLD activation for each participant in each treatment, contact the first author.) A significantly ($p = .02$) greater proportion of the children in the morphological treatment group (5 out of 6) than in the phonological treatment group (0 out of 4) had an increase in BOLD activation on the fMRI phoneme-mapping task in the left fusiform gyrus. A significant treatment group effect ($p = .05$) was also observed in the left posterior insula, again with a greater proportion of children in the morphological treatment group (4 out of 6) than in the phonological treatment group (0 out of 4) showing increased (posttreatment > pretreatment) BOLD activation on the fMRI phoneme-mapping task (see Figure 4 insert). After treatment, significantly more children in the phonological treatment

group (4 out of 4) than in the morphological treatment group (2 out of 6) showed increased activation in left anterior insula and left and right superior temporal gyrus and superior frontal gyrus during the fMRI morpheme-mapping task ($p = .05$ for all comparisons; see Figure 5 insert).

Thus, following instructional treatment, BOLD activation increased in five posterior brain regions (four on the left). Morphological treatment was associated with increases in brain activation during fMRI phoneme mapping, whereas phonological treatment was associated with increases in brain activation observed during fMRI morpheme mapping. These crossover effects are consistent with triple word form awareness and mapping theory, which predicts that children learn to read by creating mental maps of the interrelationships among the word forms (see Discussion). These results may be dependent on age and stage of reading development as the children in this study were in fourth, fifth, and/or sixth grade.

3. Cross-Mapping of the Word Forms Related to Behavioral Measures

To explore further the crossover effects observed in the first analysis, we examined correlations between levels of activation during fMRI morpheme mapping and phoneme mapping in specific brain regions and accuracy on behavioral measures of morphological and phonological processing.

Correlations between brain and behavioral measures of morphological and phonological processing. Pearson correlations were calculated for the entire sample of children with dyslexia (regardless of treatment group) to determine whether posttreatment brain activation was associated with posttreatment performance on behavioral tests of morphological processing and phonological processing. Table 5 reports results for regions where a correlation was significant.

Following treatment, activation during fMRI morpheme mapping in the scanner did not correlate significantly with performance on the Morpheme Signals test in any region except the right precentral gyrus, and this correlation was negative ($r = –.64$; $p = .04$), indicating that better morpheme mapping, as assessed behaviorally, was associated with less activation in this region during fMRI morpheme mapping. However, following treatment, there were significant positive correlations, possibly indicative of crossover effects, between brain activation during fMRI morpheme mapping and performance on the WA subtest in five brain regions (see Table 5). None of the correlations between fMRI morpheme mapping and WA had been significant prior to testing.

Following treatment, brain activation during fMRI phoneme mapping was not significantly correlated with performance on the WA subtest in any region except the right superior frontal gyrus and the right superior temporal gyrus. In addition, these correlations were negative, indicating that better phoneme mapping, as as-

TABLE 5
Statistically Significant Correlations Between fMRI Activation in Specific Brain Regions and Performance on Psychometric Tests of Comparable Constructs in Children With Dyslexia After Treatment

	Correlation With Morphological Signals Test				*Correlation With Word Attack Test*			
	fMRI Phoneme Mapping Task		*fMRI Morpheme Mapping Task*		*fMRI Phoneme Mapping Task*		*fMRI Morpheme Mapping Task*	
Brain Region	*z*	*p*	*z*	*p*	*z*	*p*	*z*	*p*
Left anterior cingulate	.80	.006						
Right cerebellum	.69	.02						
Left anterior insula							.62	.05
Left inferior frontal gyrus	.77	.009						
Left inferior temporal gyrus	.67	.03						
Right middle frontal gyrus							.85	.002
Left middle frontal gyrus	.83	.003					.64	.04
Left posterior parietal	.81	.005					.63	.05
Right posterior parietal							.67	.03
Right precentral gyrus			–.64	.04				
Left superior frontal gyrus	.66	.04						
Right superior frontal gyrus					–.67	.03		
Right superior temporal gyrus					–.72	.02		

Note. fMRI = functional magnetic resonance imaging; *z* = average *z* score.

sessed behaviorally, was associated with less activation during fMRI phoneme mapping in these regions. However, there were significant positive correlations between performance on the Morphological Signals test and individual brain activation during fMRI phoneme mapping in eight specific regions. None of these correlations, possibly indicative of crossover effects, had been significant prior to treatment. Seven of these correlations were positive, indicating a relationship between more brain activation and higher test scores (see Table 5).

In sum, these crossover effects for the imaging tasks and behavioral measures provide additional, converging evidence that children with dyslexia in the upper elementary grades may construct mental maps of how the phonological and morphological word forms and their parts are interrelated (see Discussion).

4. Changes in IFG Related to Treatment Responding

Effects of treatment on relationship of fMRI brain activation in IFG and behavioral measures. Children in the control group showed significantly greater left than right activation in IFG during fMRI phoneme mapping (at both

Time 1 and Time 2, $p < .001$). The children with dyslexia also showed greater activation of left than right IFG during fMRI phoneme mapping, but not to the same extent ($p = .03$ before treatment; $p = .11$ after treatment). Although the treatment did not significantly decrease activation of right IFG activation (in fact, it went up slightly for the whole group with dyslexia), for the participants who *did* decrease activation over time in right IFG, their phonological-decoding (WA) score went up (and vice versa). This pattern of results explains why there is no effect for treatment in general on the right IFG (Aylward et al., 2003). However, the significant correlation showed that there was an association between increased (posttreatment > pretreatment) phonological-decoding skill and decreased (posttreatment < pretreatment) activation in right IFG. In addition, a measure of laterality of IFG activation was computed, using a formula that is often used to assess laterality of structural volumes—(right – left)/0.5 (right + left), with positive numbers indicating $r >$ l and negative numbers indicating $l > r$. This laterality measure before treatment was negatively associated with the phonological-decoding score after treatment ($r = –.74$, $p = .014$). Thus, the greater an individual's initial discrepancy between right and left (right > left) IFG activation, the lower his/her phonological decoding after treatment, that is, the less the response to intervention. An alternative way of explaining this relationship that predicts treatment response is that the greater the initial left–right discrepancy, with left > right, the higher the phonological decoding after treatment. Such comparisons of homologous structures may prove fruitful in future imaging studies that assess brain response to instructional interventions.

Effects of treatment on relationship between individual structural and chemical activation in right IFG. Some of the children in the Aylward et al. (2003) fMRI study had also participated in the Richards et al. (2002) fMRS study and Eckert et al. (2003) structural MRI study; thus, measures of lactate activation before and after instructional treatment and surface areas of right and left pars triangularis had been obtained for the same children. The surface areas were based on analysis of pretreatment structural MRI scans. The following results are based on those children who received instructional treatment and for whom both structural MRI and pre- and posttreatment fMRS were available.

Because children with dyslexia had significantly smaller left and right pars triangularis surface area measures compared to children in the control group (Eckert et al., 2003), we examined the relation between left or right pars triangularis surface areas and both pre- and posttreatment lactate activation on fMRS for a lexical decision task, which required the child to decide if both aurally presented words could be real words (i.e., have word-specific semantic and phonological representations). The purpose of these analyses was to determine if the anatomical measures could account for atypical frontal activation measures often observed in children with dyslexia while performing language tasks during fMRI brain scanning (Aylward et al., 2003; S. E. Shaywitz et al., 2003). Children in the

control group exhibited a statistically significant relationship between surface area of right pars triangularis and pretreatment lactate activation during lexical decision, $r(8) = –.852$, $p < .01$, and between surface area of right pars triangularis and posttreatment lactate activation during lexical decision, $r(8) = –.833$, $p < .01$. Lactate activation, an index of neural efficiency, during lexical judgment was never associated with left pars triangularis surface area in children in the control group.

For fMRS scanning, children with dyslexia did not exhibit any significant relationships between par triangularis anatomy and pretreatment lactate activation during lexical judgment. There were, however, significant relationships between surface area of par triangularis neuroanatomy and posttreatment lactate activation. The right pars triangularis exhibited a negative linear relation with right anterior lactate activation in children with dyslexia, $r(9) = –.714$, $p < .05$; 1 outlier removed (see Figure 6). Reading intervention appeared to have normalized the typical relationship between right pars triangularis size and right anterior lactate activation during lexical judgment in the children with dyslexia. In addition, following treatment, the left pars triangularis exhibited a positive linear relation with left anterior lactate activation, $r(9) = .813$, $p<.01$; 1 outlier removed (see Figure 7). Although children who were good readers did not show this relation-

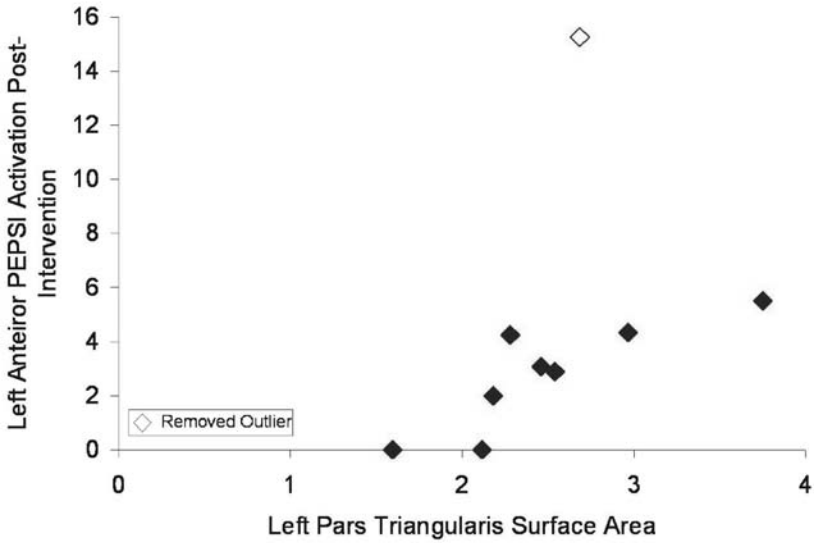

FIGURE 6 Right pars triangularis surface area (measured from MRI structural images) is plotted against right anterior lactate activation (which includes the right pars triangularis) during the lexical task (measured from MR spectroscopic imaging—PEPSI) for participants with dyslexia. There was a negative correlation between these two different modalities—the greater pars triangularis area correlates with less PEPSI activation.

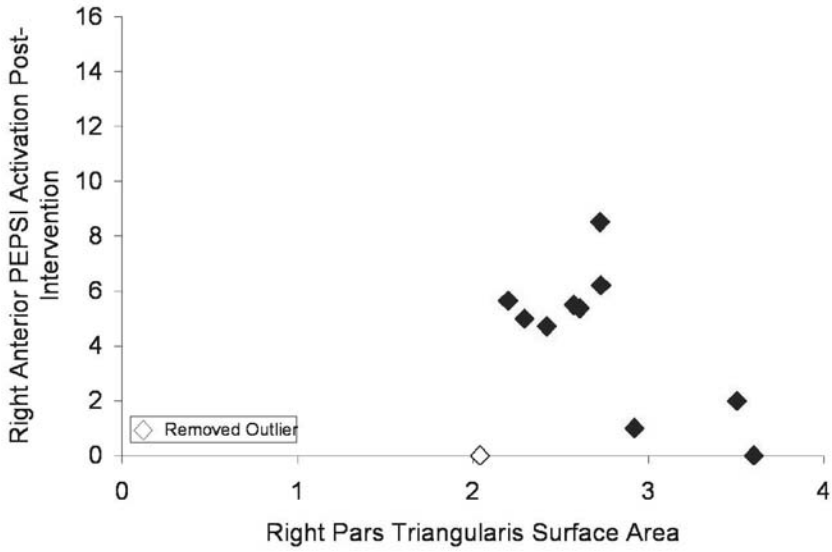

FIGURE 7 Left pars triangularis surface area (measured from MRI structural images) is plotted against left anterior lactate activation (which includes the left pars triangularis) during the lexical task (measured from MR spectroscopic imaging—PEPSI) in participants with dyslexia. There was a positive correlation between these two different modalities—the greater pars triangularis area correlates with greater PEPSI activation.

ship, that could change over the course of development. Studies of adults with dyslexia suggest that the amount of left IFG activation during reading tasks is highest for adults with superior reading accuracy (S. E. Shaywitz et al., 2003). Children with dyslexia in this study with the large left pars triangularis surface area and increased left anterior lexical activation may be more accurate readers than children with dyslexia who have small left pars triangularis and who exhibit left anterior lexical activation. Also, note that Temple et al. (2002) found a relationship between right IFG and improved phoneme blending and B. A. Shaywitz et al. (2004) found increased bilateral activation in IFG in the experimental treatment group a year after treatment had ended (see Table 2). Taken together, these results suggest some anomalies in right IFG and its relationship to left IFG in developmental dyslexia.

DISCUSSION

The discussion is organized to address the four questions that serve as a theme for this special issue.

1. What Are Your Most Important Findings?

Methodological application. Combining fMRI group maps and individual fMRI brain activation within regions that were shown to activate reliably on group maps has promise for clinical application of fMRI studies. For example, individual brain imaging during performance of language tasks before and after instructional treatment might be used to evaluate treatment responding of individual children with dyslexia or to predict which children will have the greatest response to specific treatment methods. Pending changes in the implementation of federal law for serving students with educationally handicapping conditions will place greater emphasis on response to core curriculum and supplementary instruction in identifying students for specialized instruction in special education. Response to instruction might be evaluated for individual students at the brain level as well as behavioral level.

Significance of the experimental design. The purpose of this study was to determine the effects of two reading treatments on fMRI brain activation during two language processes that are critical to reading: phoneme mapping (assigning sounds to letters) and morpheme mapping (understanding the relationship of suffixed words to their roots). To examine treatment-specific brain response, individual fMRI *z* scores were averaged within each of 13 anatomical regions that were selected because they had significant clusters of activation in the group analysis. The distribution of increased and decreased activation was then compared for individuals in each of the two treatments to which children with dyslexia were randomly assigned. Morphological treatment was significantly associated with increased fMRI activation (posttreatment > pretreatment) within the left fusiform gyrus and left posterior insula during fMRI phoneme mapping. Phonological treatment was significantly associated with increased brain activation within the left anterior insula, left superior temporal gyrus, and right superior frontal gyrus during fMRI morpheme mapping. Following two different kinds of instructional treatment, fMRI brain scans during two kinds of language-mapping tasks, each theoretically linked to one but not the other of the two treatments, showed evidence of treatment-specific responding: Individual brains responded differently, depending on the instructional treatment received, in specific brain regions. This pattern of results is based on comparison of two instructional treatments, which provides stronger evidence of the link between teaching and brain response than experimental designs that have only one instructional treatment. The goal of designs including two treatments (rather than a treatment and control group) is to evaluate whether brain response is treatment-specific. The theoretical significance of the treatment-specific effects is considered next.

2. What Are Your Most Surprising Findings?

Neuropsychological significance of crossover effects between different word forms. The crossover effect of morphological treatment on efficiency of energy utilization during phonological judgment, as indexed by lactate activation, has been previously reported (Richards et al., 2002). Previously reported behavioral results have also shown that morphological treatment resulted in significantly greater gains in rate of phonological decoding, as assessed by the Test of Word Reading Efficiency (TOWRE; Torgesen et al., 1999) than did phonological treatment (Berninger et al., 2003). In a phenotyping study of children and adults with dyslexia in a family genetics project, a second-order word form factor underlying first-order phonological, orthographic, and morphological word form factors fit models better than specific first-order word form factors alone in predicting oral-reading accuracy and rate, reading comprehension, and writing expression in both children and adults with dyslexia (Berninger et al., 2006). The second-order word form factor may be evidence of abstract computations among the word form factors and their parts that are readily accessible to readers and writers.

The crossover effects on word form processes based on instructional and correlational studies in this article provide additional, converging evidence that the brain engages in computations among the phonological, morphological, and orthographic word forms and their parts. Phonological treatment was associated with significantly greater increases in activation of the following specific regions of *individual brains* during fMRI morpheme mapping than was morphological treatment (see Figure 5): in *left anterior insula* (associated with segmental phonology and articulation processes; Ackermann & Riecker, 2004), *left superior temporal gyrus* (associated with phonological processing; Booth et al., 2002; Simos et al., 2002; and cross-modal mapping of orthography and phonology as in visual rhyming; Booth et al.), and *right superior frontal regions* (associated with changes following phonological treatment in Temple et al., 2003). Morphological treatment was associated with significantly greater increases in activation of other specific regions of individual brains during fMRI phoneme mapping than was phonological treatment (see Figure 4): in *left fusiform gyrus* (associated with cross-modal mapping of phonology and orthography as in auditory spelling; Booth et al., 2002) and in *left posterior insula* (that activated in good readers but not in children with dyslexia on a task requiring attention to phonology and semantics; Corina et al., 2001). Likewise, correlational analyses between posttreatment fMRI activation within the 13 brain regions and test scores indicated that activation during fMRI phoneme mapping was not correlated with phonological test scores, but was highly correlated in several regions with morphological test scores. Conversely, posttreatment activation during fMRI morpheme mapping was correlated with posttreatment phonological test scores but not with morphological test scores.

Taken together, the previous findings summarized at the beginning of this section and the new findings about crossover effects support triple word form awareness and mapping theory (Berninger et al., 2006) and suggest that specific brain regions may be engaged in computational mapping of relationships across word forms (see Figures 4–7). Berninger and Richards (2002) proposed that the reading brain is constructed as children initially learn to relate existing phonological word forms to the orthographic word forms they are creating and eventually to relate phonological and morphological words forms to those orthographic word forms for increasingly morphologically complex written words. See Nagy, Diakidoy, and Anderson (1993) for the developmental course from simple to complex morphological awareness. The current results provide preliminary evidence regarding which brain regions are involved in these computations for creating mental maps of the mapping relationships among word forms to decode written words and to create the autonomous orthographic lexicon (Richards et al., 2006). Richards et al. (2005) reported additional studies of word form mapping processes during the intermediate grades; they contrasted two language-mapping tasks at a time in a set that included not only the phoneme mapping and morpheme mapping (no phonological shift) tasks in the current study but also tasks for morpheme mapping with phonological shifts and orthographic mapping. Additional studies are obviously needed with larger samples to verify these preliminary observations supporting triple word form theory that informs the phenotyping and genotyping studies in the family genetics study, the tasks in the brain-imaging studies, and instructional components in the treatment studies of the UWMLDC.

Significance of the right and left IFG. At least eight reports in the literature have documented that planum symmetry or reversed asymmetry is not associated with a profile in which only reading is impaired (reviewed by Leonard, 2001). Rather, planum anomalies are better predictors of more basic language comprehension problems (Eckert & Leonard, 2000). The ascertainment procedures for the child probands in the UW studies excluded children with severely impaired aural language comprehension. The third and fourth new findings reported in this article and studies in other research groups (e.g., B. A. Shaywitz et al., 2004; Temple et al., 2003) point to anomalies in right IFG and its relationship to left IFG that may shed light on the difficulties some individuals with dyslexia experience. The bilateral inferior frontal system may be part of a network providing executive support for language, which often falls outside the normal range in individuals with dyslexia (Berninger et al., 2006). Bilateral surface area of par triangularis in IFG is associated with phonological, orthographic, and RAN (Eckert et al. 2003). IFG is also associated with syntactic processing (Embick, Marantz, Miyashita, O'Neil, & Sakai, 2000). Bilateral activation in IFG has been associated with verbal working memory (Paulesu, Frith, & Frackowiak, 1993), but the operculum rather than the

par triangularis in IFG contributes directly to phonological working memory (Nixon, Lazarova, Hodinott-Hill, Gough, & Passingham, 2004).

Thus, the inferior frontal regions may be involved in all levels of language including those related to word form, the phonological loop of working memory, and the executive functions that regulate working memory. Left inferior prefrontal cortex coactivates with posterior word form regions, controlled retrieval of semantic information in left temporal gyrus, and controlled retrieval of phonological information in left posterior frontal and parietal regions (Gold & Buckner, 2002), thereby providing executive support for language systems. Although right inferior frontal regions are not activated to the same extent as those on the left, they may play some role in this executive management of the language system, perhaps by inhibiting irrelevant language processes. Further research is needed on this topic.

3. What Are the Implications of Your Findings for Teaching Struggling Readers?

Instructional significance of triple word form theory. Early in reading development, children with dyslexia require explicit instruction in mapping existing phonological word forms in their long-term and working memory onto orthographic word forms they are constructing (Berninger & Richards, 2002). Early intervention that teaches phonological awareness and phonics (alphabetic principle) helps children construct these mental maps and results in brain changes (B. A. Shaywitz et al., 2004; Simos et al., 2002; Simos et al., this issue). Later in reading development, children with dyslexia require explicit instruction in mapping morphological and phonological word forms in their long-term and working memory onto orthographic word forms that are increasingly longer and of Latin, French, and Greek origin (Aylward et al., 2003; Berninger & Richards, 2002; Carlisle, 1994; Henry, 2003; Nagy, Osborn, Winsor, & O'Flahaven, 1994; Richards et al., 2002). Carlisle (1994), Henry (2003), and Nagy et al. (1994) contained practical instructional recommendations for teaching children to coordinate phonological, morphological, and orthographic word forms and their parts. As Nagy explained it to children, words live in families just like children do; to learn to read and spell, children need to learn how families of sounds, families of word parts for meaning, and families of letter units work together harmoniously. Explicit instruction in word forms and their interrelationships can be embedded in instruction that also teaches vocabulary (Stahl & Nagy, 2006) and comprehension (Carlisle & Rice, 2002), as recommended by the National Reading Panel (2000) and implemented in our instructional treatment (Berninger, 2000; Berninger & Abbott, 2003; Berninger et al., 2003).

4. What Is the Next Step in Your Research?

The next steps in this programmatic research are to differentiate biologically and behaviorally *dyslexia* and *language learning disability*. Dyslexia is associated with defi-

cits in phonological, orthographic, and rapid naming subphenotypes (Berninger, Abbott, Thomson, & Raskind, 2001), whereas language learning disability is associated with these and additional deficits in morphological and syntactic awareness, word retrieval, and other processes, including verbal mediation, related to using language to self-regulate the learning process for oral and written language (Berninger & O'Donnell, 2004). These subtle language learning disabilities, which require formal assessment to identify, are not obvious at the level of language production (see Shankweiler et al., 1995) but rather exert their effects at the metalinguistic level (Stahl & Nagy, 2006). Although the distinction is often made between specific language impairment (affecting aural/oral language) and dyslexia (affecting written language), which may share common phenotypes (see Bishop & Snowling, in press), language learning disability (Butler & Silliman, 2002) is a newer concept. Children with language learning disability are slower in learning aural/oral language but not so delayed that they qualify for a diagnosis of specific language impairment, and they often are the fast responders to early intervention for language delay; however, even though they may reach normal limits, they may have persisting problems in morphological and syntactic awareness that impair their ability to use verbal mediation in school learning, learning new oral and written vocabulary, and developing age-appropriate reading comprehension.

We plan to investigate differences in children with dyslexia and those with language learning disabilities because the latter are often not qualified for services in the schools because they do not show IQ-achievement discrepancies even though their learning disabilities can be documented by assessing specific language subphenotypes (see Berninger & O'Donnell, 2004). Also, confounding these two subtypes may explain differences across groups conducting genetics research. See Chapman et al. (2003, 2004) for the definitional variation not only within the United States but also across countries that is complicating research on the genetic foundations of reading disabilities. We hope to compare these two subtypes of learning disabilities on the basis of phenotyping, genotyping, brain imaging, and effective instruction. The phenotyping and genotyping studies will compare the two subtypes on phonological processes within a working memory architecture—phonological, morphological, and orthographic word forms for temporary storage, the phonological loop for learning new spoken and written words (Baddeley, Gathercole, & Papagano, 1998), and executive support for language (Berninger et al., 2005). Those with dyslexia are more likely to be impaired in phonological awareness whereas those with language learning disabilities are more likely to be impaired in morphology and syntactic as well as phonological awareness (Berninger & O'Donnell, 2004). Given that S. E. Shaywitz et al. (2003) showed that the developmental outcome of dyslexia is best described in terms of connectivity among brain regions rather than isolated regions of activation, we will extend our initial connectivity studies showing the disconnection of cerebellum from occipital-temporal, temporal-parietal, and frontal regions in dyslexia (Stanberry et al., 2004) to comparison of patterns of connectivity in dyslexia and language learning disability.

CONCLUSION

The significance of the imaging studies reviewed in Table 2 on nature–nurture interactions and the new findings regarding distinctive word forms and their crossover effects is that effective educational treatments for biologically based reading problems in children of normal intellectual functioning may require explicit instruction in awareness of phonological, morphological, and orthographic word forms and their parts and interrelationships.

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