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White matter defects in a genetic brain malformation

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ABSTRACT

Background: Multiple lines of evidence have suggested that developmental dyslexia may be associated with abnormalities of neuronal migration or axonal connectivity. In patients with periventricular nodular heterotopia—a rare genetic brain malformation characterized by misplaced nodules of gray matter along the lateral ventricles—a specific and unexpected reading disability is present, despite normal intelligence. We sought to investigate the cognitive and structural brain bases of this phenomenon.

Methods: Ten adult subjects with heterotopia, 10 with dyslexia, and 10 normal controls were evaluated, using a battery of neuropsychometric measures. White matter integrity and fiber tract organization were examined in six heterotopia subjects, using diffusion tensor imaging methods.

Results: Subjects with heterotopia and those with developmental dyslexia shared a common behavioral profile, with specific deficits in reading fluency. Individuals with dyslexia seemed to have a more prominent phonological impairment than heterotopia subjects. Periventricular nodular heterotopia was associated with specific, focal disruptions in white matter microstructure and organization in the vicinity of gray matter nodules. The degree of white matter integrity correlated with reading fluency in this population.

Conclusions: We demonstrate that a genetic disorder of gray matter heterotopia shares behavioral characteristics with developmental dyslexia, and that focal white matter defects in this disorder may serve as the structural brain basis of this phenomenon. Our findings represent a potential model for the use of developmental brain malformations in the investigation of abnormal cognitive function. ***Neurology*® 2007;69:2146–2154**

GLOSSARY

DTI = diffusion tensor imaging; **FA** = fractional anisotropy; **PNH** = periventricular nodular heterotopia; **ROI** = region of interest.

Dyslexia is one of the most common learning problems in the general population, affecting 5% to 17% of children.[1] It has typically been defined as a specific, unexpected impairment in reading despite adequate intelligence and educational exposure. The core deficit in most individuals with dyslexia seems to be one affecting phonological processing, or the ability to manipulate the sound segments of words.[2] However, many individuals with dyslexia have fluency-based reading problems,[3] including problems with rapid letter, word, and sentence reading and the ability to perform other rapid naming tasks, and the concurrence of both phonological problems and fluency difficulty may be of particular significance.[4]

Multiple functional neuroimaging studies in dyslexic and normal readers have implicated a complex brain network for reading that seems to involve mostly the perisylvian

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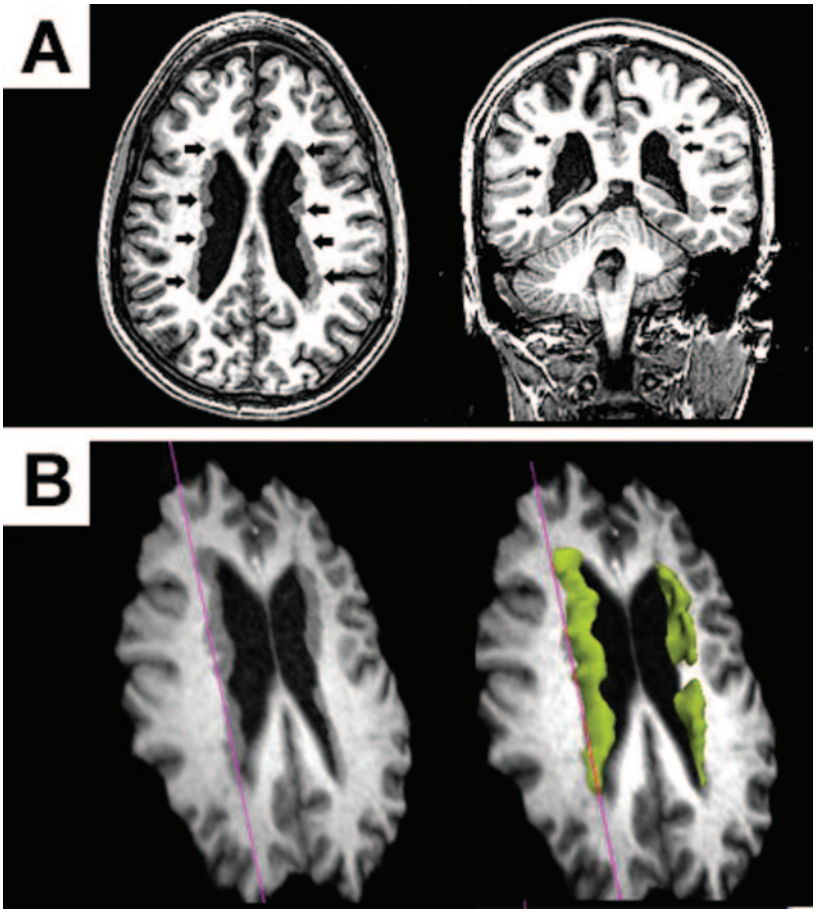
Figure 1 Brain imaging of subjects with periventricular nodular heterotopia



(A) Axial (left) and coronal (right) T1-weighted anatomic brain images from a subject with periventricular nodular heterotopia (PNH) demonstrate the presence of misplaced, or heterotopic, gray matter nodules (black arrows) located bilaterally along the lateral walls of the lateral ventricles, at times forming a confluent mass along the ventricular wall and at times protruding into the ventricular lumen. (B) Automated segmentation analysis of gray and white matter by fractional anisotropy in another PNH subject allows for three-dimensional visualization of confluent periventricular heterotopic gray matter (green).

region of the left hemisphere.[5,6] However, anatomic neuroimaging studies have shown mixed results when gray matter structures in this and other brain regions in dyslexic readers are compared with those of normal readers.[7,8] Instead, several lines of evidence suggest that a functional disconnection of relevant cortical regions may be a potential basis for reading difficulties.

For example, postmortem histologic examination of brains from dyslexic individuals has demonstrated the presence of ectopic neurons in the molecular layer of cerebral cortex,[9] raising the possibility of faulty neuronal migration and subsequent disruptions in axonal connectivity. Two recently identified dyslexia susceptibility genes, DCDC2 and ROBO1, encode proteins that may be involved in axonal pathfinding or neuronal migration.[10,11] Abnormal patterns of cortical activation seen during PET scans have also suggested the possibility of connectivity problems in dyslexia.[12,13] Finally, diffusion tensor imaging (DTI), a noninvasive, MRI-based method that allows for analysis of white matter microstructure and visualization of fiber tracts, has demonstrated a correlation between white matter integrity and word reading ability in children and adults.[14-17]

We have previously shown that patients with the genetic brain malformation of periventricular nodular heterotopia (PNH) have impaired reading despite normal intelligence, attention, working memory, and educational exposure.[18] PNH, which can be associated with mutations in the FLNA gene, is characterized by misplaced nodules of gray matter that line the lateral ventricles of the brain bilaterally (figure 1),[19] representing neurons that fail to migrate properly from the ventricular zone during fetal brain development. Patients typically present with seizures in adolescence, but they generally have no gross neurologic disability,[20] despite this remarkable alteration in gray matter architecture.

Here we show that whereas patients with PNH have very distinctive neuroanatomic abnormalities, they share common behavioral features with individuals with developmental dyslexia, in particular a prominent impairment in reading fluency. Moreover, we demonstrate that this reading fluency deficit is associated with white matter defects adjacent to the periventricular nodules, suggesting a structural correlate for this particular feature of dyslexia.

METHODS **Subjects.** Ten PNH subjects were recruited from direct clinician referrals and from a database of subjects who had participated in a genetic study of the condition. Subjects were included if they were 18 years or older and had an MRI diagnosis of PNH based on the presence of at least one periventricular nodule of gray matter signal intensity. All had been diagnosed with PNH after clinically presenting with seizures; none was diagnosed or selected based on cognitive impairment of any type. Six of these subjects had MRI with DTI performed in this study; they did not differ prominently from the four others in demographic

features or heterotopia characteristics, and although they had slightly higher intelligence and rapid naming scores, these differences were not significant. Five of the subjects in this report had results of other behavioral testing described previously.[18]

Ten dyslexic subjects 18 years or older were recruited through a learning disability center associated with a local university. All spoke English as a first language, were physically healthy, and had no history of psychiatric or neurologic disorders. All reported a history of reading difficulty that had been identified in childhood and had required special literacy instruction. For confirmation of a persisting reading problem in this population, subjects were tested using the neuropsychometric battery described below. Those who (1) performed more than 1 SD below the population mean on any measure of word reading (Word ID or Word Attack from the Woodcock Reading Mastery Tests–Revised, Sight Word Efficiency or Phonetic Decoding Efficiency from the Test of Word Reading Efficiency) and (2) performed more than 1 SD below their own full-scale IQ on any measure of word reading, were classified as dyslexic and included in the study (see Niogi and McCandliss[17] for discussion of similar criteria).

Ten normal reader subjects 18 years or older were recruited through local universities. All spoke English as a first language, were physically healthy, and had no history of psychiatric or neurologic disorders. All denied any history of reading problems or learning disabilities and were tested using the neuropsychometric battery described below. Those who had both verbal and performance IQ scores within the normal range and who performed within 1 SD of the population mean on all word reading measures listed above were classified as normal readers and included in the study.

All subjects gave informed consent. The study was carried out according to research protocols approved by the institutional review board of the Beth Israel Deaconess Medical Center, Boston.

Behavioral testing. Intelligence was measured using the Wechsler Adult Intelligence Scale or the Wechsler Abbreviated Scale of Intelligence, which yield verbal, performance, and full-scale standard scores.[21,22] A wide range of component reading skills, word reading skills, and connected text reading skills were assessed. Phonological processing was evaluated using the Comprehensive Test of Phonological Processing.[23] Three tasks of the Rapid Automatized Naming/Rapid Alternating Stimulus test previously linked to dyslexia in older age groups (letters, digits, objects) were administered.[24-26] Word-level reading was assessed with untimed real-word and nonword decoding tests (Word ID and Word Attack subtests of Woodcock Reading Mastery Tests–Revised)[27] and timed, rapid real-word and nonword decoding tests (Sight Word Efficiency and Phonetic Decoding Efficiency subtests of the Test of Word Reading Efficiency).[28] Connected-text reading was assessed using the Gray Oral Reading Test Third Edition[29] and the Passage Comprehension subtest of the Woodcock Reading Mastery Tests–Revised.

Neuroimaging. Brain MRI with DTI was performed using a 3-T GE VH/1 scanner with the product head coil. Anatomic images were acquired using a T1-weighted, three-dimensional, magnetization-prepared, rapid-acquisition, gradient-echo (MPRAGE) volume acquisition (TE1 = MIN, TI = 400 milliseconds, flip = 10, FOV = 240 mm, matrix size 256 × 256 voxels, slice thickness = 1.5 mm, no skip). DTI was performed using a diffusion-weighted, single-shot, spin-echo, echo-planar, imaging sequence (TE1 = MIN, TR = 10000 milliseconds, FOV = 240 mm, matrix size 256 × 256 voxels, slice thickness = 2.0 mm, no skip, NEX = 1). A b-value of 1000 was used, and 15 noncollinear directions were calculated. The diffusion-weighted sequence was performed three times for each subject during a single session.

Regions of interest (ROIs) for fractional anisotropy (FA) analysis of white matter were drawn in two ways on anatomic images and FA maps using MRIcro software,[30] by two of the investigators working together. For hemispheric white matter FA calculation, multiple ROIs were hand drawn bilaterally in the centrum semiovale, corona radiata, and internal capsule for each subject, carefully excluding gray matter in periventricular nodules as well as regions of cortex and normal deep gray matter. Hemispheric white matter FA was then calculated for each subject by averaging the mean FAs in these ROIs. For an analysis of the effect of heterotopic nodules on overlying focal white matter FA, multiple ROIs were hand drawn for each subject, with half overlying one or more periventricular nodules and the other half in the homologous contralateral region of white matter not overlying a nodule. Mean FA from all ROIs overlying nodules was then compared with that from all ROIs not overlying nodules.

Fiber tractography was performed with DTIStudio software available from Johns Hopkins University, based on the fiber assignment by continuous tracking method.[31] Fiber tracking was performed from all the voxels within the brain (using a brute-force approach) with both orthograde and retrograde initiation along the direction of the principal eigenvector in each voxel. Propagation in each fiber tract was terminated if a voxel with FA < 0.4 was reached or if the angle of tract became > 70 degrees during tracking. Results that penetrated manually segmented ROIs were then visualized, either in three-dimensional space or in two dimensions coregistered onto anatomic images.

Statistical analysis. Differences in behavioral scores among PNH subjects, dyslexic subjects, and normal readers on the various cognitive and reading tasks were analyzed for significance, using a univariate analysis of variance with post hoc comparisons. Pearson correlation coefficients were calculated for the relationships between FA measures in PNH subjects and various behavioral scores. A paired Student t test was used to compare FA values between ROIs overlying periventricular nodules in PNH subjects and homologous contralateral ROIs not overlying nodules. A significance threshold of $p < 0.05$ was used for all comparisons.

RESULTS

Phonological, rapid naming, and reading skills. Thirty adult subjects from three groups (10 with PNH, 10 with dyslexia, and 10 normal readers) were evaluated, using a battery of neuropsychometric measures. Normal readers had a higher male:female ratio and were younger on average, but these differences were not significant. Verbal, performance, and full-scale IQ scores were closely comparable among the three groups (table 1).

Component reading skills, including phonological processing and rapid automatized naming,

Table 1 Characteristics of subjects with periventricular nodular heterotopia, subjects with dyslexia, and normal readers

	Periventricular nodular heterotopia	Dyslexic readers	Normal readers	Statistical comparison
Age, mean (range)	35.1 (19–48)	34.6 (22–47)	25.5 (19–46)	F=3.256; p=0.0541
Sex, M:F	2:8	3:7	7:3	p = 0.0698
Handedness, R:L	8:0	6:1	7:1	p = 0.4667
Verbal IQ, mean (SD)	104.0 (15.9)	105.7 (9.6)	108.8 (7.8)	F=0.4715;p=0.6291
Performance IQ, mean (SD)	100.5 (7.7)	105.2 (10.4)	109.1 (9.8)	F=2.105; p=0.1415
Full-scale IQ, mean (SD)	103.3 (10.9)	105.0 (8.9)	110.4 (6.6)	F=1.697; p=0.2022

Univariate analysis of variance was used to analyze differences in mean age, verbal IQ, performance IQ, and full-scale IQ among the three groups. Fisher exact test was used to analyze differences in sex and handedness proportion among the three groups; in these cases, p values presented are for the comparison between the two extreme proportions. Handedness was not recorded for all subjects.

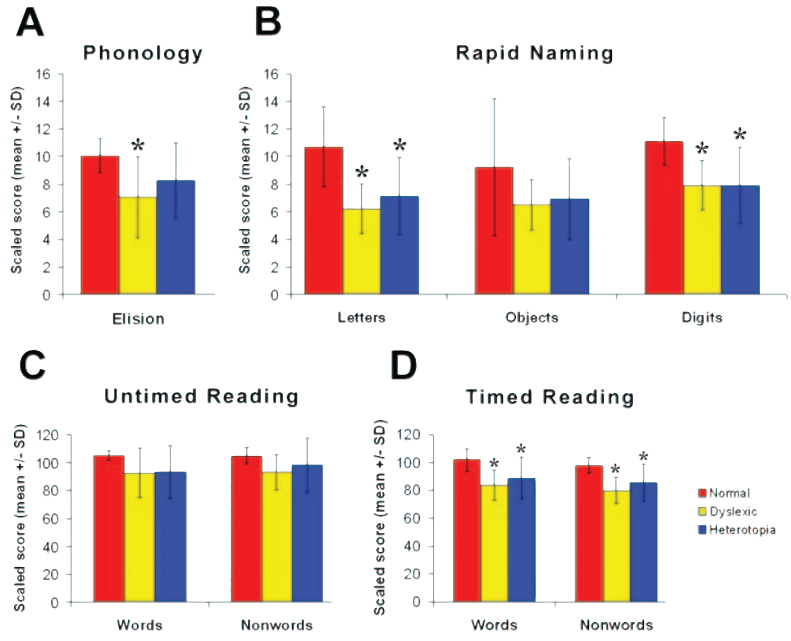
were assessed. Subjects with PNH and subjects with dyslexia demonstrated worse phonemic awareness (as measured by Elision) than normal readers, and this difference was significant for subjects with dyslexia (figure 2A). Subjects with PNH and subjects with dyslexia shared a common profile on measures of rapid automatized naming, demonstrating significantly lower scores than normal readers on the letters and digits subtests; a similar, though nonsignificant, trend was found on the objects subtest (figure 2B).

At the word reading level, no difference among the three groups was found in untimed real-word and nonword reading tasks (Word ID and Word Attack; figure 2C), whereas subjects with PNH and subjects with dyslexia were significantly worse than normal readers on measures of timed, rapid real-word and nonword reading (Sight Word Efficiency and Phonetic Decoding Efficiency; figure 2D).

Passage reading of connected text (Gray Oral Reading Test) demonstrated a trend in PNH subjects and dyslexic subjects toward poor accuracy, rate, and fluency, though this was not significant. Passage comprehension as evaluated by two independent measures (Gray Oral Reading Test, Woodcock) was intact for PNH subjects and dyslexic subjects.

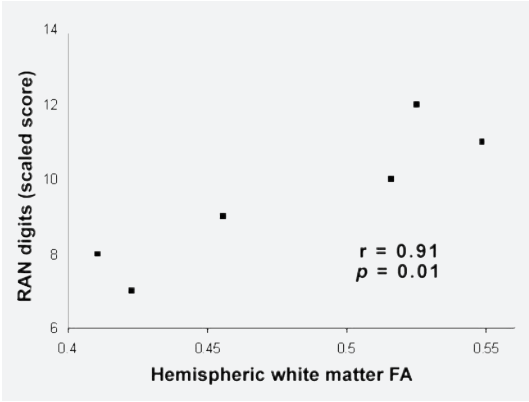
White matter integrity and relationship to reading ability. Because the reading disability in PNH seemed to be characterized primarily by difficulties with fluency and rapid naming, we hypothesized that variations in hemispheric white matter microstructure in PNH might serve as the neuroanatomic substrate for this behavioral finding, because acquired white matter abnormalities have been associated with reaction time and processing speed deficits in other populations,[32,33] and there is accumulating evidence of white matter microstructural changes in patients with dyslexia.[14-17]

Figure 2 Performance of subjects with periventricular nodular heterotopia, subjects with dyslexia, and normal readers on word reading and reading-related tasks



(A) Subjects with periventricular nodular heterotopia (PNH) and subjects with dyslexia performed worse than normal readers on the Elision subtest of the Comprehensive Test of Phonological Processing, a measure of phonemic awareness; this difference was significant for subjects with dyslexia. (B) Subjects with PNH and subjects with dyslexia showed a similar profile on tests of rapid automatized naming. Both groups were significantly worse than normal readers on the letters and digits rapid automatized naming subtests. Both groups showed a trend toward worse performance on the objects subtest as well, though this was not significant. A discrepancy was seen in the performance of PNH subjects and dyslexic subjects on tasks of word reading, depending on whether the tasks were presented in a time-sensitive manner. Reading of real words and nonwords in an untimed way (C; Word ID and Word Attack subtests of Woodcock Reading Mastery Test–Revised) was performed well by PNH subjects and dyslexic subjects when compared with normal readers. In contrast, reading of real words and nonwords in a setting in which subjects were asked to perform the tasks as quickly as possible and scaled scores were time sensitive (D; Sight Word Efficiency and Phonetic Decoding Efficiency subtests of Test of Word Reading Efficiency) revealed that PNH subjects and dyslexic subjects performed significantly worse than normal readers. Asterisks indicate significance.

Figure 3 Correlation of reading fluency with hemispheric white matter integrity in periventricular nodular heterotopia



Scatterplot showing the relationship between performance on the rapid automatized naming (RAN) digits subtest (scaled score) and hemispheric white matter fractional anisotropy (FA) for six subjects with periventricular nodular heterotopia. As described in Methods, hemispheric white matter FA was calculated by averaging the mean FAs across multiple regions of interest drawn bilaterally to exclude normal cortical and deep gray matter and heterotopic gray matter nodules. Pearson correlation analysis demonstrated that the relationship depicted was significant.

Six PNH subjects underwent magnetic resonance-based DTI, and hemispheric white matter FA, a global measure of white matter integrity derived from the directional diffusivity of water, was analyzed by calculating a composite score across multiple ROIs hand drawn bilaterally for each subject to exclude the periventricular nodules as well as cortical gray matter and normal deep gray matter. Hemispheric white matter FA was significantly lower in subjects with lower scores on one measure of reading fluency, rapid naming of digits (figure 3), and a similar trend was seen with another fluency measure, rapid naming of letters (table 2). No relationship was seen with measures of phonological processing or word reading. FA in the left superior corona radiata and left posterior limb of the internal capsule, two specific white matter fiber bundles previously linked to word reading skills in dyslexic and normal readers,[15,17] showed no relationship with measures of reading fluency, word reading, or phonological processing in PNH subjects.

The focal effect of gray matter heterotopia on white matter microstructure. To explore the specific effect of heterotopic gray matter on the integrity of subcortical white matter, FA was calculated in ROIs drawn in areas of white matter directly overlying periventricular heterotopic nodules in subjects with PNH; comparison was then made with FA from homologous contralateral ROIs that did not overlie nodules. Asymmetric nodule location thus allowed for the use of each subject as his own control; in this way, normalizing (warping) PNH images for comparison with control subjects was avoided, because that may have introduced unexpected distortions caused by heterotopic gray matter. Mean FA was lower (0.43 vs 0.48; $p = 0.03$) in the ROIs over nodules than in the homologous contralateral ROIs not over nodules, suggesting focal and specific alterations in white matter microstructure over deep heterotopic gray matter.

Cortico-cortical fiber tract organization. Because FA analysis suggested focal white matter alterations over nodules, we sought to explore these regions using fiber tracking methods. Three-dimensional fiber tracts in regions overlying gray matter heterotopia were visualized, using tractography software. Fiber tracts traveling through the adjacent white matter from and to other regions of cortex were seen to deviate around the periven-

Table 2 Relationship of white matter fractional anisotropy to behavioral measures in periventricular nodular heterotopia

	Hemispheric white matter FA		Left superior corona radiata FA		Left posterior limb of internal capsule FA	
	r	*p*	*r*	*p*	*r*	*p*
RAN (letters)	0.78	0.07	0.20	0.71	−0.04	0.94
RAN (digits)	0.91*	0.01	0.34	0.51	0.20	0.70
Real word reading (Word ID)	0.28	0.60	−0.29	0.57	−0.63	0.18
Nonword reading (Word Attack)	0.58	0.22	−0.02	0.97	−0.36	0.48
Elision	0.61	0.20	0.08	0.89	−0.25	0.63

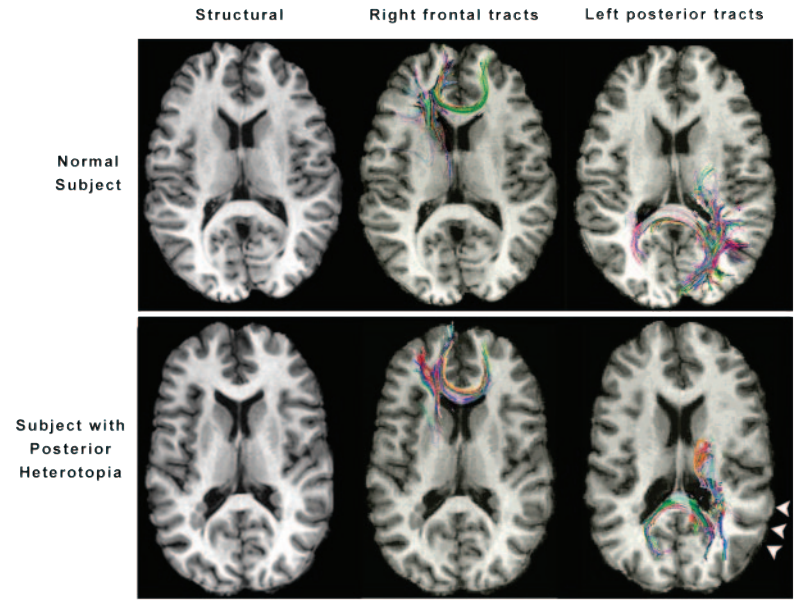
Pearson correlation coefficient (*r*) for relationship between FA and behavioral scaled score is indicated in each cell. Two-tailed *p* values are presented.
*Significant.
FA = fractional anisotropy; RAN = rapid automatized naming.

tricular nodules, but in general, no fiber tracts were seen emanating from or projecting into the nodules themselves. Strikingly, more superficial segments of subcortical white matter overlying gray matter nodules seemed to have a consistent paucity of well-organized fiber tracts.

Coregistration of visualized fiber tracts onto two-dimensional anatomic MRI images for multiple PNH subjects (figures 4 and 5) confirmed the specificity of white matter disorganization with regard to heterotopic nodule location. Subjects with posterior heterotopic nodules demonstrated disorganized white matter over the nodules but normally organized frontal white matter (figure 4, bottom row), whereas subjects with frontal heterotopic nodules demonstrated disorganized white matter anteriorly but normally organized posterior white matter (figure 5).

DISCUSSION Dyslexia is a complex, heterogeneous disorder that affects the capacity of the brain to acquire one of the most fundamental skills of modern human communication, the ability to read. We have used the anatomic and behavioral study of a genetic brain malformation characterized by neuronal migration failure to explore one specific aspect of reading disability—namely, reading fluency. Our work takes advantage of an unusual opportunity to study the structural basis of cognitive function: the association of a well-defined developmental brain malformation with a specific behavioral profile.

Figure 4 Specificity of white matter fiber tract disorganization: Normal control and subject with posterior periventricular nodular heterotopia



Images in each row comprise an axial, T1-weighted, structural MRI image (left), visualized fiber tracts in the right frontal subcortical white matter and genu of the corpus callosum (middle), and visualized fiber tracts in the left posterior white matter and splenium of the corpus callosum (right). Images in the top row, from a normal control subject without brain malformation, demonstrate that normal frontal and posterior white matter contains callosal, projection, and intrahemispheric cortico-cortical fibers in organized bundles. Images in the bottom row, from a patient with bilateral posterior periventricular nodular heterotopia, demonstrate that the left posterior white matter is abnormally organized: fiber tracts deviate around the periventricular nodules, and there is a distinct paucity of organized fiber tracts in the gyri overlying the nodules (white arrowheads). Right frontal white matter appears normally organized. Fiber tracts are depicted only unilaterally in each image, to improve figure clarity.

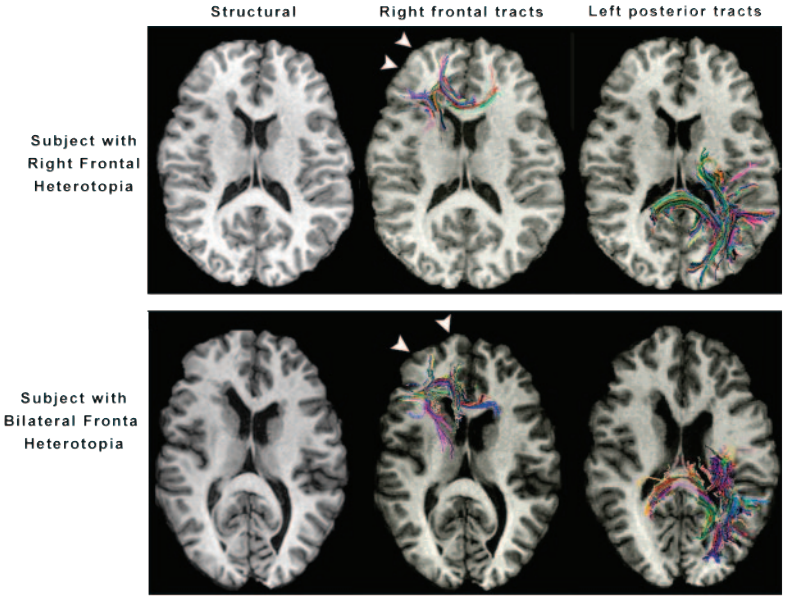
Most studies of dyslexia have demonstrated the centrality of a phonological processing deficit.[34] Although systematic research on the role of phonological processes in reading failure and intervention has proven highly predictive for many individuals, the heterogeneity of reading disabilities and the complexity of reading breakdown suggest that a unidimensional view of reading may be too simplistic. In many subjects with dyslexia, additional deficits, including sensorimotor problems or naming speed deficits, are also present.[35] Individuals who have a double deficit—both phonological difficulties and naming speed impairment—may benefit from remediation methods that are not solely phonologically based,[36] and reading fluency in general tends not to improve with remediation as much as reading accuracy does.[37]

Behavioral profiles can also change over time. In adults with dyslexia, for example, fundamental word decoding skills may become quite accurate after years of educational experience and reading practice, whereas fluency-based deficits can remain and often serve as the sole markers of reading breakdown in this "compensated" population.[38] Indeed, the dyslexic adults in our study seem to demonstrate a compensated behavioral profile, in which single-word decoding skills are normal but both phonological skills and naming speed remain impaired when compared with normal reader controls.

The form of reading disability associated with PNH seems to be mainly fluency based, although there was also a trend toward worse phonological skills in this population compared with normal readers. Other studies have found that a relatively small subset of dyslexic individuals as a whole have pure fluency problems without significant phonological deficits. These individuals do not typically display decoding problems or a general decrease in speed of processing; rather, they show isolated difficulty with the fluent processing of letters, words, and connected text.[4] The behavioral profile of our reading-disabled PNH subjects is most similar to that of those individuals.

There has been increasing neuroimaging evidence that abnormalities in cortico-cortical connectivity may be important in many individuals

Figure 5 Specificity of white matter fiber tract disorganization: Subjects with frontal periventricular nodular heterotopia



Images in each row comprise an axial, T1-weighted, structural MRI image (left), visualized fiber tracts in the right frontal subcortical white matter and genu of the corpus callosum (middle), and visualized fiber tracts in the left posterior white matter and splenium of the corpus callosum (right). Images in the top row, from a subject with a single, large, right frontal periventricular nodule, demonstrate that the right frontal white matter is abnormally organized: fiber tracts deviate around the large periventricular nodule, and there is a distinct paucity of organized fiber tracts in the gyri overlying the nodules (white arrowheads). Images in the bottom row, from a subject with bilateral frontal heterotopia, demonstrate a similar disorganization of right frontal white matter. In both subjects, left posterior white matter appears normally organized. Fiber tracts are depicted only unilaterally in each image, to improve figure clarity.

with dyslexia. A decrease in FA, a measure of white matter integrity, has been reported in the temporoparietal white matter in a group of adults with poor reading, and FA in a segment of left temporoparietal white matter in particular correlates with the degree of word reading ability in adult normal readers and dyslexic readers.[14] Similar relationships have been observed between FA in several proximate left hemisphere white matter regions and the reading scores of young children, including normal readers and also those with reading disability.[15-17]

Isolated fluency deficits, in particular, strongly suggest the possibility of a functional disconnection of cortical regions involved in reading, because abnormalities in fiber tracts connecting these areas might be expected to lead to a difficulty with the rapid processing and integration of serial stimuli, whereas the elemental phonological and orthographical skills necessary for reading accuracy might remain relatively unaffected. Indeed, some investigators have found that rapid naming, a timed measure of automaticity of information retrieval, correlates with FA, and they have suggested that time-sensitive processing may be facilitated by increased connectivity.[16] In addition, faster learning of novel speech sounds is associated with denser parietal white matter structure, especially in the left hemisphere,[39] whereas lower FA in specific brain regions seems to be associated with slower response times.[33] Finally, detailed anatomic studies of dyslexic subjects have suggested that abnormalities in a frontal-cerebellar circuit may be particularly relevant to those individuals with rapid naming problems and the double-deficit subtype of reading disability.[40] If this is the case, then disruptions of cortico-cortical fiber tracts along many different points within the cerebral white matter might be expected to lead to a common behavioral profile of reading fluency impairment.

Our findings strongly support the hypothesis that disconnection of cortical regions plays a critical role in reading fluency. We had previously shown that the degree of reading impairment in PNH subjects is worse in those whose nodules are anatomically more widespread, rather than restricted in distribution.[18] Our current findings suggest an explanation: it may be the degree to which long cortico-cortical fiber tracts are affected along their paths that influences the subjects' reading performance, rather than the specific locations of gray matter nodules themselves. Indeed, whereas hemispheric white matter FA correlated strongly with performance on reading fluency tasks, we found no such correlation using FA in the left superior corona radiata or posterior limb of the internal capsule—specific white matter regions that have been associated with word reading ability in other studies.[15,17] Although our ability to detect such a correlation may have been limited by sample size and a restricted FA range in PNH, these findings suggest that fluency deficits may arise from more widespread white matter disruptions than decoding deficits, which may localize more precisely to specific regions in the left hemisphere.

There are several limitations to our work. The sample size is small, although PNH is a rare malformation, and our findings are consistent across subjects. A larger number of subjects in a future study might allow for a more refined analysis of the effect of nodule location on behavioral measures. Of necessity, our results are only correlative in nature. Although it is highly plausible that the abnormalities of white matter connectivity in PNH lead to the observed reading fluency problems, it is conceivable that no causal relationship exists or that years of difficulty with reading lead to structural changes within the cerebral white

matter. A longitudinal study of young children with PNH might help to address some of these issues, although the rarity of the condition and the usual delay in diagnosis until at least adolescence, after the development of seizures, would significantly limit subject recruitment. All of our PNH subjects have had seizures, but the lack of correlation between reading impairment and severity of epilepsy,[18] and the presence of a correlation between decreasing reading fluency scores and decreasing white matter integrity, suggest that it is the effect of the malformation itself, rather than epilepsy or anticonvulsant use, that leads to our behavioral findings. Finally, tractography methods do not allow us to identify the specific anatomic fates of white matter fiber tracts, only their degree of directional organization. Although disorganized or circuitous fiber pathways could theoretically maintain cortico-cortical connectivity, it is reasonable to assume that such pathways would not be optimally efficient and could result in functional impairment. Functional connectivity might be addressed using functional MRI to examine patterns of gray matter coactivation during reading-related tasks.

Our findings do raise the possibility that similar brain malformations characterized by neuronal migration failure and the presence of heterotopic gray matter might share common behavioral features with PNH. However, most such disorders are associated with a significant degree of global cognitive impairment, unlike PNH, making detailed behavioral assessment more challenging, and potentially limiting the ability to obtain high-quality DTI. There are several potential mechanisms by which neuronal migration failure might lead to the observed white matter microstructural changes, including disruptions in radial glial cell function or the formation of aberrant fiber tracts emanating from affected overlying cortex, but the investigation of these is likely to require molecular and microscopic techniques in animal model systems rather than in vivo human neuroimaging.

Malformations of cortical development include not just disorders of gray matter heterotopia but many other conditions in which the normal process of brain development is disrupted during embryonic and fetal life.[41] Some of these result from abnormalities in the proliferation of neuronal progenitor cells, resulting in too many or too few mature neurons; others, like PNH, result from abnormalities in the migration of neurons from proliferative zones to their ultimate destinations in the cerebral cortex; and yet others result from abnormalities in cerebral cortical organization. As advances are made in our understanding of the molecular and genetic bases of many such malformations, it becomes increasingly important to understand the cognitive and functional consequences of cortical maldevelopment, especially as these disorders are being clinically diagnosed with increasing frequency because of the widespread use of brain MRI.[42]

Historically, much of what we know about brain–behavior relationships has come from the study of acquired lesions affecting the mature brain. More recently, functional neuroimaging has provided the capability to study the anatomic basis of physiologic behavior noninvasively in normal subjects. Our work, and that of others,[43,44] supports the longstanding conception that developmental brain malformations can serve as an alternative model for our understanding of brain–behavior relationships, one that may be particularly relevant to the study of neurodevelopmental disabilities such as dyslexia.

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A structural basis for reading fluency: White matter defects in a genetic brain malformation

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controlled studies for MS, only active comparator studies be performed.

First, by performing active comparator studies (noninferiority studies or superiority studies without a placebo group), the issue of the ethics of placebo-controlled studies becomes moot. Second, while it is true that something is lost by omitting placebo groups, something is gained by the use of active comparator groups and I think that what is gained outweighs what is lost.

From a statistical standpoint, it seems that patient populations recruited for a previously performed placebo-controlled study and for a planned active comparator study may not be the same, and for that reason active comparator studies are inappropriate. However, when considering which MS medication to use, for example, the great majority of clinicians base their decisions on results of published studies without considering the details of strict comparability of the patient populations in the studies.

Medical care is delivered on that basis. While placebo-controlled studies provide information as to whether a medication is effective, active comparator studies are valuable to clinicians since they provide at least some information as to whether the test medication is effective and importantly, how it compares to the EET, which is valuable information to clinicians.

The statistician may argue that something is lost because the recruited patient populations may not be the same. For example, in a planned study comparing a beta interferon—shown to be effective in a previous placebo-controlled study—and a new medication, something is lost by not performing an active comparator study. As a non-statistician, I would argue that in instances where an EET for an illness has been demonstrated in placebo-controlled studies, trials of new medications should be performed vs the EET.

Placebo-controlled studies have been the gold standard of treatment trials. But just as the United States went off the gold standard in 1933, possibly it is time to make a similar change in considering treatment trials.

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Reply from the Authors: We thank Dr. Tenser for his interest in our article[1] and for his comments.

We agree that active comparator studies of experimental agents against EET therapy can provide clinical guidance and can contribute to demonstrating efficacy and safety (thus benefit/risk) of a new compound in comparison to EET.

In our opinion, for active comparator studies in MS, a superiority design is preferable to a non-inferiority design, the latter of which can be an invitation to a poor quality study and requires an arbitrary choice for what is considered to be a tolerable difference for inferiority. In addition, inherent noise in measuring MS outcomes (such as Expanded Disability Status Scale) and variability in patient responsiveness to EET will tend to favor an evaluation of non-inferiority when no signal—only noise—is being detected.

However, when ethically and practically acceptable, a placebo-controlled study design is more informative and may be more efficient in terms of numbers of subjects and duration of studies. In addition, some regulatory agencies currently require a placebo arm to be included in study designs—even superiority studies—to provide a gauge of assay sensitivity of the experimental agent.

Our intent was not to promote placebo-controlled studies over their alternatives, but to provide perspective and guidance on the ethics of randomized clinical trials in MS, with a focus on placebo-controlled studies. Consideration of ethics is a necessary prerequisite for providing further and better treatment options available to patients with MS without unnecessary delays.

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CORRECTION

A structural basis for reading fluency: White matter defects in a genetic brain malformation

In the article "A structural basis for reading fluency: White matter defects in a genetic brain malformation" by B.S. Chang et al. (*Neurology*® 2007;69:2146–2154), author Stephen Wong should have been listed as Wong ST. The authors regret the error.