Functional and morphometric brain dissociation between dyslexia and reading ability

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In functional neuroimaging studies, individuals with dyslexia frequently exhibit both hypoactivation, often in the left parietotemporal cortex, and hyperactivation, often in the left inferior frontal cortex, but there has been no evidence to suggest how to interpret the differential relations of hypoactivation and hyperactivation to dyslexia. To address this question, we measured brain activation by functional MRI during visual word rhyme judgment compared with visual cross-hair fixation rest, and we measured gray matter morphology by voxel-based morphometry in dyslexic adolescents in comparison with (*i*) an age-matched group, and (*ii*) a reading-matched group younger than the dyslexic group but equal to the dyslexic group in reading performance. Relative to the age-matched group ($n = 19$; mean 14.4 years), the dyslexic group ($n = 19$; mean 14.4 years) exhibited hypoactivation in left parietal and bilateral fusiform cortices and hyperactivation in left inferior and middle frontal gyri, caudate, and thalamus. Relative to the reading-matched group ($n = 12$; mean 9.8 years), the dyslexic group ($n = 12$; mean 14.5 years) also exhibited hypoactivation in left parietal and fusiform regions but equal activation in all four areas that had exhibited hyperactivation relative to age-matched controls as well. In regions that exhibited atypical activation in the dyslexic group, only the left parietal region exhibited reduced gray matter volume relative to both control groups. Thus, areas of hyperactivation in dyslexia reflected processes related to the level of current reading ability independent of dyslexia. In contrast, areas of hypoactivation in dyslexia reflected functional atypicalities related to dyslexia itself, independent of current reading ability, and related to atypical brain morphology in dyslexia.

inferior frontal region | inferior parietal lobule | voxel-based morphometry | functional MRI | compensation

Dyslexia is a developmental condition characterized by low reading achievement in people who otherwise have cognitive abilities, motivation, and education necessary for accurate and fluent reading (1). Dyslexia, estimated to affect 5–17% of children and 80% of all individuals with a learning disability (2, 3), is characterized by inaccurate and/or slow, effortful reading that typically originates with weakness in the phonological processing of language (4–8).

The brain basis of dyslexia has been examined by functional and structural neuroimaging. Functional imaging studies regularly report hypoactivation in dyslexia, especially in the left parietotemporal region, which may support the mapping of phonology onto orthography, and in the left fusiform region, which may support skilled orthographic decoding (9–12). Hyperactivation in dyslexia has also been observed, most frequently in left inferior frontal gyrus (IFG) (13–19). Hyperactivation in left IFG, a region associated with articulation and naming (20), may reflect compensatory processes engaged by dyslexic individuals attempting to overcome dysfunctions of posterior cortical areas subserving phonological and orthographic processes (17). The hypothesis that in dyslexia hypoactivation reflects fundamental weakness in reading processes and that hyperactivation reflects reading difficulty can be tested directly by two pairs of comparisons in reading and in neuroimaging. First, one can compare a dyslexic group and a typical-reading, age-matched control group (age-matched group). The dyslexic group will have worse reading scores and would be expected to exhibit hypoactivation in left posterior (parietotemporal and fusiform) regions and hyperactivation in left IFG. Then, a second comparison can be made between a dyslexic group and a typical-reading control group equated for reading ability by being younger than the dyslexic group (reading-matched group). The hypothesis is that areas of hypoactivation in the age-matched comparison will remain hypoactivated even in comparison with the reading-matched group, because hypoactivation in these regions is associated with dyslexia rather than current reading ability. In contrast, if brain regions of hyperactivation are recruited in relation to reading ability, then activation differences between dyslexic and age-matched groups should be eliminated, because the two groups are equated for current reading ability. These results would support the view that left IFG hyperactivation reflects the reading difficulty of the task (which is more difficult for dyslexic than nondyslexic children and more difficult for younger than older, typical-reading children), whereas posterior hypoactivation reflects dyslexia rather than reading difficulty.

Functional differences in dyslexia may be related to morphological differences that can be measured in the same regions by voxel-based morphometry (VBM). Atypical brain function likely reflects atypical brain structure in dyslexia, although it is unclear what imaging methods are sensitive to microstructural variation that underlies dyslexia. By using volumetric measurements and VBM, structural differences between dyslexic and control groups

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Abbreviations: CON-age, control group matched by age; CON-read, control group matched by reading level; fMRI, functional MRI; DYS-age, dyslexia group matched by age; DYS-read, dyslexia group matched by reading level; ID-ss, Woodcock Reading Mastery Test word identification subtest score(s); IFG, inferior frontal gyrus; IPL, inferior parietal lobule; MFG, middle frontal gyrus; PET, positron-emission tomography; ROI, region of interest; VBM, voxel-based morphometry; WASI, Wechsler Abbreviated Scale of Intelligence.

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have been found in regions that grossly overlap with functional differences, including the parietotemporal and occipitotemporal regions, IFG, and cerebellum (21). The precise structure–function relations are unknown, because no single study of dyslexia has compared both structural and functional MRI (fMRI) differences. One study related activation differences in dyslexic and control adults, as measured by positron-emission tomography (PET) (22), to VBM differences in the same groups in a subsequent analysis (23) and found both increased and decreased gray matter volumes in left posterior temporal and occipital regions in which they previously reported reduced brain activation. In regards to the present hypothesis, if VBM abnormality reflects the microstructural anatomic etiology of dyslexia, then one would expect VBM differences in areas of hypoactivation, but not necessarily in areas of hyperactivation where intact tissue may support compensatory processes.

We designed this study to test the hypotheses that: (*i*) Left posterior hypoactivation in dyslexia is related to dyslexia rather than reading ability; (*ii*) left frontal hyperactivation in dyslexia is related to reading ability rather than dyslexia; and (*iii*) morphological differences as measured by VBM are related to regions of hypoactivation. We performed a multimodal neuroimaging study of dyslexic adolescents and compared the brain measures with two control groups, an age-matched group and a younger, reading-matched group. During fMRI, participants performed a real-word rhyme judgment task aimed to invoke the sort of phonological analysis of orthographic input that is thought to be a core causal deficit of dyslexia.

Results

Demographics and Behavioral Results. The need to equate age in one comparison and reading ability in another comparison resulted in the creation of two partially overlapping groups of participants: The first dyslexic group matched by age (DYS-age) to a control group (CON-age) ($n = 19$ per group), and the second dyslexic group matched by reading level (DYS-read) to a control group (CON-read) ($n = 12$ per group). The DYS-age group performed significantly worse than the CON-age group on all standardized measures of reading and on the in-scanner rhyme task [$P < 0.001$; see supporting information (SI) Table 1]. Nonverbal IQ was measured by the Wechsler Abbreviated Scale of Intelligence (WASI) Matrix Reasoning subtest and converted to a *t* score, which reflects a standardized (age-adjusted) mean of 50 (SD of 10). The DYS-age group had a mean *t* score of 54.4, which was above the age mean of 50 but significantly lower than the CON-age group [$t_{(36)} = 2.70$, $P = 0.01$]. To confirm that there was a discrepancy between IQ and reading skill, we compared WASI scores standardized for age with the Woodcock Reading Mastery Test word identification subtest scores (ID-ss). The DYS-age group had significantly higher WASI-ss compared with ID-ss [$t_{(18)} = 10.86$, $P < 0.001$]. The CON-age group did not show a significant difference between WASI-ss and ID-ss [$t_{(18)} = 0.46$, $P = 0.66$]. The DYS-read group was significantly older than CON-read group [$t_{(22)} = 7.20$, $P < 0.001$], but there were no significant differences on any reading measure or on in-scanner performance (SI Table 1). The DYS-read group also had significantly higher WASI-ss compared with ID-ss [$t_{(11)} = 5.29$, $P < 0.001$]. The CON-read group did not show a significant difference, but there was a trend for significantly higher WASI-ss compared with ID-ss [$t_{(11)} = 2.07$, $P = 0.06$]. Their ID-ss were, however, well above the norm of 100. The matching procedure was performed between each of the two dyslexic groups and their respective control groups, but the two dyslexic groups and the two control groups were also similar to one another in many regards, except for age and rhyme-task accuracy for the two control groups (SI Table 1 and *SI Text*).

fMRI Activation Patterns During Phonological Processing. The CON-age group had significantly greater activation for the rhyme than the rest condition in multiple brain regions, including left inferior frontal, parietotemporal, and occipitotemporal regions (see SI Fig. 3). The CON-age group had significantly greater activation for rhyme → rest than the DYS-age group in three posterior brain regions, the left inferior parietal lobule (IPL), and the left and right fusiform and lingual gyri (Fig. 1*a* and SI Table 2). The DYS-age group had significantly greater activations than the CON-age group in the left IFG, left middle frontal gyrus (MFG), left caudate, and right thalamus for rhyme → rest (Fig. 1*a* and SI Table 2). When gender or IQ was regressed out of the analysis, the results remained nearly identical, so gender and IQ were not considered in further analyses.

Functional regions of interest (ROIs) were defined by regions that exhibited significantly greater or less activation in the DYS-age group than the CON-age group, and mean contrast estimates (linear combination of beta estimates) were extracted for each individual's rhyme → rest contrast images from these regions for all four groups. The DYS-age group exhibited hypoactivation relative to the CON-age group in the three posterior regions [left IPL, $t_{(36)} = 3.84$, $P < 0.001$; left fusiform/lingual gyri: $t_{(36)} = 4.63$, $P < 0.001$; right fusiform/lingual gyri, $t_{(36)} = 3.57$, $P = 0.001$], and hyperactivation in the two left frontal and two subcortical areas [left IFG, $t_{(36)} = 5.13$, $P < 0.001$; left MFG, $t_{(36)} = 3.67$, $P = 0.001$; left caudate, $t_{(36)} = 4.94$, $P < 0.001$; right thalamus, $t_{(36)} = 3.68$, $P = 0.001$].

The critical analyses focused on the comparisons of the DYS-read and CON-read groups in the same ROIs. The CON-read group exhibited significantly greater activations than DYS-read group in the left IPL [$t_{(22)} = 2.12$, $P = 0.05$] and left fusiform/lingual gyri [$t_{(22)} = 2.20$, $P = 0.04$], and the magnitudes of difference were similar to what had been seen with the age-matched comparison (Fig. 1*b*). The difference in right fusiform/lingual activation that had been significant in the age-matched comparison was no longer significantly different in the reading-matched comparison [$t_{(22)} = 0.76$, $P = 0.46$]. In contrast, for the reading-matched DYS-read and CON-read groups, there were no differences in activation in the four regions of hyperactivation observed in the age-matched comparison [left IFG, $t_{(22)} = 0.53$, $P = 0.60$; left MFG, $t_{(22)} = 0.001$, $P = 1.00$; left caudate, $t_{(22)} = 0.44$, $P = 0.67$; and right thalamus, $t_{(22)} = 0.49$, $P = 0.63$]. Similar results were found when gender was regressed out of the analysis.

Activations in left parietal and bilateral fusiform/lingual regions were significantly greater for rhyme → rest in both control groups ($P < 0.05$), except for the left IPL in the CON-read group [$t_{(11)} = 1.06$, $P = 0.32$]. In both dyslexic groups, there were significantly greater activations for rest → rhyme in left IPL [DYS-age, $t_{(18)} = 2.75$, $P = 0.01$; DYS-read, $t_{(11)} = 2.86$, $P = 0.02$] and no significant differences between conditions in left and right fusiform/lingual regions ($P > 0.05$).

Across all 30 typical-reading control participants, the left IFG showed an age-dependant decrease in activation ($r = -0.46$, $P = 0.01$), but this was not the case not in the 23 dyslexic participants ($r = -0.24$, $P = 0.27$). In the left IPL, there were no significant correlations between age and activation in control ($r = 0.09$, $P = 0.64$) or dyslexic individuals ($r = -0.23$, $P = 0.29$). Across all 30 typical-reading control participants, there was a performance-related shift of activation (rhyme → rest) from left frontal to left parietal regions, such that activation in left IFG was negatively correlated with rhyme performance ($r = -0.41$, $P = 0.02$), whereas activation in left IPL was positively correlated with rhyme performance ($r = +0.40$, $P = 0.03$). In dyslexic individuals, however, there were no significant associations between rhyme performance and brain activation (left IFG, $r = -0.21$, $P = 0.35$; left IPL, $r = -0.22$, $P = 0.32$).

VBM Gray Matter Volume. The CON-age group had greater total gray matter volume than the DYS-age group [$t_{(36)} = 4.00$, $P < 0.001$], but there was no significant difference between reading-

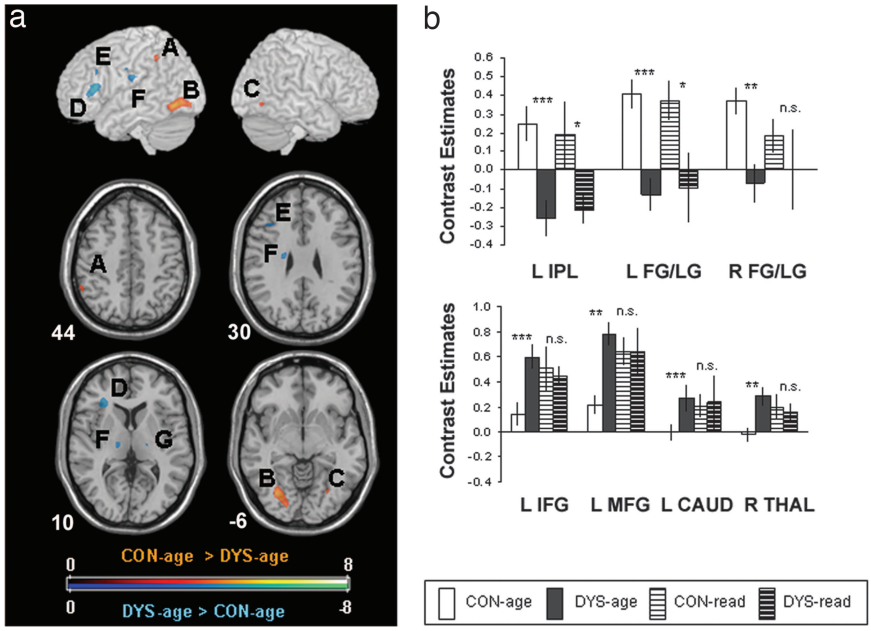

Fig. 1. Group differences in brain activation during phonological processing. (*a*) Regions showing significant differences in activation between the age-matched control group (CON-age) and dyslexic group (DYS-age). Regions in red–yellow exhibited hypoactivation in the dyslexic group; regions in blue–green exhibited hyperactivation in the dyslexic group. The color bar depicts *t* values. A, left IPL (L IPL); B, left fusiform gyrus/lingual gyrus (L FG/LG); C, right fusiform gyrus/lingual gyrus (R FG/LG); D, left IFG (L IFG); E, left MFG (L MFG); F, left caudate (L CAUD); G, right thalamus (R THAL). (*b*) Mean contrast estimates for all four groups extracted from ROIs showing age-matched group differences and plotted for each of the four groups: CON-age, DYS-age, CON-read, and DYS-read. (*Upper*) Areas of hypoactivation in the dyslexic group in the age-matched comparison, two of which remained significantly different in the reading-matched comparison. (*Lower*) Areas of hyperactivation in the dyslexic group in the age-matched comparison, none of which remained significantly different in the reading-matched comparison. Error bars represent SEM. n.s., not significant; $P > 0.1$; *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.001$ between groups.

matched groups [$t_{(22)} = 1.55$, $P = 0.14$; see SI Table 1]. Hence, we included total gray matter volume as a covariate of no-interest in further analyses. The CON-age group had significantly greater regional gray matter volume than the DYS-age group in bilateral brain regions, including bilateral IPL, superior temporal, precentral, and insula regions (Fig. 2*a* and SI Table 3). When gender or IQ were regressed out of the analysis in addition to total gray matter volume, the results remained nearly identical, so gender and IQ were not considered in further analyses.

To examine structure-function relations, we examined voxels in all functionally defined ROIs that exhibited hypofunction or hyperfunction in the age-matched fMRI contrasts. The only region that showed a significant difference between control and dyslexic groups was the left IPL ROI, where there was greater gray matter volume in the CON-age group than the DYS-age group (Fig. 2*b* and SI Table 4). No region exhibited significantly greater gray matter volume in the DYS-age than the CON-age group.

Mean gray matter volume measures from the left IPL ROI were extracted for each individual in all four groups. The DYS-age group exhibited less gray matter volume than the CON-age group [$t_{(36)} = 2.68$, $P = 0.01$]. Regressing out IQ resulted in a trend for significant

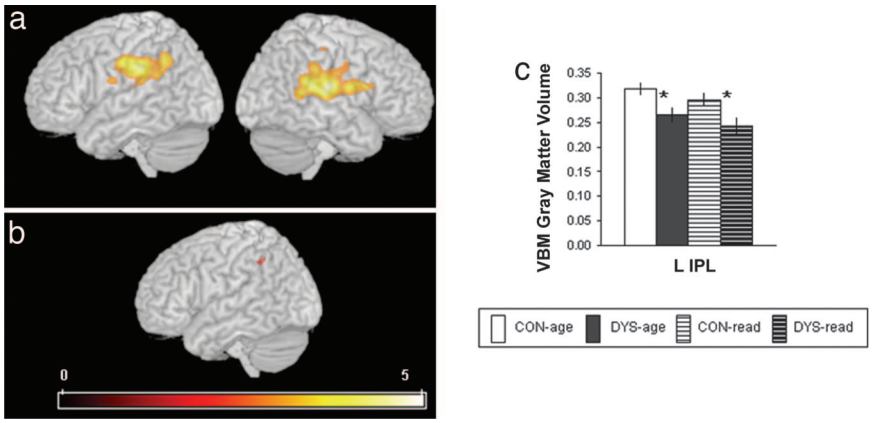

Fig. 2. Group differences in gray matter volume. (*a*) Regions showing significant differences in gray matter volume in the age-matched comparison (CON-age versus DYS-age). Regions in red–yellow exhibited reduced volume in the dyslexic group (SI Table 3). (*b*) Left IPL (L IPL) region showing significant differences in gray matter volume in the age-matched comparison (CON-age versus DYS-age) in regions identified in the fMRI analyses (Fig. 1*a*). The region in red–yellow exhibited reduced volume in the dyslexic group. The color bar depicts *t* values (SI Table 4). (*c*) Mean gray matter volume for all four groups from ROI showing age-matched group differences in L IPL (see *b*) and plotted for each of the four groups: CON-age, DYS-age, CON-read, and DYS-read. Bar graph shows significantly reduced gray matter volume in the dyslexic group relative to the age-matched and reading-matched groups. Error bars represent SEM. *, $P < 0.05$ between groups.

difference [$F_{(1,34)} = 3.66$, $P = 0.064$]. In the critical analysis comparing reading-matched groups, the DYS-read group exhibited significantly less gray matter volume relative to the CON-read group in the left IPL ROI [$t_{(22)} = 2.20$, $P = 0.04$].

Discussion

This study revealed a fundamental dissociation between dyslexia and reading ability in regard to brain function and morphology. Dyslexic individuals, when compared with age-matched typical reading individuals, exhibited hypoactivation in three posterior brain regions, and hyperactivation in four frontal and subcortical regions. When dyslexic individuals were compared with younger individuals matched on reading ability, the hypoactivation remained in two left-hemisphere posterior regions, but the hyperactivation was eliminated in all four frontal and subcortical regions. Thus, hyperactivation in the dyslexic group could be accounted for by reading ability, whether that ability was related to normal development (younger age) or dyslexia. In contrast, hypoactivation in left posterior cortex was related to dyslexia per se. Furthermore, the same left IPL region that exhibited functional hypoactivation in dyslexia also exhibited reduced gray matter volume in dyslexia relative to both age-matched and reading-matched groups. This finding establishes a structure–function relation in the brain basis of dyslexia. Finally, typical development from ages 7 to 16 in phonological ability (measured by in-scanner rhyme-task performance) was characterized by a shift with decreasing activation in the left IFG and increasing activation in the left IPL. This anterior-to-posterior developmental shift did not occur in dyslexic individuals.

In a prior study using the same phonological task with younger children ages 8–12, we compared activation between fifth-grade dyslexic children and age-matched, typical-reading fifth-grade children and reading-matched, typical-reading third-grade children (24). In that study, there were hypoactivations in dyslexic, age-matched children in six regions, including two left parietotemporal regions (in the same Brodmann area, but in a slightly different location). Activation in all six regions remained significantly reduced in comparison with reading-matched third grade children. Thus, both studies found hypoactivation in the left parietotemporal region that was associated with dyslexia but could be accounted for by reading ability. The prior study, however, did not address the nature of hyperactivation (because none was observed), nor did it examine morphological correlates of dyslexia.

There is a remarkable convergence of evidence across many imaging studies for hypoactivation in the left parietotemporal region in dyslexia, although the precise location of the hypoactivation varies considerably across studies that vary also in tasks used and participant characteristics (13, 18, 25–35). In the present study, the left IPL was the only brain region that exhibited both structural and functional atypicalities in dyslexia, and neither atypicality was accounted for by reading ability. Indeed, the functional atypicality was so great that dyslexic participants exhibited the opposite pattern of activation relative to typical readers; whereas the typical-reading groups had greater activation for the active rhyme task than the passive rest task, the dyslexic groups had greater activation for the passive rest task than the active rhyme task (as in refs. 24, 30, and 33). The parietotemporal region and IPL in particular are involved in phonological storage (36) when processing the sounds of spoken language (phonemes) and for mapping orthography onto the phonologic structure of the language system (9–11). Thus, a severe dysfunction in this brain region would sharply compromise phonological processes essential for learning to read.

The left parietotemporal region has also exhibited morphological atypicality in dyslexia in a number of studies. We found reduced gray matter volume in the left parietotemporal region, as have prior studies (37, 38). The reduced gray matter volume may reflect a morphological abnormality that underlies dyslexia. Further, diffusion tensor imaging (DTI) studies examining white matter microstructure in dyslexia have consistently reported atypicalities in this brain region (39–41). The present VBM analysis and a prior DTI analysis (40) reported bilateral morphological atypicalities in dyslexia, with only the left-hemisphere difference related to language or reading deficits. If these anatomical differences reflect the microstructural etiology of dyslexia, then the structural imaging studies suggest that the developmental brain basis of dyslexia follows a bilateral neurobiological pathophysiology, with the left hemisphere atypicality affecting phonological functions important for reading.

One other study examined both functional (PET) and structural (VBM) differences in a single dyslexic group (22, 23). Regions with increased and decreased gray matter volume were found in the dyslexic group, and a negative correlation between gray matter volume and reading skill in a left occipitotemporal location somewhat different from our study. Atypical increases in gray matter volume were interpreted as reflecting ectopias and dislaminations in gray matter and atypical decreases as atrophic changes due to reduced local connectivity (42). The difference in the results between studies could be due to many factors including differences in participants (e.g., children versus adults) and analytic methods.

The second posterior region that exhibited a dyslexia-specific hypoactivation was the left fusiform gyrus (the activation spread from the left fusiform gyrus to the left lingual gyrus). This region encompasses the visual word form area that responds preferentially to learned orthographies and that may be a component of a skilled visual word-recognition pathway (12). Hypoactivation in the left occipitotemporal region in dyslexic compared with age-matched typical-reading groups has often been observed (13, 22, 43, 44). The present study shows that this hypoactivation is related to dyslexia rather than to reading ability. Prior VBM studies have reported reduced gray matter in this region (23, 37, 38), but we did not find significant differences in gray matter volume between groups. The negative finding, however, does not preclude the possibility of structural abnormalities in this region.

Hyperactivations in frontal and subcortical regions exhibited by the dyslexic group were eliminated in comparison with the reading-matched control group. There was less statistical power due to a reduction in the number of subjects in the reading-matched than the age-matched contrasts, but the magnitudes of activations were almost identical in the two reading-matched groups. Among these regions, the left IFG has often been reported to exhibit hyperactivation in dyslexia (13–16, 33). The hyperactivations occurred in multiple components of a frontostriatal–thalamic network often associated with working memory and attention (45). Thus, these hyperactivations could reflect greater working memory resources being recruited to support phonological processing when posterior language regions fail to support such processing because of immaturity (reading-matched control group) or dysfunction (dyslexic group). Furthermore, Crosson *et al.* (46) suggested that the left frontostriatal-thalamic network is involved in retrieving words from preexisting lexical stores, and that right subcortical regions may suppress right frontal structures from interfering with language production. We did not observe VBM differences in regions of hyperactivation, but other studies have found either larger (38) or smaller (37, 38, 47) volumes of left IFG gray matter in dyslexia.

The contrast between typical development and dyslexia is striking when considering the relation between left IFG and left IPL activations. In the typical-reading control group, there were age-related and phonological performance-related decreases in left IFG activation and a phonological performance-related increase in left IPL activation. This finding suggests that the typical growth in phonological performance involves a shift from

processes dependant on the left IFG to processes dependent on the left IPL, and this anterior–posterior shift is more closely tied to maturation of phonological processing than age per se. The dyslexic group, however, did not exhibit the IFG-to-IPL shift in activation associated with the growth of phonological skill in typical reading. The larger variance in age for the typical-reading than the dyslexic group may have influenced the differences in these associations, although variance on rhyme-task performance and activations (left IFG and IPL) were similar for the two groups.

One caveat for these findings is the overrepresentation of females in the reading-matched contrasts. Whereas the age-matched groups had about equal representation of males and females, the reading-matched groups had a preponderance of females. Statistical control for gender representation did not alter any outcome, but future studies with larger samples will be needed to examine possible gender differences in the neural correlates of reading in typical-reading and dyslexic groups.

Dyslexia is a complex developmental disorder that must unfold in a complex chain of mental and brain developments, and much remains unknown about the etiology of dyslexia. Research strategies that aim to dissociate neural mechanisms related to the cause versus the consequence of dyslexia may contribute to understanding that etiology. In functional imaging studies comparing populations, such as patient versus control groups, it is common to observe both hypoactivations and hyperactivations in the patient group. This finding leads to the problem of interpreting whether an atypical activation is more related to the cause of the disorder or the consequence of the disorder. Our findings suggest that, within the context of this specific study, hyperactivation was associated with the consequence of dyslexia, namely greater difficulty in performing a phonological task. Conversely, hypoactivation in left parietotemporal and occipitotemporal regions, known to be important for phonological and orthographic processes, respectively, appeared to be associated with the cause of dyslexia. Furthermore, morphological abnormality in the left parietotemporal region points to that region as an especially strong candidate for local structure–function atypicality that compromises the ability to learn to read. Successful interventions for dyslexia have yielded increased activation in neighboring locations (19, 44, 48–50), suggesting that education can induce plasticity in atypical parietal and temporal regions. Future research on morphometric changes with successful intervention warrants investigation to discover whether effective remediation also results in morphological plasticity.

Methods

Subjects. Fifty-three healthy native English speakers participated: 30 typical-reading and 23 dyslexic participants, ages 7–16 years (SI Table 1). Control participants were matched on a one-to-one basis with the dyslexic children for age (within 6 months), gender, and handedness (CON-age, $n = 19$) or for reading-level, gender, and handedness (CON-read, $n = 12$). See *SI Text* for details. The study was approved by the Stanford University Panel on Human Subjects in Medical Research. Informed assent and consent was obtained from each child and guardian, respectively.

Criteria and Subject Groups. Reading ability and intelligence were assessed by using standardized behavioral measures. Criteria for dyslexia were met if a child's behavioral performance fell within the following limits on age-adjusted tests: performance on single-word reading (decoding) within the lower 25th percentile, i.e., ID-ss < 90, performance on spelling (Woodcock–Johnson Spelling subtest scores) or comprehension (Woodcock Reading Mastery Test passage comprehension subtest scores) below 1 SD of the norm, i.e., WJS-ss or PC-ss ≤ 85, and estimated IQ within 1 SD of the norm, i.e., WASI Matrix Reasoning t score (WASI-t) ≥ 40. To confirm a discrepancy between IQ and reading skill in dyslexic individuals, we compared WASI-ss (converted from WASI-t; WASI-t of 50 is equal to a WASI-ss of 100) with ID-ss. Criteria for normal readers were met if a child performed >90 on all reading tests (ss > 90) and had a normal IQ (WASI-$t \geq 40$).

Task Design. A word–rhyme task was used in the scanner, for which there were two conditions: rhyme and rest. During the rhyme condition, participants judged whether or not two visually presented words rhymed (e.g., "bait" and "gate") or not (e.g., "price" and "miss") and indicated each response with a right- or left-handed button press, respectively. Word pairs were selected so that the visual appearance of the last letters of the two words could not be used to determine whether they rhymed. Stimuli were balanced for frequency of occurrence, number of letters, and syllables between the rhyme and nonrhyme trials and across blocks (51). Each trial lasted a total of 6 sec, consisting of a 4-sec period when the two words were presented simultaneously followed by a 2-sec fixation cross. Each task block consisted of a 2-sec cue period followed by five trials (32 sec total). During the rest block, subjects saw a 15-sec fixation cross on the screen. The entire scan was 223 sec long, including two practice trials at the beginning, and consisted of four rhyme blocks and five rest blocks.

Image Acquisition. Imaging-related procedures were performed at the Lucas Center (Stanford University) by using a 3T Signa LX (GE Medical Systems, Milwaukee, WI). fMRI data were acquired by using whole-brain imaging with a T2*-sensitive gradient echo spiral in/out pulse sequence (52) [echo time = 30 msec; repetition time = 1 sec; flip angle = 90°; field of view (FOV) = 240 mm; acquisition = 64 × 64 voxels; temporal frames = 223, 15 slices, 7-mm thickness, 0-mm skip, anterior commissure–posterior commissure aligned]. Sixteen inplane axial T1-weighted anatomical scans were also collected by using the same prescription as the fMRI data. Three-dimensional, high-resolution anatomical scans were acquired by using a spoiled gradient echo pulse sequence (echo time = 2 msec; repetition time = 9 msec; flip angle = 15°; 2 NEX scan) and produced 124 coronal T1-weighted images with a field of view of 24 cm and voxel sizes of 0.94 × 0.94 × 1.2 mm.

fMRI Data Analysis. Statistical analysis was performed with SPM2 statistical parametric mapping software (Wellcome Department of Cognitive Neurology, London). After image reconstruction, each subject's data were slice–time corrected (ascending, reference slice 8) and realigned to the first functional volume. Sessions were normalized by using the mean functional volume resampled to 2 × 2 × 2-mm voxels in Montreal Neurological Institute stereotaxic space (12 nonlinear iterations, 7 × 8 × 7 nonlinear basis functions, medium regularization, sinc interpolation). Spatial smoothing was done with a Gaussian filter (8 mm, full-width, half-maximum). Each subject's data were high-pass-filtered at 94 sec and analyzed by using a fixed-effects model.

Group analysis was performed with a random-effects model (53) by using the rhyme versus rest contrast images (one per subject per contrast). First, activation patterns of normal readers were examined by submitting rhyme → rest contrast images to a one-sample t test [$P = 0.001$ uncorrected; extent threshold (ET) = 10]. A two-sample t test was then performed to examine significant difference in brain activation between DYS-age and CON-age ($P = 0.001$ uncorrected; ET = 10). This group comparison defined functional ROIs as regions that showed significant differences between DYS-age and CON-age. Contrast estimates were extracted from each functional ROI for each subject, and brain activation was compared between DYS-age and CON-age and between DYS-read and CON-read ($P < 0.05$). Contrast estimates were further evaluated by performing a

one-sample t test to examine whether each group showed significant positive or negative activation ($P < 0.05$). Contrast estimates were correlated with age and in-scanner rhyme-task performance ($P < 0.05$).

VBM Analysis. Statistical analysis was performed by using SPM2. Optimized and modulated VBM techniques were performed as described by Good *et al.* (54). Normalization parameters comprised a 12-parameter affine transformation and nonlinear normalization with $7 \times 8 \times 7$ basis functions. Smoothing was done with an isotropic Gaussian kernel with a full-width, half-maximum of 8 mm. Gray matter partitions were spatially normalized (12-parameter affine transformation and $7 \times 8 \times 7$ basis functions) by using the customized gray matter template separately. The deformation parameters obtained from the normalization process of gray matter partitions were applied to the original raw images in native space to create optimally normalized whole-brain images, which were recursively segmented. Jacobian modulated (reflecting gray matter volume) images were smoothed with a kernel with a full-width, half-maximum of 12 mm. Jacobian determinants of the spatial transformation matrix [an index of the amount of volumetric compression that each voxel is subjected to when stretching, shearing, and compressing the images into stereotaxic space (54, 55)] and total gray matter volume were compared between groups to avoid confounding effects due to differences in shapes and gray matter volume. There were no significant differences in the Jacobian determinants. Furthermore, we performed analyses with both a custom template and an adult template and obtained similar results. To maintain consistency with the fMRI data, we report the results from scans that were normalized by using the adult template.

We examined regional gray matter differences between groups by using a one-way analysis of covariance, regressing out total gray matter volume and using a threshold similar to or more stringent than other VBM studies of dyslexia, with a joint-expected probability distribution with height ($P = 0.01$) and extent ($P = 0.01$) thresholds corrected at the whole-brain level (56).

Statistical images were overlaid onto the MRIcro template image for 3D viewing. Peak coordinates of brain regions with significant effects were converted from Montreal Neurological Institute to Talairach space by using the mni2tal function. Brain regions were identified from these X, Y, and Z coordinates by using Talairach Daemon (Research Imaging Center, University of Texas Health Science Center, San Antonio, TX) and confirmed with the Talairach atlas (57).

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