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Neural Changes following Remediation in Adult Developmental Dyslexia

Clinical Study

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Summary

Brain imaging studies have explored the neural mechanisms of recovery in adults following acquired disorders and, more recently, childhood developmental disorders. However, the neural systems underlying adult rehabilitation of neurobiologically based learning disabilities remain unexplored, despite their high incidence. Here we characterize the differences in brain activity during a phonological manipulation task before and after a behavioral intervention in adults with developmental dyslexia. Phonologically targeted training resulted in performance improvements in tutored compared to nontutored dyslexics, and these gains were associated with signal increases in bilateral parietal and right perisylvian cortices. Our findings demonstrate that behavioral changes in tutored dyslexic adults are associated with (1) increased activity in those left-hemisphere regions engaged by normal readers and (2) compensatory activity in the right perisylvian cortex. Hence, behavioral plasticity in adult developmental dyslexia involves two distinct neural mechanisms, each of which has previously been observed either for remediation of developmental or acquired reading disorders.

Introduction

The brain's capacity to reorganize itself in response to acute or developmental neural injury is crucial for effective rehabilitation of cognitive and sensorimotor skills. Models of neural plasticity and recovery of function have been derived from research on animals (for review, see Kaas, 2002). With the advent of functional brain imaging, these models have been expanded to account for the complex neuronal mechanisms underlying the behavioral recovery of patients with acquired brain damage (for reviews, see Chen et al., 2002; Cramer, 1999, 2003; Rijntjes and Weiller, 2002; Taub et al., 2002).

Physiological correlates of behavioral gains in language and motor improvement (herein referred to as "plasticity") have been found in adults with stroke-induced deficits (for a review, see Rijntjes and Weiller, 2002). For example, reports in adults with acquired language and reading deficits have demonstrated training-induced changes, with several studies noting increased activity in right hemisphere temporal regions in response to rehabilitation, homologous to the dominant hemisphere areas typically engaged in tasks of reading (Adair et al., 2000) and comprehension (Musso et al., 1999). Another pattern of plasticity was reported by Small and colleagues, who found a shift from the left inferior parietal cortex to the left fusiform gyrus in a patient following phonologically based reading intervention 17 years after her stroke (Small et al., 1998). In contrast, studies of developmental dyslexia in children who received phonologically based reading remediation have demonstrated that reading improvement is associated with the "normalization" of previously underactivated left hemisphere brain regions (Aylward et al., 2003; Richards et al., 2000; Shaywitz et al., 2004; Simos et al., 2002). The mechanisms for reading recovery in adults with developmental dyslexia have not yet been investigated. However, the findings in developmental and acquired reading disorders raise the potential for identifying neural correlates of reading remediation and effective intervention strategies for adults with developmental dyslexia.

Developmental dyslexia is a widespread disorder. In the US and UK, it is the most common learning disability, accounting for 80% of all learning disabilities and affecting 5%–17% of the population (Katusic et al., 2001; Shaywitz et al., 1990). It is characterized by impaired reading acquisition and poor phonological awareness skills that cannot be explained by low intelligence or poor educational opportunities (Bradley and Bryant, 1983; Frith, 1999; Lyon, 1995; Shaywitz, 1998), as well as abnormalities in sensory perception (for review, see Stein and Walsh, 1997). The prominent characteristic of a weakness in phonological awareness in dyslexia concerns the inability to segment and manipulate the constituent sounds of the oral language (e.g., say bend without the /b/ sound). Kindergarten and first grade performance on a range of phonological awareness tasks (e.g., initial sound deletion or rhyme detection) predict later reading and spelling skills of typically developing and reading-impaired children (Bradley and Bryant, 1983; Torgesen et al., 1994; Wagner et al., 1997). Throughout schooling, phonological awareness continues to be highly correlated with several aspects of reading ability, including accuracy of reading single real words and nonwords (decoding) and spelling (Shaywitz et al., 1999). Formal studies in clinics and classrooms have demonstrated that teaching the principles of phonological awareness to all children can raise scores on multiple measures of reading ability and is the most effective approach to treating individuals with dyslexia (Rayner et al., 2001; Swanson, 1999; Torgesen et al., 2001).

Positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have revealed the neural signature of adult normal reading (e.g., Bookheimer et al., 1995; Fiez and Petersen, 1998; Price, 1997; Pugh et al., 1996; Turkeltaub et al., 2002) and

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phonological processing (e.g., Gelfand and Bookheimer, 2003; Poldrack et al., 1999; Price et al., 1997; Rumsey et al., 1997a). Brain imaging studies have also characterized the anomalous patterns of neuronal activation associated with reading and phonological processing in adults with persistent or compensated developmental dyslexia (e.g., Brunswick et al., 1999; Demonet et al., 1992; Flowers et al., 1991; Horwitz et al., 1998; Ingvar et al., 1993; Paulesu et al., 1996; Pugh et al., 2000; Rumsey et al., 1997b; Shaywitz et al., 1998). Employing various experimental approaches and paradigms (e.g., the detection or judgment of rhymes, nonword reading, and implicit reading), these studies have localized dysfunctional phonological processing in dyslexia to left-hemisphere perisylvian regions. Differences in task-related signal change in the left temporoparietal and occipitotemporal cortices have emerged as the most consistent findings in studies of dyslexia in the alphabetic writing system (Paulesu et al., 2001; for review, see Eden and Zeffiro, 1998). However, it has been demonstrated that in nonalphabetic scripts, where reading places less demands on phonemic processing and the integration of visual-orthographic information is crucial, dyslexia is associated with underactivity of the left middle frontal gyrus (Siok et al., 2004).

Reading and phonological processing problems in dyslexia persist into adulthood, and even compensated adult dyslexics continue to exhibit deficits in processing the phonological aspects of language (Flowers, 1995; Paulesu et al., 1996). The majority of the dyslexic population are adults, many of whom suffer significant financial and emotional consequences (Maughan et al., 2003). Yet our knowledge about treatment outcomes in this population is relatively small, and the functional reorganization following treatment is unknown. The neurobiological basis for plasticity in adults is likely to be different than in children, as reading and its associated skills in the pediatric population are dynamic and continuously changing throughout development. For example, only 28% of children with a diagnosis of dyslexia in first grade were similarly classified 2 years later (Shaywitz et al., 1992), suggesting that among children there may be intervening variables at work. For example, reading acquisition entails stages or phases which are protracted throughout childhood (Ehri, 1999) and are associated with experience and developmentally driven physiological changes. Specifically, the frontal lobes are the last to mature (Chugani, 1998; Fuster, 2002; Huttenlocher and Dabholkar, 1997) and are not recruited by children during reading and reading-related skills to the same extent as by adults (Schlaggar et al., 2002; Simos et al., 2001; Turkeltaub et al., 2003). In adults on the other hand, the behavioral manifestations of dyslexia are relatively stable. Hence, any brain changes underlying behavioral plasticity can confidently be interpreted as treatment effects as opposed to the development of cognitive and sensorimotor systems coincidental with the time span of the treatment. In other words, plasticity is likely to manifest differently in a system that is mature and stabilized.

In our first experiment, we tested and confirmed earlier findings of hypoactivity in left perisylvian regions underlying phonological processing in dyslexia, in this case during a sublexical sound deletion task. To examine the physiological consequences of phonologically based intervention, we then employed a controlled design in which half our adult dyslexic sample received 112 hr of structured, multisensory phonological intervention (see Experimental Procedures). They were contrasted pre- and postintervention to a group of dyslexics who did not receive treatment. Based on previous brain imaging studies investigating neuronal plasticity following recovery of language in stroke patients who received therapy (Adair et al., 2000; Musso et al., 1999; Small et al., 1998) and those delivering phonologically based intervention in children (Aylward et al., 2003; Richards et al., 2000; Shaywitz et al., 2004; Simos et al., 2002), we envisioned three possible mechanisms that could underlie behavioral plasticity in adults with developmental dyslexia: (1) increased engagement of the normal left hemisphere network found in nonimpaired readers, consistent with the findings of pediatric reading remediation; (2) a compensatory mechanism wherein new areas are recruited within the left or right hemisphere as has been reported as a mechanism supporting the functional recovery of stroke patients; or (3) some combination of the two.

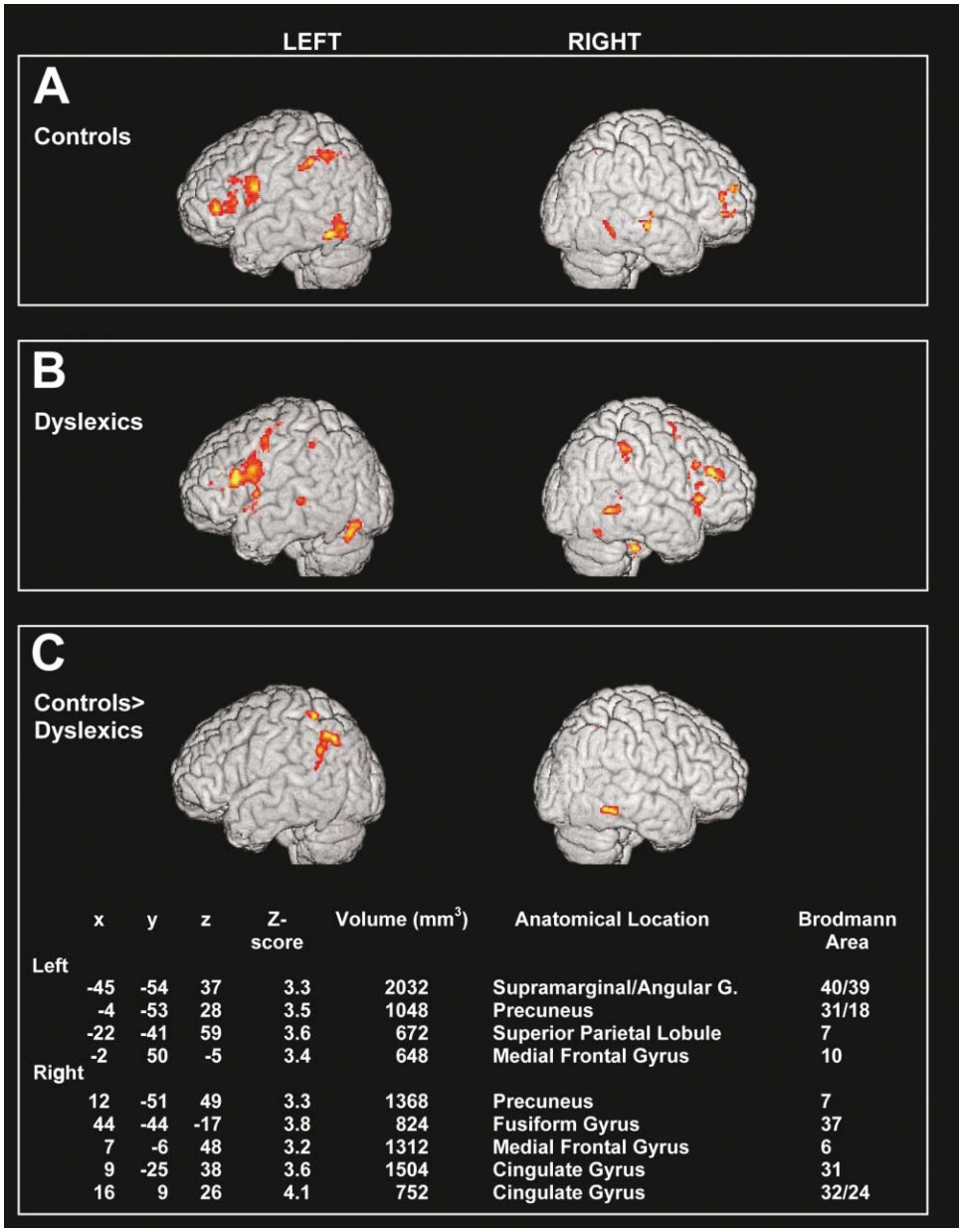
Results

Behavioral Profiles of Dyslexic versus Typical Readers

Table 1 (panel A) summarizes the behavioral profiles of the study participants, demonstrating significant differences in oral reading of single real words, nonwords, and paragraphs (accuracy, rate, and comprehension) between the dyslexic ($n = 19$) and typical readers ($n = 19$) on standardized measures. However, during the acquisition of fMRI data, performance on a simple phonological processing task resulted in no significant differences between the two groups (each group achieved greater than 80% accuracy), meeting our goal of minimizing performance-related confounds (Poldrack, 2000; Price and Friston, 1999). The dyslexic and control groups did not differ in the amount of head motion recorded during the scans.

Brain Activity Underlying Phonological Processing in Dyslexic versus Typical Readers

During the acquisition of fMRI data, subjects fixated on a crosshair and listened to aurally presented words, which they either (1) repeated (Word Repetition) or (2) repeated after deleting the initial phoneme (Sound Deletion). Maps of task-related activity were created by subtracting the Word Repetition condition from the Sound Deletion condition, revealing regions involved in phonological manipulation, while controlling for common sensory and motor aspects of the target and control tasks. Figures 1A and 1B display the task-related signal changes underlying sublexical phonological processing in the nondyslexic and dyslexic groups. A between-group contrast revealed significantly less activity in the dyslexic group (Figure 1C) in both hemispheres, most notably the left inferior parietal (BA 39 and BA 40) and superior parietal (BA 7) regions ($p < 0.001$ and cluster spatial extent of >80 voxels). Hypoactivity in parietal cortex in the dyslexic group is consistent with previous



	x	y	z	Z-score	Volume (mm^3)	Anatomical Location	Brodmann Area
Left							
	-45	-54	37	3.3	2032	Supramarginal/Angular G.	40/39
	-4	-53	28	3.5	1048	Precuneus	31/18
	-22	-41	59	3.6	672	Superior Parietal Lobule	7
	-2	50	-5	3.4	648	Medial Frontal Gyrus	10
Right							
	12	-51	49	3.3	1368	Precuneus	7
	44	-44	-17	3.8	824	Fusiform Gyrus	37
	7	-6	48	3.2	1312	Medial Frontal Gyrus	6
	9	-25	38	3.6	1504	Cingulate Gyrus	31
	16	9	26	4.1	752	Cingulate Gyrus	32/24

Figure 1. Functional Anatomy of Phonological Manipulation in Normal Readers, Dyslexic Readers, and Normal Readers Greater Than Dyslexic Readers

Task-related signal change was derived by contrasting simple Word Repetition of an aurally presented word with repeating words after performing Sound Deletion on the first phoneme. Localization is based on stereotaxic coordinates in x (medial-lateral), y (antero-posterior), and z (superior-inferior) directions and refers to the location of maximal activation within a cluster (indicated by the highest Z score). Areas of significant activity within 15.0 mm of the cortical surface are projected to the surface of the brain ($Z = 3.10$; $p < 0.001$, uncorrected; limited to clusters >80 contiguous 2 mm cubic voxels). Brain activity attributed to phonological manipulation in normal readers (A) was observed in left occipitotemporal, inferior parietal, and inferior frontal cortex, consistent with previous studies. The thalamus and cerebellum were also bilaterally active (these deeper foci are not seen in the figure). In the right hemisphere, the following regions were identified: inferior and middle temporal cortex as well as middle frontal gyrus. The dyslexic group (B) showed activity related to phonological manipulation in bilateral inferior parietal, inferior frontal, middle temporal cortex, precuneus, and cerebellum. A between-group statistical comparison of the control and dyslexic groups (C) revealed less activity in the dyslexic group in left inferior parietal regions (supramarginal and angular gyri), superior parietal lobule, precuneus, and medial frontal gyrus. Dyslexic subjects also displayed less activation in several right hemisphere regions compared to controls: the occipitotemporal junction, as seen in the figure, and medial structures including precuneus, medial frontal, fusiform, and cingulate gyri (not seen in these lateral projections).

investigations of phonological processing and reading in dyslexia in pediatric (Shaywitz et al., 2002; Simos et al., 2000; Temple et al., 2001) and adult populations (Brunswick et al., 1999; Pugh et al., 2000; Rumsey et al., 1997b; Shaywitz et al., 1998). Although we did not find the widely reported underactivity in the left occipito-

temporal junction or BA 37 (Brunswick et al., 1999; Paulesu et al., 2001; Rumsey et al., 1997b; Shaywitz et al., 1998), this region was hypoactive in the right hemisphere of the dyslexic group. Some studies have also reported left hyperactivation in adult dyslexics in the inferior frontal gyrus for some tasks (Brunswick et al., 1999; Shaywitz et al., 1998) but not for others (Brunswick et al., 1999; Paulesu et al., 1996; Rumsey et al., 1994, 1997b); here, we did not observe hyperactivity in the IFG but rather found less activity in several medial right hemisphere areas, including medial frontal and cingulate gyrus.

Behavioral and Physiological Outcomes following Intervention

Next we investigated whether the behavioral and physiological deficits observed in our dyslexic sample could be altered by training in phonological processing. Eight to ten weeks following the initial study described above (comparing dyslexic and nondyslexic adults), the dyslexic group returned to the laboratory to repeat the behavioral evaluation and fMRI scanning protocols. Between the two visits, half the dyslexic group, the "intervention group," underwent intensive, phonologically based instruction for 8 weeks (see Experimental Procedures). The other half of the dyslexic group, the "nonintervention group," did not participate in any instruction. We contrasted psychoeducational measures and fMRI data in the dyslexic subjects at these two time points.

Behavioral Outcomes following the Intervention

We assessed behavioral change in the following three domains: (1) skills that were directly targeted by the intervention program (phonological processing through the auditory and visual modalities); (2) single-word reading skills that are supported by phonemic awareness (nonword and real word decoding); and (3) secondary reading measures not directly targeted by the intervention (oral paragraph reading accuracy, rate, and comprehension). While skills in the first domain involving phonological processing would be expected to improve because of task-specific training, the intervention would ultimately be more useful if it demonstrated generalization and extension to those categories of reading skills captured in the latter two domains. This combination of measures allowed us to characterize the effect of the intervention not only on phonological processing skills but also on reading itself (Torgesen et al., 1994; Wagner et al., 1997).

As shown in Table 1 (panel B), prior to the intervention, the two dyslexic groups did not differ on measures of oral single-word, nonword, and paragraph reading. As anticipated, skills that were directly targeted by the instructional method (phonological processing through auditory and visual modalities) improved significantly following the intervention (Figure 2A). Significant improvements were also observed for the two measures of phonological transfer efficiency (Figure 2B): these consisted of reading nonwords, an effective indicator of a person's knowledge about English pronunciation and critical for sounding out novel words, as well as the Phonemic Transfer Index, a measure of how well individuals generalize their knowledge about real-word pronunciation to the reading of analogous nonwords. There were also gains in single real-word reading, but these did not reach statistical significance. Turning to the third domain, gains observed on oral paragraph reading accuracy were significant (Figure 2C), whereas oral paragraph reading rate and comprehension did not change. In sum, following the therapy, phonological awareness changed significantly; this improvement was reflected both in skills directly targeted by the intervention and in those reading skills heavily reliant on phonological awareness. This improvement also generalized to higher-order paragraph reading accuracy, even though commensurate reading rate and comprehension gains were not observed.

Physiological Consequences of the Intervention

Task-related activity measured during phonological processing was compared between the intervention and the nonintervention groups before and after the training. First-level contrasts of [Sound Deletion versus Word Repetition] were used in a subsequent ANOVA with a voxel-wise critical threshold of $p < 0.001$ and cluster spatial extent of >80 voxels to provide protection against family-wise type I error. Figure 3 illustrates brain regions that demonstrated a significant Group $\times$ Session interaction, displaying those areas exhibiting enhanced activity in the intervention group following the treatment. Significant intervention-related increases underlying phonological manipulation were observed in left hemisphere inferior parietal lobule (BA 40), intraparietal sulcus (BA 40/7), and fusiform gyrus (BA 37; see Figure 3 in bold). There also were small increases in the left middle frontal gyrus (BA 46) and medial aspects of the left hemisphere, including the thalamus, but these fell short of meeting conventional statistical significance. In the right hemisphere, numerous foci of significant increases were observed, with more pronounced changes in posterior superior temporal cortex and angular gyrus (BA 22/39), superior (BA 7) parietal cortex, as well as inferior frontal (BA 45/46) cortex. These latter two regions are homotopic to areas seen in normal readers in the left hemisphere. In addition, small treatment-related increases were seen in three smaller foci within the right frontal lobe, but these did not reach statistical significance.

While there were numerous regions of increased brain activity in the treatment group following the intervention, only one area, the left medial occipital gyrus (BA 37/19, at location $x = -50$, $y = -76$, $Z = 8$) was found to be less active following the intervention. This finding is consistent with the idea proposed by Pugh et al. (2001) that increased phonological processing would induce less engagement of the occipitotemporal cortex and greater reliance on the parietal cortex.

In summary, following a course of phonologically based instruction, adults with persistent dyslexia enjoyed measurable gains in phonological processing skills. This improved understanding of the phonological features of language was transferred to some aspects of reading ability, leading to improved accuracy on nonword decoding and oral paragraph reading. Physiological correlates of improved phonological awareness indicate a dual neurobiological mechanism, eliciting changes through increased activity of the left parietal cortex (as observed for typical readers), as well as

Table 1. Demographic and Behavioral Profile of Subjects

	A: Control versus Dyslexic Groups					B: Dyslexic Groups				
	Control Group (n = 19, 13 males)		Dyslexic Group (n = 19, 14 males)		Statistical Difference	Nonintervention Group (n = 10)		Intervention Group (n = 9)		Statistical Difference
Subject Characteristics	Mean	SD	Mean	SD	p Value	Mean	SD	Mean	SD	p Value
Chronological age (years)	41.1	9.7	44.0	9.4	ns	43.8	8.5	44.2	10.9	ns
Full IQ (WASI)	116.4	9.3	101.9	12.6	$p < 0.0005$	107.4	9.5	95.8	13.2	$p < 0.05$
Performance IQ	115.0	10.2	103.7	16.2	$p < 0.05$	110.0	11.2	96.7	18.5	ns
Verbal IQ	113.5	8.9	99.5	9.1	$p < 0.0001$	102.7	8.5	95.9	8.9	ns
Real word reading (WRAT)	109.6	6.3	85.6	11.9	$p < 0.0001$	87.9	11.2	83.0	12.9	ns
Nonword reading (WJR)	119.3	11.6	90.7	9.8	$p < 0.0001$	93.4	10.3	87.8	8.9	ns
Accuracy (GORT)	14.2	2.3	6.4	3.7	$p < 0.0001$	7.1	3.8	5.6	3.7	ns
Rate (GORT)	12.8	2.7	5.8	3.9	$p < 0.0001$	6.9	3.8	4.7	3.9	ns
Comprehension (GORT)	12.4	2.3	8.6	4.0	$p < 0.005$	9.6	4.4	7.4	3.5	ns

Nineteen dyslexic and nineteen nondyslexic participants were identified based on their reading-related skills (see Experimental Procedures). Compared to the controls, the dyslexic group was significantly impaired on measures of single real-word and nonword decoding and oral paragraph reading. The dyslexic group was further divided into "intervention" and "nonintervention" groups, and their resulting group means are displayed. Both groups of dyslexics were matched on reading abilities prior to the training. For a description of the reading measures, see Experimental Procedures.

through compensatory mechanisms in the right hemisphere perisylvian regions, most notably parietal cortex.

Discussion

Research in adult human and nonhuman primates has demonstrated cortical plasticity following rehabilitative training or experience-driven changes (induced by learning or sensory deprivation) at the physiological (Rauschecker, 1995; Karni et al., 1998) and anatomical level (Amunts et al., 1997; Draganski et al., 2004; Penhune et al., 2003). Using functional brain imaging the neuronal reorganization that accompanies behavioral recovery in adults has been examined following stroke, yet there has been no such demonstration in the more prevalent developmental disorders. A better under-

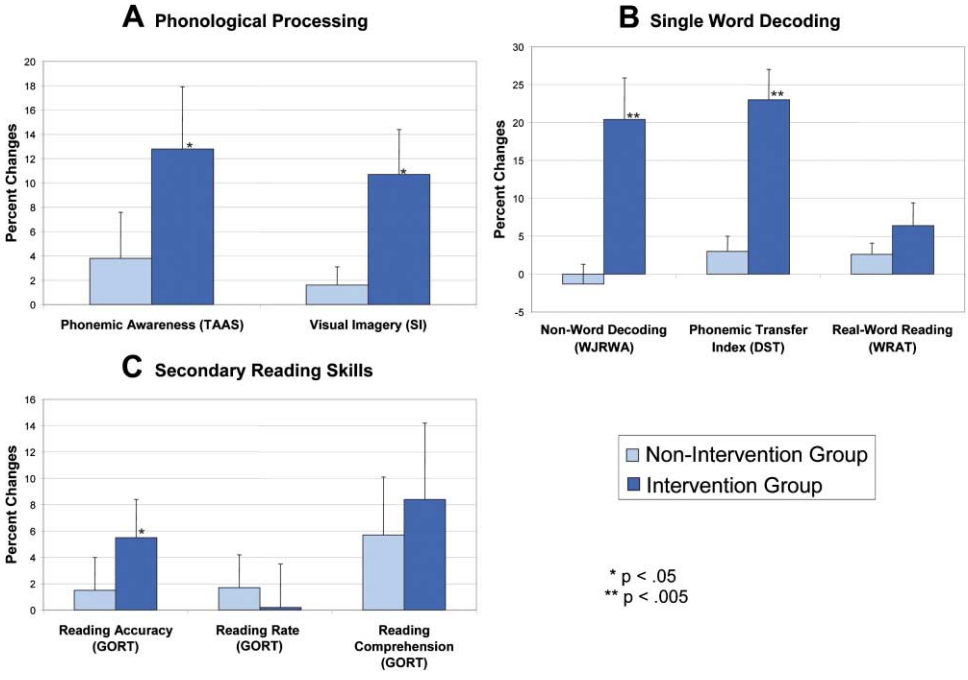
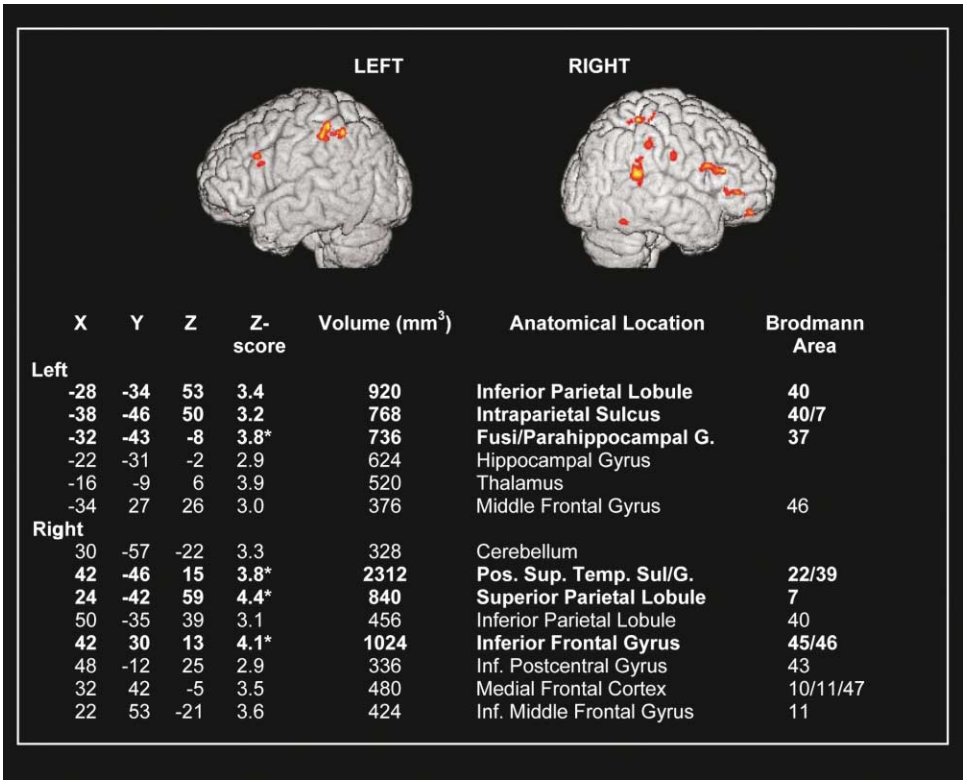


Figure 2. Phonological Processing and Reading-Related Changes following Training in the Dyslexic Intervention and Nonintervention Groups

Significant gains were observed in several measures, including (A) phonological processing in the aural and visual modality, (B) nonword decoding, phonemic transfer, reading accuracy, and (C) oral paragraph reading accuracy but not rate or comprehension. Percent changes are plotted so that tests with different scales can be more easily compared. (A) Phonological Processing: Test of Auditory Analysis Skills (TAAS) and Visual Symbol Imagery (SI). (B) Single-word Decoding Skills: Woodcock-Johnson-Revised Word Attack subtest (WJRWA), Decoding Skills Test (DST), and Wide Range Achievement Test (WRAT). (C) Secondary Reading Skills: Gray Oral Reading Test Third Edition (GORT), accuracy, rate, and comprehension. For the source of these measures, see Experimental Procedures.



X	Y	Z	Z-score	Volume (mm^3)	Anatomical Location	Brodmann Area
Left						
-28	**-34**	**53**	**3.4**	**920**	**Inferior Parietal Lobule**	**40**
-38	**-46**	**50**	**3.2**	**768**	**Intraparietal Sulcus**	**40/7**
-32	**-43**	**-8**	**3.8***	**736**	**Fusi/Parahippocampal G.**	**37**
-22	-31	-2	2.9	624	Hippocampal Gyrus	
-16	-9	6	3.9	520	Thalamus	
-34	27	26	3.0	376	Middle Frontal Gyrus	46
Right						
30	-57	-22	3.3	328	Cerebellum	
42	**-46**	**15**	**3.8***	**2312**	**Pos. Sup. Temp. Sul/G.**	**22/39**
24	**-42**	**59**	**4.4***	**840**	**Superior Parietal Lobule**	**7**
50	-35	39	3.1	456	Inferior Parietal Lobule	40
42	**30**	**13**	**4.1***	**1024**	**Inferior Frontal Gyrus**	**45/46**
48	-12	25	2.9	336	Inf. Postcentral Gyrus	43
32	42	-5	3.5	480	Medial Frontal Cortex	10/11/47
22	53	-21	3.6	424	Inf. Middle Frontal Gyrus	11

Figure 3. Functional Anatomy of Phonological Manipulation following Reading Remediation

Task-related signal changes underlying phonological processing were computed by contrasting Word Repetition with Sound Deletion of aurally presented words for both dyslexic groups prior to and following the intervention and entered into an ANOVA. A Group $\times$ Session interaction revealed intervention-related increases during phonological manipulation in left parietal cortex and fusiform gyrus, indicative of functional increases in regions previously reported as activated by normal readers. This fusiform region extended into the left BA 37, but anterior and inferior to what is considered the "visual word form" area (Cohen et al., 2002). Right hemisphere increases included posterior superior temporal sulcus/gyrus and parietal cortex, thereby representing right hemisphere homologs of regions usually seen in the left hemisphere in good readers. Significantly activated areas are shown in bold in the accompanying table ($Z = 3.10$; $p < 0.001$, uncorrected and extended in clusters of at least 80 contiguous 2 mm cubic voxels; *$p < 0.05$, corrected for multiple comparisons). Left middle frontal cortex (BA 46) and right hemisphere frontal regions also increased, but fell short of the statistical threshold.

standing of the neurobiological basis of treatment in developmental dyslexia, as for clinical recovery in stroke, could be used to guide the remediation process of this disorder.

Poor phonological awareness is the hallmark of developmental dyslexia. Our first experiment examined the neural bases of oral sound deletion, employing a task frequently used in neuropsychological evaluations of dyslexia (for example, see Wagner et al., 1999). In normal readers, sublexical sound manipulation of aurally presented words invoked task-related signal change predominantly in left hemisphere regions. In contrast, the dyslexic group demonstrated relatively less activity in parietal regions, consistent with previous findings in studies employing phoneme detection, rhyme judgment, and nonword reading tasks (Brunswick et al., 1999; Pugh et al., 2000; Rumsey et al., 1997b; Shaywitz et al., 2002; Shaywitz et al., 1998; Simos et al., 2000; Temple et al., 2001). In our second experiment, we identified the physiological correlate of phonologically based remediation in adults, which was measured as increased activity in bilateral parietal cortex and right hemisphere perisylvian structures.

Several conclusions can be drawn from these results: (1) long after the termination of formal schooling, adult dyslexic readers can make significant gains in phonological processing skills that support efficient reading, while those that depend on repeated text exposure (e.g., reading fluency and comprehension) are resistant to change under these training conditions; (2) the left inferior parietal cortex, noted here and in previous studies to be hypoactive in individuals with dyslexia, increases in activity following phonologically based instruction; and (3) right parietal and perisylvian activity demonstrates compensatory mechanisms. Together, these findings provide evidence that dyslexic adults are not, as may have been assumed, unable to profit from remedial practice. In fact, the same strategies that are effective in teaching children phonological awareness skills are helpful in adults. Further, they are accompanied by neural changes known to underlie reading remediation of developmental dyslexia in childhood (Aylward et al., 2003; Shaywitz et al., 2004; Simos et al., 2002; Temple et al., 2002) combined with those previously observed during the rehabilitation of adults with acquired dyslexia (Adair et al., 2000; Musso et al., 1999).

Physiological Differences in Adults with Dyslexia

In dyslexia, microstructural anomalies in the brain cause differences detectable at the physiological level (Gala-

burda et al., 1985; Livingstone et al., 1991). A significant aspect of our study of lifelong dyslexia is that treatment-driven change is not confounded by spontaneous recovery as has been observed in stroke patients. We were able to identify the neural signature of aberrant activity associated with dyslexia, verifying previous reports, and relate this finding to the intervention-driven changes. Prior to the intervention, we identified less task-related activity in left inferior parietal regions (supramarginal and angular gyri) in the dyslexic group. As these findings are consistent with recent pediatric studies of dyslexia (Shaywitz et al., 2002; Simos et al., 2000; Temple et al., 2001), it is unlikely that the observed hypoactivity of this region in adulthood is a consequence of a lifetime lack of reading and phonological awareness experience. However, it should be noted that brain imaging studies of dyslexia have not yet employed the reading-level matched design that is prevalent in behavioral studies of reading disabilities and that would address this question directly (for example, see Turkeltaub et al., 2004). Nevertheless, an increase of activity in left parietal cortex following targeted intervention suggests reversible pathophysiology. Changes in this region were also observed in remediation studies of children (Aylward et al., 2003; Shaywitz et al., 2004; Simos et al., 2002; Temple et al., 2001), with only a few of these studies also showing increased activity in the left superior temporal and inferior frontal cortex.

Phonological Intervention Generalizes to Reading Accuracy but Not Secondary Reading Skills

Significant growth in text and nonword reading accuracy occurred concurrently with gains made in phonological awareness and suggests some generalization of phonological processing skills to reading. The implications of this finding are 2-fold. First, school-based methods for teaching strive for a "transfer of learning": postintervention gains should not only be observed on trained exemplar items, but also on untrained transfer items, indicating that learners are able to generalize their newly acquired skills (Benson et al., 1997). In this regard, intervention studies of dyslexic children have reported mixed results. It has been questioned to what degree individuals with dyslexia can apply grapheme-phoneme correspondence rules to related knowledge domains (Lovett et al., 1989). Some reports, including the present study, are supportive of at least some degree of generalization to other reading skills (Torgesen et al., 2001).

Second, whether the behavioral changes are "specific" or "general" has important implications for interpreting the neural mechanisms underlying this specific behavioral change. Previous investigations into the neuronal correlates of reading intervention in children have largely relied on measures of single-word reading. Our behavioral results emphasize the complex and also somewhat limited nature of the changes following phonologically based intervention in the context of other reading skills, such as reading speed and comprehension. The changes in brain activity during an aural phoneme manipulation task are likely to be specifically related to gains in phonological processing. Any improvement in reading comprehension would have made it difficult to interpret our results in terms of brain function without the inclusion of a reading comprehension task. Future brain imaging studies will need to investigate the physiological correlates of different reading-related tasks and their modulation following interventional strategies, so that the brain-behavioral relationships can be more clearly understood. For example, programs targeting reading speed by employing repeated readings of continuous text might not be expected to bring about changes in the same regions observed in the present study.

Phonological awareness is considered to be essential for developing good word decoding skills, and these in turn facilitate the acquisition of reading comprehension and reading fluency. In our adults, reading rate and comprehension did not improve following the intervention, indicating that phonological awareness intervention may not be sufficient to tackle these secondary deficits frequently seen in dyslexia, at least for adults over an 8 week period. However, we cannot rule out the possibility that advances in phonological processing can eventually lead to reading comprehension gains in the long term. Reading comprehension is highly correlated with reading rate (Dowhower, 1987), and rate improves with continued exposure and repetition once individuals know how to sound out words (for review, see Meyer and Felton, 1999). Eight weeks of practice may be insufficient to see measurable changes in reading rate, as extra time is needed to apply newly acquired decoding skills. Reading rate, however, was also reported to be treatment resistant on long-term follow-up (2 years) in dyslexic children who received a similar intervention, even though reading accuracy increased (Torgesen et al., 2001), thereby underscoring the need for further research into reading fluency and reading comprehension using alternative approaches (Wolf and Segal, 1999) and raising the possibility that these secondary deficits involve brain regions that could be modulated by training techniques other than the one examined in our study.

Left and Right Hemisphere Increases with Gains in Phonological Awareness

Our results demonstrate that in adult developmental dyslexia behavioral plasticity is realized by both enhancement of left lateralized language areas and engagement of right hemisphere regions. Individuals who demonstrate impaired phonological and reading skills into adulthood represent the most resistant cases of dyslexia and may therefore exhibit the most pronounced pathophysiology. The recruitment of right hemisphere areas could therefore reflect training-dependent processes in the context of restricted availability of left-hemisphere regions, in much the same way as reported in stroke patients (Rijntjes and Weiller, 2002). However, other interpretations need to be considered.

The intervention-driven right hemisphere increases are conspicuous when considering that pediatric remediation studies do not report such changes during phonological tasks (Aylward et al., 2003) and even suggest a decrease of right hemisphere utilization following intervention (Simos et al., 2002). This suggests that the neural mechanisms of remediation may be different in adults than in children. Alternatively, this disparity might be attributable to the fact that our population had not yet reached the final phases of the recovery process, and while some reading-related skills normalized as a conse-

quence of intervention, the gap was not closed in all skill domains. Nevertheless, it is noteworthy that the gains in nonword reading in our adult dyslexic population were of the same magnitude as those previously reported in children, whereas the data on text reading fluency in the pediatric neuroimaging studies is not known. Only long-term outcome studies with multiple occasions for behavioral and neurophysiological assessment will be able to evaluate the exact nature of the dynamic neuronal processes underlying these stages. This is especially important in light of the finding that adult cortical plasticity is achieved in phases associated with staged cortical and noncortical changes (Doyon et al., 2003) and that the evolution in brain activation patterns over the recovery period following stroke is related to the degree of behavioral improvement (Ward et al., 2003).

Interestingly, some tasks that result in highly lateralized activity in younger adults draw on bilateral regions in older adults (for review, see Reuter-Lorenz, 2002). This phenomenon of age-dependent right hemisphere involvement might be accounted for in terms of compensatory recruitment or a reversal of the process of increased specialization of neural systems which typify early development. Our adult dyslexics demonstrated some right hemisphere engagement prior to the intervention, perhaps reflecting that a degree of compensation was already present and that it increased following the training.

Neural Mechanisms of Training-Induced Plasticity

Studies performed in nonhuman primates have demonstrated large-scale reorganization for sensory systems, seen as shifts in sensory topography, in some cases involving reorganization over extensive distances within the brain (Rauschecker, 2002). The degree of plasticity exhibited by the mature brain might be greater than originally believed (Kaas, 2002; Nudo et al., 1996), but the formation of new intracortical connections is very limited (Kaas, 2002) and an unlikely cause of adult plasticity. Another mechanism entails the potentiation of cortical areas that become more active consequent to dysfunction elsewhere in the brain (Hallett, 2001). In acute cortical damage, this "unmasking" mechanism is thought to be responsible for the recovery observed following cerebral damage in acquired dysphasia (Weiller et al., 1995). It is surmised that previously existing but not utilized inputs of the normal functional anatomy become expressed. Such dramatic functional shifts to the contralateral hemisphere are not unlike those following left hemisphere brain lesions acquired early in life, for example, inducing language representation in the homotopic areas of the undamaged right hemisphere (Staudt et al., 2002). We can only speculate about the underlying mechanism/cause of plasticity in the case of adult reading remediation, and future studies addressing this question need to take into consideration models that account for changes at the molecular, anatomical, physiological, and behavioral level. However, our results suggest that the mechanism of change will depend in large part on the nature of the intervention.

We can consider the possible relationship between the components of the intervention and the neuroplastic changes observed in our adult dyslexic subjects. One locus of substantial change included parietal cortex, which was the site of pathophysiology (left hemisphere) and recovery (bilaterally). It has been demonstrated that visual mental representation of orthographic information occurs in parietal cortex (Kosslyn et al., 1997). Further, Bartolomeo and colleagues reported an alexic patient who had lost his ability to perform mental imagery of letters following a stroke in the left temporoparietal region (Bartolomeo et al., 2002), yet he was able to ameliorate this problem by tracing the contours of the letters, a strategy employed in the intervention program used here. A report on an alexic patient who received a similar treatment program as the one administered to our subjects demonstrated a lack of left parietal cortex activity during nonword reading prior to the treatment and an increase in activity in the homologous right hemisphere region following the treatment (Adair et al., 2000). The role of the parietal cortex in reading has traditionally been described in the context of phonological processing (Shaywitz et al., 2002), but the exact nature of its function is poorly understood. Phonological processing involves the integration of multisensory inputs of phonemic and orthographic representations and may utilize the multimodal integration mechanisms that are characteristic of posterior parietal cortex (Elkington et al., 1992; Stein, 1989; Xing and Andersen, 2000).

In order to develop more targeted and effective reading interventions, future studies will also require detailed analysis of each of the components that comprise viable intervention programs. These investigations would benefit from the inclusion of multiple dyslexic control groups that undergo a variety of interventions that differ by one critical component, the efficacy of which can therefore be critically evaluated. Presumably, the intervention format and its neurobiological targets may differ in languages where the orthography is shallower and decoding skills develop more efficiently than they do in English (Paulesu et al., 2001).

Conclusions

The neurobiological route by which intervention programs improve behavioral performance has been investigated in stroke patients and in children with developmental dyslexia, but the question of how these brain areas are affected by specific training procedures in adults with developmental dyslexia has not yet been addressed. Task-related activity during phonological manipulation was measured prior to and following an 8 week, phonologically based intervention program. Compared to the nonintervention group, the dyslexic intervention group improved on measures of phonological processing and word reading. They also displayed significant enhancement in the use of left hemisphere parietal cortex and numerous right hemisphere regions. We conclude that this compensation resulted from a failure to fully utilize the processing capacities of those left parietal regions typically involved in phonological processing. Together, these findings suggest that adults with persistent characteristics of dyslexia are capable not only of responding positively to intensive intervention, but demonstrate changes in functional neuroanatomy attributable to training. The physiological mecha-

nisms of adult phonologically based intervention are interpreted as a combination of two processes previously reported independently in studies of developmental or acquired reading disorders: (1) an increase in areas seen in typical readers, as has been demonstrated in remediation studies of children with developmental dyslexia, and (2) compensation in areas not usually associated with the task, a mechanism that has been found in rehabilitation of acquired reading disorders following stroke. These findings provide important information for understanding adults with developmental dyslexia and for developing more specialized, effective interventions for this population.

Experimental Procedures

Subject Selection

Healthy dyslexic subjects were included in the study if, despite at least average ability and educational opportunity, they (1) had a lifelong history of dyslexia based on reading scores and (2) as adults also exhibited deficits on measures of phonological processing. Individuals in the control group had no history of any learning disability and scored at least in the average range on all reading and phonological processing tests as adults. One dyslexic subject was eliminated due to failure to perform the fMRI activation task, and one control subject was eliminated after not completing the study protocol. This left 19 dyslexic (14 males, 5 females) and 19 control subjects (13 males, 6 females). The dyslexic participants were mainly drawn from a larger cohort, consisting of adults who had been seen by the clinician June Orton in North Carolina during their childhood and whose records (housed at Columbia University) allowed the determination of their reading abilities during childhood (Flowers et al., 1991). Three of the subjects in the dyslexic group were obtained through clinical referral; their evaluations demonstrated weak literacy skills and a history of childhood reading problems. Control subjects were recruited either from the same geographic area as the dyslexics ($n = 8$) or locally in the DC area through advertisement ($n = 11$). All were determined to be good readers with intact phonological processing skills, based on reported history, confirmed on the reading test battery. All subjects were without significant medical, neurological, or psychiatric illness by history. Those with a history of substance abuse or implanted metal objects were excluded. The dyslexic and control groups did not differ in age, education, or gender distribution. Adult behavioral evaluations of reading and reading-related skills were obtained at Wake Forest University Medical Center, and all of the MRI imaging and imaging-related procedures were performed at Georgetown University Medical Center, including the General Clinical Research Center. For the second study, the dyslexic sample was further subdivided into an "intervention" and "nonintervention" group based on each subject's proximity to the intervention site. As shown in Table 1, panel B, prior to the intervention the two dyslexic groups did not differ on measures of any test of reading. By chance, the intervention group scored significantly lower on overall IQ ($p = 0.04$), a difference most likely attributed to chance rather than the selection procedures.

Measurement of Intellectual Functioning, Reading, and Reading-Related Skills

IQ was measured by the Wechsler Abbreviated Scale of Intelligence (WASI; Wechsler, 1999), which yields verbal, nonverbal (performance), and full-scale standard scores (mean = 100, SD = 15). A wide range of phonological processing and reading skills were assessed prior to and following the intervention. (1) Phonological processing: Test of Auditory Analysis Skill (TAAS) (Rosner and Simon, 1971) and Visual Symbol Imagery (SI) (Bell, 1997). (2) Single nonword and real-word decoding: Woodcock Johnson-Revised Word Attack subtest (WJRWA) (Woodcock and Johnson, 1989); Phonemic Transfer Index from Decoding Skills Test (DST) (Richardson and Dibenedetto, 1985) for ratio of nonword to real-word accuracy and Wide Range Achievement Test (WRAT) reading subtest (Wilkinson, 1993). (3) Secondary reading skills: oral paragraph reading accuracy, rate, and comprehension on Gray Oral Reading Test Third Edition (GORT) (Wiederholt and Bryant, 1994). A general linear model with full-scale IQ covaried was used to identify tests that showed significant improvement in the intervention group as compared to the score differences over the same period in the nonintervention group. For these measures to be compared to one another more easily, percent gains are reported for all tasks in Figure 2.

Intervention Procedures

The intervention employed in the present study was a widely used, phonologically based commercial program delivered at Wake Forest University Medical Center by staff from the Lindamood-Bell Learning Corporation. The program utilizes auditory, visual, and sensorimotor stimulation in a highly structured manner, a technique referred to as a "multisensory approach" commonly employed by special education tutors to remediate dyslexic students (Birch, 1999). It included training in sound awareness, establishment of the rules for letter-sound organization, sensory stimulation, and articulatory feedback (Lindamood and Lindamood, 1971). Also, imagery strategies were used to visualize and manipulate letters and words. This approach reinforces the relationship between sounds and printed letters and words (Bell, 1997). When employed in classroom or clinical settings and compared to a control group, these types of approaches result in significant increases in both phonological processing and single-word reading skills in children (Torgesen et al., 2001; Wise et al., 1999) and adults (Alexander et al., 1991; Truch, 1994). Participants received the training in small group settings in daily 3 hr sessions for 8 weeks. All subjects completed the program and, on average, had 112.5 hr of tutoring.

Imaging Procedures

During a neutral baseline condition, subjects fixated on a central cross. For the two activation conditions, subjects also maintained fixation on a central cross while single-words were delivered binaurally over headphones. In the Word Repetition condition, subjects repeated each word presented over the headphones. In the "Sound Deletion" task, subjects were asked to repeat the word after deleting the initial sound (e.g., in response to the stimulus "cat," the response would be "at"). In this way, the stimuli and subject response were similar in terms of sensorimotor demands, but the Sound Deletion task stressed phonological processing more than the Word Repetition task. Using a "box-car" fMRI design, the two conditions were alternated and fixation periods were interleaved between the two task conditions (to provide a rest period). Subjects remained cognizant of the two alternating experiment conditions by observing the state of the crosshair: "+" was an indication of the Word Repetition condition and "x" the Sound Deletion condition. The single syllable words for both conditions were matched for word frequency. The subjects' spoken responses were recorded via an adapted microphone and then scored for accuracy. An interleaved acquisition technique was used to reduce interference from auditory noise produced by the scanner and motion artifact associated with speaking in the scanner (Eden et al., 1999; Talavage et al., 1999) by taking advantage of the 2–8 s hemodynamic delay (Buckner et al. 1996; Bandettini et al., 1992). Words were presented (and responses made by the subjects) during silent periods lasting 9 s; whole-brain volumes were acquired during the ensuing 4 s time periods. Each of the experimental tasks (Word Repetition or Sound Deletion) occurred in an epoch lasting 65 s, and the baseline fixation task lasted 26 s. A functional run consisted of four epochs of word repetition, four epochs of Sound Deletion, and eight epochs of fixation, making the total run time 13 min.

fMRI data were acquired using an echo planar imaging (EPI) sequence on a 1.5 Tesla Siemens Vision MRI System (TE = 40 ms, TR = 13 s, 64 × 64 matrix, 48 ascending slices of 3.0 mm thickness, 0.6 mm skip, yielding 3.6mm cubic voxels). A separate high-resolution T1-weighted MPRAGE volume was acquired to aid anatomical localization of the functional data. For all functional runs, head motion detection and correction, volume intensity normalization, spatial filtering, spatial normalization to an EPI template (Montreal Neurological Institute reference brain within Statistical Parametric Mapping (SPM), Wellcome Department of Cognitive Neurology, London), and conversion into space defined by the Talairach atlas were per-

formed using MEDx (Sensor Systems, Sterling, VA). Subject-specific effects were estimated using a fixed-effects model for the contrast of interest (Sound Deletion versus Word Repetition). These estimates were then entered into a second-level between-group analysis (controls versus dyslexics), treating groups as a random effect and using a two-sample unpaired t test at each voxel. The resulting probability map was converted to a Z score map. Next, to identify the task-related signal increases observed in the comparison of the two dyslexic groups following the intervention period, the estimates from the first-level analysis (Sound Deletion versus Word Repetition) were entered into an analysis of variance (ANOVA) to investigate the effect of Group $\times$ Session interactions. For all results, we list areas that achieve significance corresponding to a Z score of at least 3.10 ($p < 0.001$, uncorrected) for clusters of at least 80 contiguous 2 mm cubic voxels surviving this critical threshold, thereby reducing the probability of family-wise type I error. These maxima are displayed in bold in Figures 1 and 3. For the ANOVA Group $\times$ Session interaction, Figure 3 also indicates which maxima are significant at $p < 0.05$, corrected for multiple comparison (indicated by *). It also includes those maxima that fell short of conventional significance, as this allowed us to explore if there were subthreshold changes in the inferior frontal cortex following intervention.

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