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Neural correlates of rapid auditory processing are disrupted in children with developmental dyslexia and ameliorated with training: An fMRI study

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Abstract. *Purpose:* Developmental dyslexia, characterized by unexpected difficulty in reading, may involve a fundamental deficit in processing rapid acoustic stimuli. Using functional magnetic resonance imaging (fMRI) we previously reported that adults with developmental dyslexia have a disruption in neural response to rapid acoustic stimuli in left prefrontal cortex. Here we examined the neural correlates of rapid auditory processing in children.
Methods: Whole-brain fMRI was performed on twenty-two children with developmental dyslexia and twenty-three typical-reading children while they listened to nonlinguistic acoustic stimuli, with either rapid or slow transitions, designed to mimic the spectro-temporal structure of consonant-vowel-consonant speech syllables.
Results: Typical-reading children showed activation for rapid compared to slow transitions in left prefrontal cortex. Children with developmental dyslexia did not show any differential response in these regions to rapid versus slow transitions. After eight weeks of remediation focused primarily on rapid auditory processing, phonological and linguistic training the children with developmental dyslexia showed significant improvements in language and reading skills, and exhibited activation for rapid relative to slow transitions in left prefrontal cortex.
Conclusion: The presence of a disruption in the neural response to rapid stimuli in children with developmental dyslexia prior to remediation, coupled with significant improvement in language and reading scores and increased brain activation after remediation, gives further support to the importance of rapid auditory processing in reading development and disorders.

Keywords: Developmental dyslexia, fMRI, rapid auditory processing, remediation, training, children

1. Introduction

Developmental dyslexia, which may affect 5–17% of children, is a specific learning disability characterized by difficulties with accurate and/or fluent word recognition, poor spelling, and poor decoding performance. The difficulty in reading is disproportionate relative to other cognitive abilities (e.g., IQ), and can-

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not be explained by poor vision or hearing deficits, or lack of adequate motivation and educational opportunities. There is a developing consensus that developmental dyslexia typically results from a deficit in the phonological processing of language (e.g., Bradley & Bryant, 1978; Brady & Shankweiler, 1991; Snowling, 1981; Vellutino, 1979). Learning to read an alphabetic language requires mastering grapheme-phoneme correspondences (i.e., mapping the sounds of auditory language to the letters of the written language system). Individuals with developmental dyslexia appear to have a weak representation of the sounds of language, and this in turn makes it difficult to relate those sounds to written letters.

There is considerable evidence that there are neurological abnormalities in dyslexia (Shaywitz, 1998). Imaging studies of people with dyslexia have found abnormalities in gray and white matter brain structures (e.g., Beaulieu et al., 2005; Deutsch et al., 2005; Hoeft, 2007; Jancke, Siegenthaler, Preis, & Steinmetz, in press; Klingberg et al., 2000). Numerous functional neuroimaging studies using different tasks that require phonological processing have found reduced activation in temporoparietal regions in groups with developmental dyslexia compared to typical-reading groups (Temple, 2002). However, these studies almost exclusively employed visual stimuli for testing phonological processing in developmental dyslexia.

Although considerable research supports the hypothesis that the underlying core deficit of developmental dyslexia is a phonological processing deficit, the precise etiology of this deficit remains the focus of intense research. One hypothesis suggests that developmental dyslexia may be caused by a deficit in specific brain circuitry that processes rapidly changing auditory information (Miller, Delaney, & Tallal, 1995; Tallal, 2004; Tallal & Gaab, 2006). This “auditory temporal processing deficit hypothesis” suggests that processing of oral language can be impaired due to the inability to process the rapid spectro-temporal characteristics of phonemes or sounds. This in turn is posited to disrupt essential components of language learning, beginning with the acquisition of phonological representations which has been shown to be one of the key elements necessary for learning to read.

Many studies have shown that children with developmental dyslexia are significantly impaired in their ability to discriminate, sequence, or remember brief, acoustic stimuli differing in frequency when they are presented sequentially with very short inter-stimulus intervals. Similarly, these individuals have difficulties discriminating between consonant-vowel pairs (e.g., ba/da) that mainly differ intrasyllabically within the first 40 ms of the syllable, but not between syllables incorporating longer duration intrasyllabic acoustic differences (Breier et al., 2001; Reed, 1989; Steffens, Eilers, Gross-Glenn, & Jallad, 1992; Tallal, 1980; Tallal & Piercy, 1974; Tallal & Stark, 1981). However, other studies failed to find a rapid auditory temporal processing deficit in developmental dyslexia (e.g., Chiappe, Stringer, & Siegel, 2002; Mody, Studdert-Kennedy, & Brady, 1997; White et al., 2006). This discrepancy across studies has been attributed to differences in severity of deficit and developmental age of subjects as well as stimulus and methodological differences. However, this remains an active area of research inquiry (see Tallal & Gaab, 2006 for review).

To our knowledge, only one fMRI study has examined specifically the “auditory temporal processing deficit hypothesis” in subjects with developmental dyslexia. Temple et al. (2000) employed non-linguistic stimuli designed to mimic the spectro-temporal structure that characterizes consonant-vowel-consonant speech syllables and words. These non-speech analogue stimuli were synthesized with either very rapid (40 ms) or slowed (200 ms) frequency transitions at the beginning and end of a 600 ms stimulus (modeled after Belin et al., 1998). A high or low fundamental frequency was added to these stimuli for the purpose of allowing them to be categorized according to pitch. Blocks incorporating rapid or slow transitions were presented, and subjects were instructed to indicate whenever they detected a high pitched sound. Adult typical-readers showed left prefrontal activation in response to the stimuli with rapidly changing, relative to slowly changing, frequency transitions. Adults with developmental dyslexia showed no differential left frontal response for rapid relative to slow transitions. This finding supports the idea that dyslexia includes dysfunction of the brain circuit that processes rapidly changing non-linguistic auditory percepts.

Three adults with developmental dyslexia participated in a remediation program which specifically targets rapid auditory temporal processing and oral language deficits. After training, two adults improved substantially in their language abilities as well as their ability to process rapidly changing auditory stimuli. These two also showed increased activation in left prefrontal cortex for rapidly changing relative to slowly changing frequency transitions. These fMRI results identify left prefrontal regions as normally being sensitive to rapid relative to slowly changing acoustic stimulation, insensitive to the difference between such stimuli in adults with developmental dyslexia, and plastic enough in adulthood to develop such differential sensitivity after intensive training.

The question whether remediation-induced functional plasticity can also be observed in children with developmental dyslexia was the aim of another study which employed the same remediation program (Fast ForWord-Language®), but aimed at assessing the neural correlates of phonological processing (Temple et al., 2003). Before training, the children with developmental dyslexia exhibited an absence of the left temporo-parietal activation and a displacement of the left prefrontal activation exhibited by typical-reading children performing a phonological task (Temple et al., 2001). After training, the twenty children with developmental dyslexia had significantly improved oral language and reading performance. Also after training, the children with developmental dyslexia showed increased activations in the left temporo-parietal and left prefrontal regions during phonological task performance, bringing brain activation in these regions closer to that seen in typical-reading children. Additionally, children with developmental dyslexia showed a correlation between the magnitude of increased activation in left temporo-parietal cortex and improvement in oral language ability. Thus, language-processing and reading abilities were improved after intensive acoustic training, and the improvement in language skills were significantly correlated with increased activation in regions associated with phonological processing. Furthermore, this study was the first to show the potential value of fMRI as an independent method for evaluating, at the metabolic level, the efficacy of behavioral intervention programs in children. Following this study, a similar finding was reported that demonstrated increased activation in children with developmental dyslexia following a phonologically based remediation in left hemisphere posterior language regions and left inferior frontal gyrus, using an auditory-visual cross-modal phonological task (Shaywitz et al., 2004).

To date, only a few studies on the neural correlates of developmental dyslexia have employed auditory stimulation. Most of these studies used verbal stimuli such as listening to words and deciding whether they have a certain numbers of letters (Wood, Flowers, Buchsbaum, & Tallal, 1991), detecting syllable oddballs in the presence of “cocktail party speech” background noise (Hagman et al., 1992), word and pseudo-word rhyme detection (Corina et al., 2001; Rumsey et al., 1992), matching and conflicting audiovisual speech (Pekkola et al., 2006), and word and pseudoword repetition (McCrory, Frith, Brunswick, & Price, 2000).

To our knowledge, no fMRI study has explored the neural correlates of rapid spectro-temporal auditory processing in children with developmental dyslexia. This is of particular importance in terms of the hypothesized theoretical links among rapid auditory processing, speech perception, and reading. In order to explore this question, whole-brain fMRI was performed on twenty-two children with developmental dyslexia and twenty-three typical-reading children while listening to non-linguistic stimuli which included either rapid or slowed frequency transitions (Belin et al., 1998; Temple et al., 2000). In addition, the children with developmental dyslexia underwent an intensive intervention program (Fast ForWord Language®) that focused on rapid auditory processing within the context of both non-linguistic as well as linguistic training and then participated in a post-intervention fMRI examination.

Because the ability to distinguish certain phonemes depends on the ability to process frequency changes occurring very rapidly, we hypothesized a link between rapid spectro-temporal auditory processing and reading ability. As such, we predicted that the typical-readers would have already developed the necessary neural network involved in the processing of rapid auditory stimuli and that disruption of this neural response to rapid auditory stimuli would be seen in children with developmental dyslexia. In addition, we hypothesized that at least partial amelioration of the neural correlates to rapid spectro-temporal auditory stimuli would be seen following intervention.

2. Methods

2.1. Subjects

Twenty-two children with developmental dyslexia (mean age 10.5 (1.9)) and twenty-three typical-reading children participated in this study. All subjects were physically healthy and had no history of neurological diseases, head injury, or psychiatric disorder (including ADHD). All children were English monolinguals. Informed consent to take part in the study, approved by the Stanford University panel on Human Subjects in Medical research, was obtained from each subject and their parents prior to the experiment.

Groups were matched according to age, education, gender, handedness (Annet, 1970) and estimated non-verbal IQ (Block Design subtest from the Wechsler In-

Table 1
Subject characteristics and language/reading measures before remediation

Variable	Children with Developmental Dyslexia	Typical-Reading Children	Significance
Sample size	N = 22	N = 23	ns
Age (years)	10.8 (0.9)	10.5 (1.9)	ns
Education (grade)	5.1 (0.8)	4.8 (1.5)	ns
Handedness (# left)	3/22	4/23	ns
Gender (# female)	6/22	3/23	ns
Non-verbal IQ (WISC-III Block Design)	11.6 (3.4)	13.4 (3.6)	ns
Word reading (WJRMT-R ID)	77.4 (9.2)	108.7 (6.9)	$p < 0.00001$
Non-word decoding (WJRMT-R WA)	86.2 (12.1)	110.3 (7.3)	$p < 0.00001$
Passage comprehension (WJRMT- PC)	85.6 (10.3)	110.8 (6.6)	$p < 0.00001$
Listening comprehension (WJ-R LC)	109.5 (15.2) (n = 21)*	123.0 (14.4)	$p < 0.005$
Receptive language (CELF-3 REC)	94.5 (12.3)	118. 5 (13.6)	$p < 0.00001$
Expressive language (CELF-3 EXP)	95.0 (16.3)	111.9 (12.4)	$p < 0.0005$
Total language (CELF-3 TOT)	94.0 (14.1)	115.5 (13.4)	$p < 0.00001$
Phonological awareness (CTOPP PA)	94.2 (8.5) (n = 18)*	102.2 (9.2)	$p < 0.01$
Phonological memory (CTOPP PM)	93.3 (13.2) (n = 18)*	102.6 (12.2)	$p < 0.05$
Rapid naming (CTOPP RN)	81.8 (9.5) (n = 18)*	106.5 (9.9)	$p < 0.00001$
Alt phonological awareness (CTOPP PA2)	97.3 (7.8) (n = 18)*	103.8 (8.6)	$p < 0.05$
Alternate rapid naming (CTOPP RN2)	79.6 (14.9) (n = 17)*	98.7 (14.3)	$p < 0.0005$

All significant difference statistics are reported for 2-tailed statistic.
*Some of the children were not tested with this measurement.

telligence Scale for Children-III). The children with developmental dyslexia had a documented history of reading difficulty and were included in the developmental dyslexia group if their age-adjusted score on the Woodcock-Johnson Reading Mastery Test-Revised (AGS, Inc., Circle Pines, MN), Word Attack or Word Identification subtest was less than 85 (standard score = 100, SD = 15, Table 1). Fifteen children met the more stringent criteria of less than 85 on both subtests. Two children met a less strict criteria and scored less than 90 on one subtest, but had a score less than 85 on the Gray Oral Reading Test-3 (PRO-Ed, Inc, Austin TX) and/or the Phonological Awareness subtests of the Comprehensive Test of Phonological Processing (PRO-Ed, Inc, Austin, TX).

2.2. *Study design*

All twenty-two children with developmental dyslexia completed a battery of standardized language, phonological awareness and reading tests, were scanned once prior to the remediation, participated in the remediation program, and returned for subsequent behavioral testing and fMRI scanning using the same test battery. Twenty-three typical-reading children completed the behavioral test battery and were scanned once and twelve of these children returned after 8 weeks for, retesting on the behavioral battery and a second scan (3 female, average age = 10.0 years).

2.3. *Behavioral measures*

Subjects underwent a battery of behavioral tests including the Block Design subtest, a measure of non-verbal IQ (Wechsler Intelligence Scale for Children-III), the Woodcock-Johnson Reading Mastery Test-Revised (WJRMT-R) including the Word Identification (ID), Word Attack (WA), and Passage Comprehension (PC) subtests; The Listening Comprehension (LC) subtest from the Woodcock-Johnson-Revised (WJ-R) Tests of Achievement (Riverside Publishing, Rolling Meadows, IL); the Comprehensive Test of Phonological Processing (CTOPP) (Pro-Ed, Inc, Austin, TX) including the subtests that comprise the Phonological Awareness (PA), Phonological Memory (PM), Rapid Naming (RN), Alternate Phonological Awareness (PA2) and Alternate Rapid Naming (RN2) composite scores; and the Clinical Evaluation of Language Fundamentals-3 (CELF-3) measures that include the receptive (REC), expressive (EXP), and total (TOT) language composite scores. Two sample t-tests were performed to determine differences between typical-reading and children with developmental dyslexia in these measures as well as subject characteristics of age, education and non-verbal IQ. Chi-square test was performed to assess significant differences between groups in gender and handedness. Paired t-tests were used to assess the effects within individuals with developmental dyslexia of the remediation program or the effects of two month of regular development in the case of the typical-reading children. Additional two sample t-tests were performed to assess differences that remained between children with developmental dyslexia after remediation and typical-reading children (2^{nd} testing session) in language and reading tests. Accuracy on the pitch discrimination task performed during fMRI scanning was measured for both groups. A repeated measures ANOVA was performed to assess main effects and interaction of group (typical-reading children vs. children with developmental dyslexia) and stimulus type (rapid vs. slowed frequency transitions).

2.4. *Task and stimuli*

Stimuli and task have been reported previously (Temple et al., 2000) and are described here briefly. Stimuli were non-linguistic with a spectro-temporal structure similar to that of consonant-vowel-consonant speech syllables, with either very rapid or slowed frequency transitions at the beginning and end of a 600 ms stimulus. The stimuli incorporating rapid transitions had frequency changes occurring over 40 ms surrounding a 520 ms steady state period, while the stimuli incorporating slowed transitions extended the duration of the frequency transitions to occur over 200 ms, with a commensurate reduction in the steady state period. In addition, stimuli incorporating both rapid and slowed transitions included both high (250 Hz F0) and low (125 Hz F0) pitched stimuli. Subjects were instructed to press a button for high pitched stimuli. Sounds lasting 600 ms were presented every 2850 ms in 6 blocks of each type with 10 items per block (counterbalanced across subjects), for a total scan length of 5 min, 42 sec. In each block, half the stimuli were high pitched with a pseudo random ordering. Subjects were exposed to the stimuli outside and inside the scanner environment prior to the experiment.

2.5. *Remediation*

Children with developmental dyslexia underwent remediation using Fast ForWord Language® (Scientific Learning Corporation, Oakland, CA). Four children used the program at home, and 18 used the program at their school. All parents and /or educators were trained by representatives of Scientific Learning Corporation. Fast ForWord Language® is an interactive, adaptive, computer-based training program with 7 modules which focus on rapid auditory processing and oral language skills, including phoneme discrimination and sentence comprehension. The program consisted of 5, 20-minute training sessions per day, 5 days a week, for 8 weeks. This version of Fast ForWord Language® did not contain any orthographic stimuli. For more information on the details of the Fast ForWord Language® training program see (Tallal, 2004).

2.6. *Functional MRI acquisition*

Whole-brain imaging data were acquired on a 3T Signa LX (GE Medical Systems) using T2*-sensitive gradients echo spiral pulse sequence (Glover & Lai, 1998) (one interleave; TE = 30 ms; TR = 2.85 s; flip angle = 90; field of view = 24 cm; 64X64; 180 temporal frames; 18 axial slices (6 mm)), 7^{th} slice at AC-PC. T1-weighted and 3D-SPGR anatomical images were also acquired. Subjects' heads were immobilized using C-spine immobilization tools (HeadBed II, Cervical Immobilization device, Laerdal Medical Corp., Wappingers Falls, NY) and a chin strap.

Clustered volume acquisitions (CVA) was used for the functional scans to maximize the children's ability to hear the stimuli and to ensure maximal auditory cortical signal during stimuli (Edmister, Talavage, Ledden, & Weisskoff, 1999; Gaab, Gabrieli, & Glover, 2006). CVA is characterized by the acquisition of all slices in rapid succession at the end of one TR. This technique allows for auditory stimulus presentation during a brief period free from scanner background noise. All 18 slices were acquired in approximately 1.5 sec, followed by approximately 1.35 sec of silence. Stimuli were presented in the middle of this 1.35 s quiet period.

2.7. *Functional MRI analysis*

Images were motion corrected using AIR 3.0 (http://bishopw.loni.ucla.edu/AIR3/). Root mean-squared motion was estimated across all three directions and all time points. All subjects had less than 0.5 mm estimated motion and there was no difference in motion estimates between groups. Additional preprocessing and analysis was done using SPM99 (Wellcome Department of Cognitive Neurology, London, UK).

First, single subject fixed-effects analysis were performed in which data were best fitted at every voxel using a linear combination of the effects of interest on non-normalized data, using a high pass filter of 108 s, a low pass hrf filter, and global scaling. Images were smoothed using an 8 mm full width at half maximum Gaussian kernel. Each subject's analysis resulted in contrast images for rapid vs. slowed frequency transition comparisons.

Table 2
Training effects in children with developmental dyslexia and test-retest effects in typical-reading children

	Children with Developmental Dyslexia			Typical-Reading Children		
	Before remediation	After remediation	Sig.	1^{st} scan (n = 12)	2^{nd} scan (n = 12)	Sig.
Subjects	22 (6 F))	22 (6 F))	–	12 (3F)	12 (3 F)	–
Word reading (WJRMT-R ID)	77.4 (9.7)	87.0 (6.9)	$p < 0.0001$	108.8 (6.7)	107.7 (8.1)	$p > 0.1$
Non-word decoding (WJRMT-R WA)	86.2 (6.1)	95.5 (7.3)	$p < 0.00005$	110.6 (8.7)	108.7 (8.3)	$p > 0.1$
Passage comprehension (WJRMT-R PC)	85.6 (10.3)	89.7 (8.2)	$p < 0.005$	112.8 (4.5)	109.6 (6.5)	$p < 0.03$
Listening comprehension (WJ-R LC)	109.5 (15.2) (n = 21)*	118.6 (16.4) (n = 21)*	$p < 0.005$	120.1 (11.6)	121.3 (10.9)	$p > 0.1$
Receptive language (CELF-3 REC)	94.5 (12.3)	103 (14.5)	$p < 0.005$	118.9 (7.9)	124. 1 (9.7)	p = 0.08
Expressive language (CELF-3 EXP)	95.0 (14.4)	102.7 (16.9)	$p < 0.005$	111.9 (8.8)	114.4 (12.5)	$p > 0.1$
Total language (CELF-3 TOT)	94.0 (14.1)	102.5 (15.4)	$p < 0.0005$	115.8 (8.4)	119.8 (10.3)	$p > 0.1$
Phonological awareness (CTOPP PA)	94.2 (8.4) (n = 18)*	101.2 (13.3) (n = 18)*	$p < 0.01$	103.25 (9.3)	107 (11.2)	p = 0.06
Phonological memory (CTOPP PM)	93.3 (13.15) (n = 18)*	100.8 (15.2) (n = 18)*	$p < 0.005$	100.3 (10.3)	102.8 (12.5)	$p > 0.1$
Rapid naming (CTOPP RN)	81.8 (9.5) (n = 18)*	86.4 (10.6) (n = 18)*	$p < 0.005$	106 (6.8)	104 (11.5)	$p > 0.1$
Alternate phonological awareness (CTOPP PA2)	97.3 (7.76) (n = 18)*	104.3 (9.5) (n = 18)*	$p < 0.01$	105.8 (7.5)	104 (10.3)	$p > 0.1$
Alternate rapid naming (CTOPP RN2)	79.6 (14.9) (n = 17)*	84.3 (12.3) (n = 17)*	n.s. p = 0.2	97.3 (18.2)	96.8 (20.1)	$p > 0.1$

All significant difference statistics are reported for 2-tailed statistic.
*Some of the children were not tested with this measurement.

Secondly, a group analysis was performed using a random effects model with contrast images normalized to the MNI305 stereotaxic space using tri-linear interpolation utilizing parameters from anatomical normalization. One sample t-tests were conducted to look for differences between rapid and slowed frequency transitions within each group.

In looking for differences between groups, a mask was created using the rapid vs. slow frequency transition contrast for the typical-readers (threshold: $p <$ 0.025). Two sample t-tests were conducted to compare the differences between the groups prior to the remediation of the children with developmental dyslexia. Furthermore, paired t-tests were employed to examine effects of training within the developmental dyslexia group as well as effects of two months of normal development in the typical-reading children. Statistical threshold was set at $p <$ 0.01, with a 20 voxel extent. No global scaling, global calculation, or grand mean scaling was performed in the group analysis. Small volume correction as implemented in SPM99 was done in the area in which we had an a-priori hypothesis. A search was performed in a spherical volume centered on the maximum focus of activity observed in previously reported normal reading adults (sphere with 15 mm radius centered at $x = -28,\ y = 38,\ z = 28$, (Temple et al., 2000)).

3. Results

3.1. Behavioral results for rapid auditory processing

Behavioral performance on the pitch discrimination task was recorded during the 1^{st} and 2^{nd} scans. For the 1^{st} scan behavioral performance was acquired for all typical-reading and 17 children with developmental dyslexia (data from five children with developmental dyslexia was lost due to equipment failure). Typical-reading children had an accuracy in pitch judgments of 88.4 (± 2.4) %, for the rapid frequency transitions and 89.5 (± 2.4) % for the slow frequency transitions. Children with developmental dyslexia had an accuracy in pitch judgments of 81.2 (± 2.7) % for the rapid and 82.6 (± 2.8) % for the slow frequency transitions. An ANOVA with a between-subject factor of group (typical-reading children /children with developmental dyslexia) and a within-subject factor of stimulus type (rapid/slow transitions) revealed that the typical-reading group was more accurate than the developmental dyslexia group [$F(1,38) = 4.05,\ p = 0.051$], but that there was no effect of stimulus type [$F(1,38) = 1.70,\ p = 0.20$] and, critically, no interaction between group and stimulus, [$F(1,38) = 0.02,\ p = 0.87$], indicating that the children with developmental dyslexia were not disproportionably less accurate for either stimulus type. No significant differences between time 1 and time 2 were seen in either group on the pitch discrimination task performed during scanning.

Table 3
Reading and language measures after remediation. Remaining differences in Language/Reading measures between children with developmental dyslexia and typical-reading children after remediation in the children with developmental dyslexia

Language and reading measure	Significance of difference between readers with developmental dyslexia post remediation and typical-readers at 2$^{\text{nd}}$ test
Word reading (WJRMT-R ID)	$p < 0.0001$
Non-word decoding (WJRMT-R WA)	$p < 0.0001$
Passage comprehension (WJRMT-R PC)	$p < 0.0001$
Listening comprehension (WJ-R LC)	$p = 0.62$
Receptive language (CELF-3 REC)	$p < 0.0001$
Expressive language (CELF-3 EXP)	$p < 0.05$
Total language (CELF-3 TOT)	$p < 0.05$
Phonological awareness (CTOPP PA)*	$p = 0.22$
Phonological memory (CTOPP PM)*	$p = 0.72$
Rapid naming (CTOPP RN)*	$p < 0.0005$
Alternate phonological awareness (CTOPP PA2)*	$p = 0.92$
Alternate rapid naming (CTOPP RN2)*	$p < 0.05$

All significant difference statistics are reported for 2-tailed statistic.
In all cases where a significant difference remains between typical-readers and children with developmental dyslexia, the typical-readers continue to have a higher score than the children with developmental dyslexia.
*Some of the children with developmental dyslexia were not tested with this measurement (see Table 2 for subject numbers).

3.2. Language and reading measures (*Table 1 and Fig. 1A*)

Before remediation, significant differences were seen between children with developmental dyslexia and typical-reading children on all language and reading measures given.

3.3. Behavioral effects of remediation (*Tables 2 and 3, and Fig. 1B and C*)

The children with developmental dyslexia showed significant improvements on all but one (CTOPP RN2) of the language and reading measures administered following remediation. In addition, in all but one (CTOPP RN2) of the measures on which the children with developmental dyslexia were initially performing more than one standard deviation below the normal mean, after remediation they performed within one standard deviation of the normal mean (WJRMT-R Word ID, Word Attack, Passage Comprehension, and CTOPP RN). The typical-reading children who underwent a second fMRI scan and second behavioral evaluation ($N = 12$), but did not undergo any remediation, did not show significant improvement in any of the reading or language measures over this two month period.

To assess whether the significant improvement in reading and language for the children with developmental dyslexia after remediation was large enough that they were no longer different from the typical-readers, a comparison was made between post remediation language/reading scores in the children with developmental dyslexia and the language/reading scores for the typically reading children (2$^{\text{nd}}$ session) (Table 3 and Fig. 1C). This analysis showed that despite significant improvement after remediation, for many of the measures there was still a significant difference between children with developmental dyslexia and typically reading children. However, for the two phonological awareness composites of the CTOPP (PA and PA2), the phonological memory subtest of the CTTOP (PM) and the listening comprehension subtest of the WJ-R, this analysis revealed that after remediation the children with developmental dyslexia were no longer significantly different from the typical-reading children (Table 3 and Fig. 1C).

3.4. FMRI results

3.4.1. Rapid auditory processing in typical-reading children (*1$^{\text{st}}$ scan*) ($N = 23$)

A number of regions showed increased activation in typical-reading children for the rapid as compared to

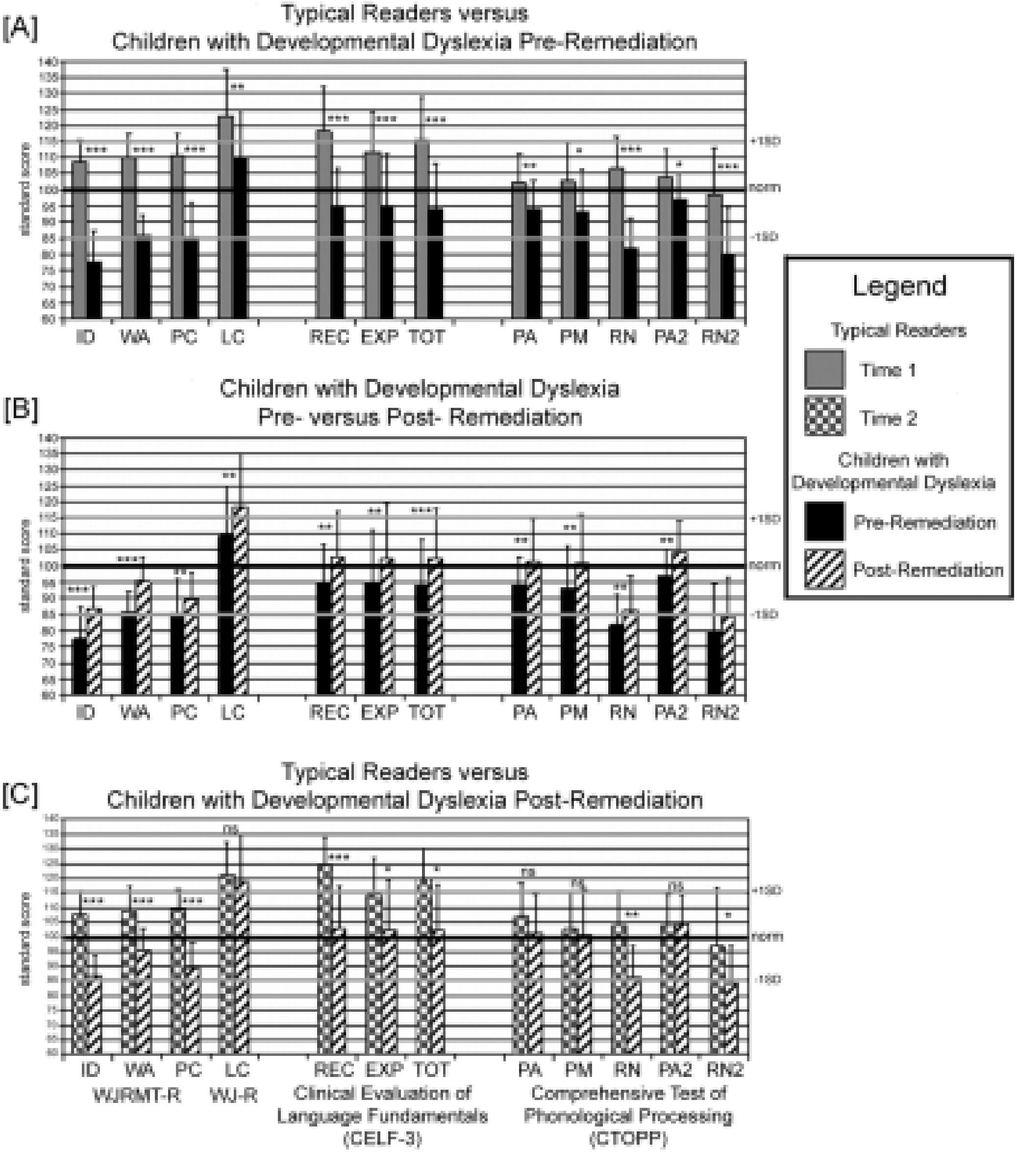

Fig. 1. Language and reading measures. Language and reading measures are shown for typical-reading children and children with developmental dyslexia. Standard score is shown on the y-axis; the solid black horizontal line indicates the norm of 100 and the gray lines indicate 1 standard deviation above and below the norm. Mean results are shown (error bars represent standard deviation) for the Word Identification (ID), Word Attack (WA), and Passage Comprehension (PC) subtests of Woodcock-Johnson Reading Mastery Test-Revised (WJRMT-R); the Listening Comprehension (LC) subtest of the Woodcock-Johnson-Revised Test of Achievement (WJ-R); receptive (REC), expressive (EXP), and total (TOT) language composites from the Clinical Evaluation of Language Fundamentals-III (CELF-3); and the phonological awareness (PA), phonological memory (PM), rapid naming (RN), alternate phonological awareness (PA2), and alternate rapid naming (RN2) composites of the Comprehensive Test of Phonological Processing (CTOPP). [A] Typical-readers and children with developmental dyslexia are shown before remediation of the children with developmental dyslexia. A significant difference was seen between typical-reading children and children with developmental dyslexia on all language and reading measures. [B] Children with developmental dyslexia before and after remediation are shown. After the children with developmental dyslexia underwent remediation, they showed significant improvement on all measures with the exception of RN2 of the CTOPP. As expected, typical-reading children showed no significant improvement at second test (see Table 1). [C] Typical-readers at time 2 and children with developmental dyslexia after remediation are shown. For many measures of language and reading, a significant difference persisted between the typical readers and the children with developmental dyslexia after they had undergone remediation. However, for measures of listening comprehension, phonological awareness, alternate phonological awareness, and phonological memory no significant differences remained between groups after remediation of the children with developmental dyslexia. $^{***}p < 0.001$, $^{**}p < 0.01$, $^{*}p < 0.05$.

Table 4
Table of activations for rapid as compared to slow stimuli for typical-reading children and children with developmental dyslexia

Region	Brodmann Area	x	y	z	Z	p (unc)	Vol (mm^3)
Rapid Stimuli Versus Slowed Stimuli Typical-reading Children (**N = 23**)							
Frontal Lobe							
*R Insula / Inferior Frontal	45	53	3	4	3.87	0.000	5.53
L Inferior Frontal / Operculum	47	−40	32	2	2.85	0.002	0.45
#L Middle / Superior Frontal	10	−22	56	12	2.70	0.003	0.37
R Anterior Cingulate / Medial frontal	32	5	47	−5	2.98	0.001	0.16
R Anterior Cingulate	24	15	−28	13	2.65	0.004	0.19
Temporal Lobe							
R Middle Temporal	21	51	−45	−4	2.69	0.004	0.07
Parietal Lobe							
*L Cingulate	23	−10	−52	22	3.31	0.000	4.58
R Cingulate	29	3	−49	8	2.65	0.004	0.42
R Postcentral Sulcus	4	29	−29	51	3.08	0.001	1.15
R Precentral Gyrus	4/6	40	−1	44	2.58	0.005	0.08
Subcortical							
Left Thalamus (Pulvinar)		−12	−34	9	2.74	0.003	0.18
Children with Developmental Dyslexia (**N = 22**)							
Temporal Lobe							
L Middle Temporal	21/37	−63	−65	6	2.74	0.003	0.02
Group Difference (**typical-reading children > children with developmental dyslexia**) ($p < 0.0001$)							
Frontal Lobe							
*L Superior Frontal	10	−16	57	16	3.95	0.000	0.43
*L Inferior Frontal / Operculum	47	−39	29	0	3.43	0.000	0.14
*R Frontal Insula / Lateral Sulcus	45	53	−2	4	3.98	0.000	2.07
*R Frontal Insula	47	36	16	−6	3.41	0.000	0.37
Parietal Lobe							
*Bilateral Cingulate	23	−2	−34	41	4.52	0.000	6.04
*L Parieto-Occipital Sulcus		−19	−54	14	3.50	0.000	0.43
L Cingulate	23	2	−31	25	3.49	0.000	0.07
*R Inferior Parietal Sulcus		29	−35	45	3.33	0.000	0.28
Subcortical							
Left Thalamus (Pulvinar)		−15	−35	9	3.17	0.001	0.02

*Shows a significant cluster threshold of $p < 0.05$.
#Shows a significant cluster threshold of $p < 0.05$ using small volume correction (see text).

the slow frequency transitions (Table 4 and Fig. 2A). Among those regions with increased response to the rapid stimuli was a region in left prefrontal cortex, extending across the left middle and superior frontal gyri (Brodmann area 10: $x = -22$, $y = 56$, $z = 12$). Given our a-priori hypothesis that a neural response to rapid auditory stimuli would be similar in adults and children, we performed a small volume correction and searched a volume centered on the maximum focus of activation observed in previously reported typical-reading adults. We found two foci with maxima located within this sphere at $x = -35$, $y = 31$, $z = 17$ and $x = -24$, $y = 41$, $z = 17$, with corrected p-values of $p < 0.0001$. Although the adults studied previously with these stimuli showed no other significant response to the rapid stimuli (Temple et al., 2000), the children in this study showed a number of additional brain areas sensitive to the rapid as compared to slowed stimuli. Other brain areas included a right anterior peri-sylvian region straddling the right insula, inferior frontal gyrus, and lateral sulcus, bilateral anterior cingulate, right postcentral sulcus, left inferior frontal gyrus/operculum, and left pulvinar nucleus of the thalamus.

3.4.2. *Rapid auditory processing in children with developmental dyslexia*

Only one small region in left middle temporal gyrus (BA 21/37: $x = -63$, $y = -65$, $z = 6$) showed more activation for rapid versus slow frequency transitions (Table 4 and Fig. 2B). Using the same small volume correction described above (15 mm sphere centered at the location responsive to rapid stimuli in adult typical-readers), no significant activation were seen in this area. To assure that the lack of significant activation for this comparison in this group was not due to thresholding, a very liberal threshold of $p < 0.1$ with no spatial extent restriction was used. Even with these criteria,

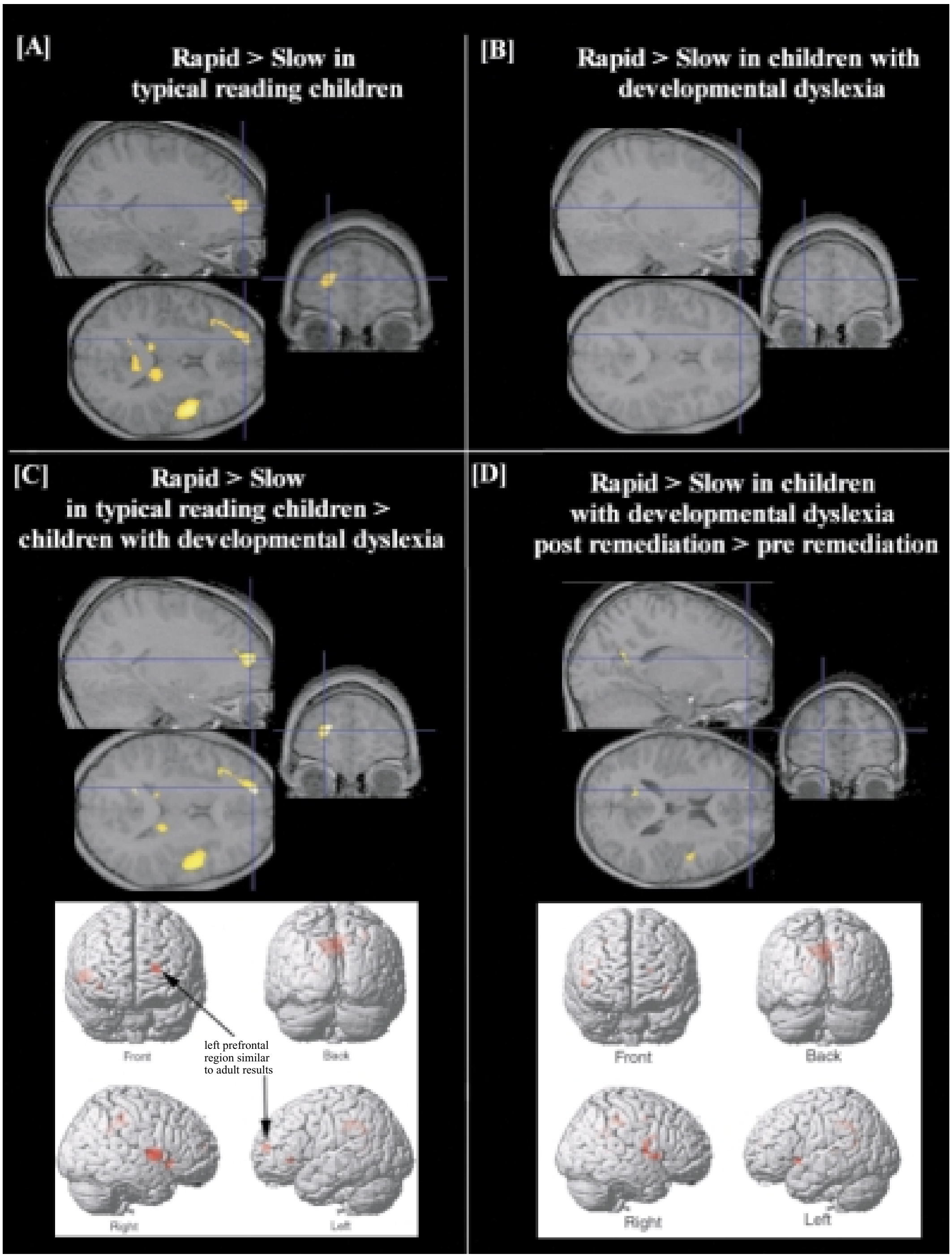

Fig. 2. Brain activation. Brain activation is shown for rapid relative to slow frequency transitions in [A] typical-reading children and [B] children with developmental dyslexia. Slices are centered at MNI coordinates −22, 56, 12. Panel [C] shows increased activations for rapid relative to slow frequency transitions in typical-reading children compared to children with developmental dyslexia as illustrated on sections centered at MNI coordinates −16, 57, 16 (above) and renderings (below). Panel [D] shows increased activation for the rapid relative to slow frequency transitions for post compared to pre remediation in children with developmental dyslexia illustrated on sections centered at MNI coordinates −18, 51, 17 (above) and renderings (below).

Table 5
Table of activations showing increases in activity after training for rapid as compared to slow stimuli

Region	Brodmann Area	x	y	z	Z	p (unc)	Vol (mm^3)
Increase in Response to Rapid vs. Slow Stimuli, Post-training as compared to Pre-training, in Regions Sensitive to Rapid Stimuli Normally in Children							
Frontal Lobe							
L Frontal Insula / Operculum	45	−35	10	−6	2.57	0.005	0.27
*R Frontal Insula	6/44	45	−5	10	2.56	0.005	1.19
R Inferior Frontal Sulcus	44	33	7	27	2.52	0.006	0.13
R Middle / Superior Frontal	8	29	−5	43	2.38	0.009	0.08
L Superior Frontal	10	−18	51	17	2.34	0.01	0.04
Parietal Lobe							
R Precuneus	31	21	−57	26	3.18	0.001	0.05
*Bilateral Cingulate	31	7	−32	42	3.10	0.001	4.5
L Parietal-occipital Sulcus		−17	−56	16	2.73	0.003	0.21
Subcortical							
L Thalamus (Pulvinar)		−7	−29	5	3.59	0.000	0.21
R Thalamus (Pulvinar)		9	−32	11	3.21	0.001	0.19
L Thalamus (DM Nucleus)		−1	−21	3	2.66	0.004	0.10

*Shows a significant cluster threshold of $p < 0.05$.

no significant activation for this comparison was seen in left prefrontal cortex.

3.5. Group differences

In order to identify which brain regions showed a significant difference between children with developmental dyslexia and typical-reading children prior to the remediation we compared the two groups directly. Because we were interested in focusing only on brain regions that seemed to be specialized for rapid processing, we restricted our analyses to regions that showed increased activation in the typical-reading children for the rapid vs. slowed frequency transition contrast. To ensure we were not attributing differences to an overly strict and restrictive mask, we used a more liberal threshold of $p < 0.025$ for the mask (extent: 20).

This analysis revealed that nearly all the brain areas that exhibited increased activation for rapid vs. the slow frequency transitions in the typical- reading children also exhibited significantly greater activation in the typical-reading than the children with developmental dyslexia. Consistent with our hypothesis, there was significantly greater activation within the left prefrontal gyrus (Brodman area 10: $x = -16,\ y = 57,\ z = 16$) in typical-reading children compared to children with developmental dyslexia. Additional brain areas that showed greater response to the rapid vs. slow frequency transitions in typical-reading children compared to children with developmental dyslexia included bilateral cingulate gyrus, right frontal insula /lateral sulcus, left parieto-occipital sulcus and left inferior frontal gyrus (Table 4 and Fig. 2C).

3.6. Neural effects of remediation

The paired t-test for the children with developmental dyslexia (post remediation > pre remediation) revealed a number of brain areas that showed increased activation for the rapid versus slowed frequency transitions after remediation compared to before remediation (Table 5 and Fig. 2D). The twelve typical-readers who underwent fMRI a second time did not show any increased activation in the second compared to the first scan. We were interested, specifically, in whether or not the children with developmental dyslexia showed increased activation after remediation in the network of brain areas that were observed in the typical-reading children in response to the rapid > slow frequency transition contrasts. Therefore, the analysis was also performed with the mask including only regions that exhibited greater activation for rapid than slow transitions in the typical-reading group. Several of the regions that showed increased brain response to rapid vs. slow frequency transitions in typical-reading children also showed increased activation following remediation in the children with developmental dyslexia, including bilateral insula, left operculum, right inferior frontal sulcus, left superior frontal regions, right precuneus, cingulate gyrus and bilateral thalamic regions. Consistent with our hypothesis, the left prefrontal region which we previously showed responsivity to the rapid versus slowed stimuli in adults (Temple et al., 2000) and typically reading children, exhibited increased activation in the children with dyslexia after remediation (Table 5 and Fig. 2D).

4. Discussion

This study is the first to reveal a network of brain areas sensitive to the rapidity of non-linguistic auditory stimuli in typical-reading children, and a disrupted response in that network in children with developmental dyslexia. Similar to a previous report with adults (Temple et al., 2000), we found that in typical-reading children, the left prefrontal cortex (astride the middle and superior frontal gyri, BA 10) exhibited activation in response to rapid vs. slow transitions. Children with developmental dyslexia, however, did not exhibit any difference in activation for rapid vs. slow transitions in this left prefrontal region. Additionally, this disrupted response was partially ameliorated through remediation that improved language and reading ability in children with developmental dyslexia.

Two behavioral factors are relevant to interpreting these findings. First, the scanner task did not require children to make temporal judgments about rapid auditory transitions. Rather, children focused on making uncorrelated pitch judgments. Thus, the neural network that responded to rapid auditory stimulation did so incidentally, automatically, and reflexively. Second, activation differences cannot be accounted for by behavioral confounds in either the typical-reading or developmental dyslexia groups. Although the typical-reading group was about 7% more accurate than the developmental dyslexia group for making pitch judgments, both groups were equally accurate in responding to rapid and slow transitions. Therefore, differences in brain responses to rapid and slow transitions, both within and between groups, cannot be ascribed to differences in performance. These findings are consistent with evidence that hypoactivations in developmental dyslexia are often related to developmental dyslexia per se rather than performance differences that arise from developmental dyslexia (Hoeft et al., 2006).

These findings point to the importance of left prefrontal cortex for auditory processing that is important for language and reading. Typical-reading children activated a left prefrontal region (BA 10) straddling the middle and frontal gyri, that was nearly identical to that seen in adults in two studies using the same stimuli (Belin et al., 1998; Temple et al., 2000) and one study which used increasingly compressed auditory sentences (Poldrack et al., 2001). In addition, typical-reading children in this study activated a left inferior prefrontal region (BA 47) during rapid as compared to slow stimuli. Other studies have also implicated left inferior prefrontal cortex as responsive to rapid auditory processing. Increased activation has been shown in left inferior frontal regions for rapid versus slow stimuli in a temporal ordering task (Gaab et al., 2005). Several other studies found increased activation of the left inferior frontal region for rapid versus slow auditory stimuli as well as the perception of voice onset time and temporal sequencing (e.g., Belin et al., 1998; Blumstein, Myers, & Rissman, 2005; Fiez et al., 1995; Gelfand & Bookheimer, 2003; Joanisse & Gati, 2003), suggesting an important role of the left inferior frontal regions in rapid auditory temporal processing and temporal sequencing, both for speech and non-speech acoustic stimuli. Furthermore, it has been suggested that left IFG is specifically engaged by higher-order phonological processing, such as is involved in segmenting the ongoing speech stream into phonemes or syllables (e.g., Burton, 2001; Poldrack et al., 2001) as well as implicit detection of word boundaries (McNealy, Mazziotta, & Dapretto, 2006) or semantic categorization (Noesselt, Shah, & Jancke, 2003). Increased activation within IFG for implicit detection of word boundaries was also positively correlated with rapid auditory processing skills (McNealy et al., 2006). Although these studies are in accord in regards to activation of left prefrontal cortex in response to rapid verbal and non-verbal auditory stimuli, the loci of activations vary across the left prefrontal cortex. Future studies will be needed to specify the different functions of different left prefrontal cortical areas in rapid auditory processing, and how these areas may interact developmentally in learning to comprehend oral language and to read.

Children with developmental dyslexia had a widespread and severe functional disruption of the neural network that was selectively responsive to rapid auditory stimulation in the typical-reading group. Typical-reading children exhibited eleven regions of activation for rapid vs. slow transitions, including left prefrontal cortex, left inferior frontal gyrus (operculum), and right frontal insula. Children with developmental dyslexia failed to exhibit differential activation for rapid vs. slow transitions in any of those regions (although the developmental dyslexia group did exhibit one atypical activation in left temporal cortex). It is as if this neural network in children with developmental dyslexia were functionally “deaf” to the differences between rapid and slow transitions.

The functional brain differences exhibited by the children with developmental dyslexia are noteworthy in that the scanner task did not involve reading or the phonological processing of auditory language. Rather, the stimuli were meaningless, non-verbal sounds that differed only in the rapidity of frequency transitions. Indeed, the children perceived this task as unrelated to reading and language, and several of the dyslexic children expressed relief about performing a task that seemed unrelated to their reading difficulty.

The findings from this fMRI study, of a lack of typical brain response in children with developmental dyslexia to stimuli incorporating rapid vs. slow frequency transitions, is consistent with the "auditory temporal processing deficit hypothesis" (Tallal, 2004) which posits that a deficit in auditory temporal processing compromises the ability to process the rapid spectro-temporal acoustic changes within phonemes that may be differentiated by a few tens of milliseconds of auditory information. This impairment leads to a broader deficit in the phonological processing of oral language, which in turn impairs learning to read. This hypothesis was supported by the present findings, because children identified by a reading disability exhibited widespread dysfunction in the neural circuitry that is sensitive to rapid auditory transitions for non-verbal sounds.

The importance of this neural circuitry for learning to read was supported by two major findings. First, children with developmental dyslexia exhibited a dysfunction in this circuit. Second, effective remediation was associated with a growth of responsiveness in those children to rapid auditory stimuli in many of the same regions that were responsive to rapid auditory stimuli in typical readers, including left prefrontal cortex. It might be hypothesized that remediation-enhanced processing of rapid auditory sounds would most directly affect phonological performance, rather than higher-order aspects of reading such as text comprehension. Indeed, the children with developmental dyslexia exhibited the most impressive gains on two tests of phonological awareness on which their scores after remediation were no longer significantly different from those of the typical-reading children. The significant improvements after remediation demonstrated broadly across the majority of the standardized phonological awareness as well as higher-order reading tests are a particularly notable finding in light of the fact that the version of the Fast ForWord Language remediation program used in this study employed auditory and spoken language only, and did not incorporate any written letter or written word stimuli.

It cannot be determined from this study whether the employed remediation program mainly improved rapid auditory processing abilities, which in turn improved language and literacy skills, or whether it improved a broader set of cognitive and motivational skills. Fast-ForWord training exercises were explicitly designed to improve foundational cognitive skills, besides rapid auditory processing important for learning, including memory, attention, processing and sequencing abilities. Several studies have reported improvement in these basic aspects of learning, including selective attention, following Fast ForWord training. For example, using auditory evoked potentials, Stevens et al. (2006) showed significantly improved auditory selective attention in children with specific language impairments following a Fast ForWord-Language remediation program. These physiological improvements were not observed in a matched control group of children who did not receive the remediation. These data suggest that one mechanism whereby Fast ForWord may improve children's language and literacy skills is via physiological improvement of selective attention mechanisms. Attention, motivation and other cognitive skills were not measured directly in our study, but we did not observe improved performance after Fast ForWord remediation on the pitch discrimination task performed during brain imaging. This suggests that the changes in metabolic activation observed with fMRI were not driven by a general increase in arousal or motivation that may result from participation in a research study, but rather by the specific cognitive and listening components of the remediation.

Evidence for a relationship between language and reading impairments and a deficient network for rapid auditory processing also comes from infant studies. Several studies have found deficient rapid auditory temporal processing abilities as well as deficient neural correlates in response to nonverbal and verbal rapid auditory stimuli in infants with a family history of developmental dyslexia (e.g., Benasich et al., 2006; Benasich & Tallal, 2002; Leppanen & Lyytinen, 1997; Leppanen et al., 2002; Molfese, 2000; van Leeuwen et al., 2006). A longitudinal follow-up study reported that amongst a large variety of behavioral, perceptual, cognitive and social variables assessed in infancy, rapid spectro-temporal processing threshold obtained at 7.5 months was the single best predictor of language outcomes at 3 years of age (Benasich & Tallal, 2002). Our current results with school-age children with developmental dyslexia provide the missing link between the previously reported deficits in rapid auditory processing abilities in infants at risk for language impairments and adults with developmental dyslexia (e.g., Temple et al., 2000), suggesting that disrupted functional networks for rapid auditory processing in infants may lead, later in development, to language and reading impairments.

The present study had some control measures, but lacked other control measures. The repeated testing of typical-reading children allowed for the examination of retesting effects per se on the language and reading measures, on scanner task performance, and on brain activations. The typical-reading children exhibited slight (non-significant) gains on only 2 of 12 language and reading measures over the two month period of this study whereas the children with developmental dyslexia exhibited significant gains on 11 of 12 language and reading measures over the same period of time, following remediation. There were no effects of repeated testing for the typical-reading group on either scanner task performance or brain activations, whereas after remediation the children with developmental dyslexia showed brain activation patterns that were more similar to those of the typical readers. There was not, however, a control group of children with developmental dyslexia who did not receive treatment. Therefore, we cannot isolate behavioral or brain changes as being associated only with this specific treatment program. The same limitations applied to our prior report of altered activations related to phonological processes following the same remediation program (Temple et al., 2001), however these findings were corroborated in subsequent studies that included a community treatment developmental dyslexia control group who received a variety of interventions commonly provided within the school setting (e.g., Shaywitz et al., 2004).

In sum, this study found that children with developmental dyslexia have a severe and widespread dysfunction in the neural circuitry that responds selectively to rapid auditory transitions of non-verbal sounds in typical-reading children. Effective remediation with the children with developmental dyslexia, which was focused on the enhancement of rapid auditory processing and oral language skills, was associated with the enhanced responsiveness to rapid auditory transitions of non-verbal sounds in the same neural circuitry, accompanied by significant improvements in language and reading skills. These findings suggest that disrupted brain responsiveness to rapid auditory transitions of non-verbal sounds may be a risk factor for developmental dyslexia, but that effective remediation can foster neural plasticity that enhances brain responsiveness to rapid auditory transitions as well as improves language and reading skills.

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