

NEUROANATOMY OF READING AND DYSLEXIA

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Since the first description of dyslexia a century ago,⁶¹ scientists have used a variety of clinical, anatomic, and cognitive tools to understand the language system and the deficits underlying dyslexia. By combining tasks developed to test cognitive theories of language with powerful new technologies like functional imaging, investigators are beginning to identify basic cognitive processes of reading and reading disability and to map them to neuroanatomic loci. These research efforts are not only an attempt to answer basic neurobiologic questions about a cognitive process so important to humans (reading), but also offer an approach for examining the neural correlates of children with dyslexia.

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In this article we examine evidence that dyslexia represents a disorder affecting linguistic systems in brain, and more specifically, one particular component of the language system, phonologic processing. We next describe the search for the neural loci of these cognitive processes, beginning with an historical overview of cerebral localization and progressing to a review of morphometric studies of dyslexia and the rationale for functional imaging studies. The final section describes our research group's experience with functional magnetic resonance (fMR) imaging studies in language and reading.

THE COGNITIVE BASIS OF READING AND READING DISABILITY

To understand reading, one must first understand the language system and the relationship between language and reading. Both reading and writing represent the language system, with writing systems providing a way to visually record the spoken word.³ Language is served by specific neural systems that evolved in man to allow the emergence of speech some 100,000 to several million years ago.³⁶ To read one must enter the language system, but unlike language, which is automatic to both speaker and listener, understanding the written representation of language must be taught.⁴⁸

Written language is based on two essential features: (1) phonemes, sounds representing the basic linguistic units; and (2) graphemes, symbols or written elements used to represent the inventory of phonemes. Phonemes serve as the basic building blocks of all spoken and written language. In an alphabet system such as English, the 26 letters of the alphabet, singly or in combination, represent the 44 phonemes comprising the language. For example, the word "bat" is composed of three separate phonemes: buh, ah, tuh. On a representational level, these letter groupings, or graphemes, serve as written proxies for phonemes and function as operational units of our writing system.

The neural substrates of the language system automatically process both speech and listening. In speaking, the phonologic units are coarticulated; they are automatically merged and blended producing no overt clue to the segmental nature of speech. In listening, there is automatic segmenting of the coarticulated utterances into their underlying phonologic elements. Although normal speech involves coarticulation of 10 to 12 phonemes per second and rapid speech 25 phonemes per second, spoken language sounds seamless. Both the coarticulation and the segmenting functions are performed automatically and unconsciously for speaker and listener, obviating the need for either to develop an awareness of the basic sound structure of language.

The task facing beginning readers can now be understood. Speaking is automatic but reading is not. To read, one must realize that written words possess an internal phonologic structure, that the orthography represents this sound structure, and that the printed word is represented by the same underlying sound or phonologic structure as the spoken word.

A thorough understanding of the cognitive basis of reading is a prerequisite for study of the neural substrate of reading and reading disability. Over the last two decades investigators have made considerable progress in developing and validating a cognitive model of reading and reading disability.^{25-27, 52, 64} Evidence from a number of lines of investigation identify phonologic processing as the specific cognitive deficit responsible for reading disability.^{50, 72, 86, 90} Most children tested after a year of schooling are found to have acquired phonologic awareness (defined as an awareness of and access to the phonologic structure of words);

however, a significant number (30%) still are unable to demonstrate such an awareness.⁵¹ These data are consistent with a reported prevalence rate for dyslexia of approximately 20% in an unselected school-aged sample comprising the Connecticut Longitudinal Study (CLS).⁵⁵ Further support for the phonologic model of dyslexia is provided by developmental studies indicating both that phonologic abilities are related to reading acquisition,^{7, 59, 91} and that explicit training in phonologic awareness improves reading in poor readers.^{2, 4, 7, 36, 58} Recent evidence from two large and well-studied populations of children with reading disability^{19, 51, 56} confirm that a deficit in phonologic processing represents the most robust and specific correlate of reading disability (Fig. 1).

Studies of older children and adolescents indicate that phonologic processing abilities continue to be the best predictor of reading, explaining 73% of the variance in decoding in a sample of 15-year-old high school students participating in the CLS.⁵² Studies in young adults support the notion that phonologic processing deficits persist.^{3, 8, 9} These deficits are most often demonstrated by

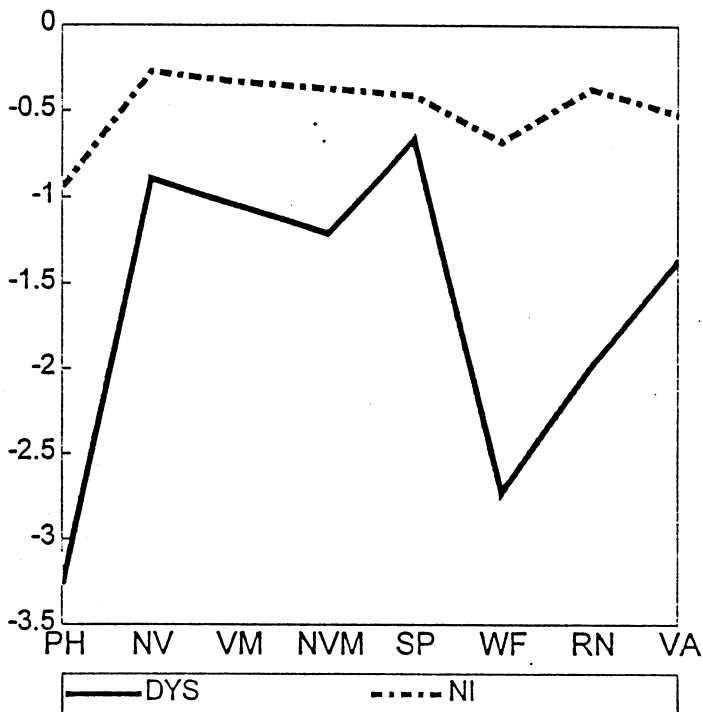


Figure 1. Performance profiles of nonreading-impaired (NI) children compared with children with dyslexia (DYS). The eight cognitive variables, shown as z scores (described in detail in references 25 and 85), are: PH, phonologic processing; NV, nonverbal (i.e., visual-spatial) processing; VM, verbal memory; NVM, nonverbal memory; SP, speech production; VOC, vocabulary/word finding; RN, rapid naming; and VA, visual attention. The more negative the z-score, the poorer the performance. Thus, dyslexic readers demonstrate poorest performance on PH and WF, relatively better performance on measures of NV, VM, and NVM, and intermediate performance on SP, RN, and VA. Nonimpaired readers are significantly better than DYS readers on all measures.

lack of automaticity in word identification, particularly in pseudoword reading. The lack of automaticity is usually manifest as an extremely slow reading rate. Other consequences of impaired phonologic processing may be apparent. In oral language, dyslexic individuals characteristically exhibit problems in naming objects, in word retrieval, and in carrying out complex articulatory sequences, owing to difficulty in quickly and accurately retrieving the appropriate phonologic representations.

These results indicate that a deficiency in phonologic processing characterizes reading disability across the life span, including both poor beginning readers and older impaired readers. For clinical applications, the phonologic model provides a definition of dyslexia⁶² that is both theoretically and empirically driven, and that replaces the previously vague definition based primarily on exclusionary criteria.¹² For research, neurobiologic investigations can now be done within the context of an empirically supported model of both reading and reading disability. Identification of phonologic processing as the core cognitive deficit provides a conceptual template for planning and interpreting studies seeking the neuroanatomic locus of dyslexia.

Current psychologic theories of word identification in reading postulate that at least three distinct computational systems are engaged by a printed word: (1) orthographic, those processes that result in letter identification; (2) phonologic, those processes that result in the identification of the phonemic constituents of the printed message; and (3) lexical-semantic, those processes that result in the successful identification of the word's meanings, rendering that information available for all higher-level processing. Debate continues on the specific ways that these processes interact to produce successful word identification.^{10, 55, 70, 78, 89} Dual-route models of reading¹¹ assume that access to a word's meaning can be accomplished via a direct orthographic-to-lexical route or through a phonologically mediated route. The phonologically mediated route involves processes that map letters or letter clusters onto phonemes or phoneme clusters (called *assembled phonology*) and processes that map these phonologic representations onto the lexical-semantic system. It had generally been assumed that the phonologically mediated route predominates in children whereas the direct access route from orthography to the lexicon develops later and is used by experienced readers; more recent evidence, however, indicates that the phonologically mediated route not only is the principal route to word identification in beginning readers but that the phonologic route continues to operate even in highly skilled readers.^{55-57, 65} We believe that the debate about the processing dynamics of language systems can be advanced by establishing links to functional neuroanatomy.

THE CEREBRAL LOCALIZATION OF READING

Brain Injury

The concept of the cerebral localization of neural function was suspected in antiquity,²⁹ and by the mid eighteenth century clinicians were aware of the influence of brain on motor and sensory functions.¹ Studies of the cerebral localization of cognitive functions in man are even more recent, beginning less than two centuries ago with Gall's proposal that mental functions were localized in the cerebral hemispheres.^{94, 96} Based on Gall's hypotheses, others began to localize cognitive functions by studying the brains of individuals who suffered from strokes or traumatic injury to brain, and began to relate the loss of

particular cognitive functions to damage to specific brain regions. Language was the first cognitive process to be localized in brain. Following Broca's discovery in 1861, other investigators related a range of cognitive functions to specific brain regions based on descriptions of patients with brain lesions. By the end of the nineteenth century brain maps of the localization of cerebral function had become quite detailed.^{18, 24}

Neuroanatomy and Morphometry

It is only in recent years that systematic neuroanatomic studies have attempted to relate abnormalities in brain structure to reading and dyslexia by using postmortem anatomic measures and structural morphometric techniques. Galaburda and associates²³ reported symmetry of the planum temporale rather than the usual pattern of a larger planum temporale on the left. Such findings were consistent with a hypothesis that dyslexia results from damage or maldevelopment of language regions in fetal life, and when the language area on the left side of the brain is damaged, there is a corresponding increase in right-hemispheric function.²⁴

The development of neuroimaging procedures offers an attractive alternative strategy to examine neuroanatomic correlates of dyslexia.⁴⁰ Although early CT studies in dyslexic individuals seemed to confirm a reversal in symmetry or lack of the normal asymmetry,^{38, 46, 54, 73} later reports failed to show any differences.^{36, 63, 75} More recent MR imaging reports have not clarified the controversy.^{17, 41, 43, 44, 47} Review of these previous studies indicates wide variations in subjects' age, sex, handedness, and diagnostic criteria for dyslexia. Lack of consistent results among studies might be explained by these factors, as well as by difficulties in reliably and accurately measuring the planum temporale.⁶¹ We used morphometric MR imaging techniques to compare the planum temporale in a sample of right-handed children with dyslexia and nonimpaired children of comparable age, IQ, handedness, and sex.⁷⁷ Our findings indicate that sex, age, and overall brain size significantly influence specific morphometric measures of brain, especially the surface area of the planum temporale. Differences in subject characteristics (e.g., sex, age, handedness, and variability in the way dyslexia is defined) as well as methodologic variations in measurement of anatomic regions of interest, such as the planum temporale, may play an important role in explaining the apparent discrepant results obtained in structural neuroimaging studies of dyslexic populations.

Although much has been learned about cerebral localization of cognitive function based on neuroanatomic studies of individuals with brain damage, these studies provide a static picture of brain anatomy rather than a dynamic view of brain function. Functional imaging, which can measure brain function during performance of a cognitive task, has become an important tool to relate brain function and structure.

Functional Imaging

A cognitive task makes processing demands on particular neural systems in the brain. Those demands are reflected by changes in brain metabolic activity, such as changes in cerebral blood flow, or changes in utilization of metabolic substrates, such as glucose. With functional imaging, it is possible to measure those changes in metabolic activity.

The first functional imaging studies used xenon 133 to measure cerebral blood flow but more recent studies use positron emission tomography (PET). PET requires intravascular administration of a radioactive isotope to the subject so that cerebral blood flow or cerebral utilization of glucose can be determined while the subject performs the task. Although much has been learned about language using PET technology,^{15, 21, 66} PET uses short-lived radioisotopes, requires a cyclotron and associated team of technicians, and suffers from relatively poor spatial and temporal resolution and sensitivity. When considering studies in children, the invasive nature of the procedure, the exposure to radiation, and the logistics of generating short-lived isotopes limit the utility of PET.

A number of previous studies have used functional imaging methods to examine brain activation patterns in dyslexic subjects.^{20, 29, 30, 53, 54, 74, 76} Review of these studies indicates a general lack of consistency in findings from study to study. An important factor is the limitation in task design imposed by the requirements of PET, because the short half-life of the radioisotope determines the time course of the experiment. One previous study used a reading task rather than a spoken language measure, but the task did not assess phonologic processing.²⁹ Recent developments in functional imaging technology and advances in task design now make it possible to circumvent these limitations.

Functional MR Imaging

A relatively new imaging technique, MR imaging, offers great potential to map the brain's response to cognitive stimuli. Because fMR imaging is noninvasive and safe, it can be used to study humans repeatedly, including children and neonates. The signal used to construct MR images changes by a small amount (typically 1% to 5%) in regions that are activated by a stimulus or task. The increase in signal results from the combined effects of increases in the tissue blood flow, volume, and oxygenation, though the precise contributions of each of these is still somewhat uncertain. At least in some conditions, the increase in activation produces a flow increase locally that introduces oxygenated blood to a degree that is greater than the increased metabolic demands, with the result that the tissue oxygen tension increases, and the venous blood becomes more oxygenated. The significance of this is that the intravascular magnetic susceptibility then more closely matches the surrounding tissue than when the vessels contain deoxyhemoglobin. In the deoxygenated state, the heme group in blood produces a significant paramagnetism that disturbs the homogeneity of the magnetic field in the environment of the vasculature, whereas in oxygenated blood the disturbance is much smaller. This in turn means that the magnetic field experienced by tissue water in the close vicinity of activated volumes is more uniform. The signal used to construct MR images is derived from the nuclear magnetization produced mainly by tissue water protons. This magnetization can be tipped away from its equilibrium alignment in the direction of an applied external field using radiofrequency pulses, and the resultant signal decays at a rate that is termed $1/T_2^*$. The decay rate is slower, and the MR signal therefore stronger, when the magnetic field is uniform. MR image intensity increases when deoxygenated blood is replaced by oxygenated blood.

A variety of MR imaging techniques can be used, but one preferred approach makes use of ultrafast imaging such as echo-planar imaging (EPI), which acquires complete images in times substantially shorter than a second. EPI can provide images at a rate fast enough to capture the time course of the hemody-

pattern of case (upper and lower) alternation. This task engages both visual-spatial and orthographic (letter) processing. In a rhyme-judgment task, subjects determine whether two nonsense word strings rhyme. This task engages visual-spatial, orthographic, and assembled phonologic processing (subjects must map the letter strings onto appropriate phonologic representations). Finally, in a semantic category task, subjects determine whether two words come from the same semantic category. This task engages visual, orthographic, phonologic, and semantic information.

Recent Studies

In initial studies, we examined 19 neurologically normal right-handed men and 19 women performing the tasks described above.⁵³ Eight regions of interest in both left and right hemispheres were chosen for analysis to ensure broad coverage of those brain regions that previous neuropsychologic and neuroimaging investigations indicated were relevant to language function.^{13, 15, 21, 66} These include the following regions for both the left and right hemispheres: lateral orbital gyrus, prefrontal dorsolateral (primarily Brodman Area 46), inferior frontal gyrus (primarily Brodman Areas 44 and 45), superior temporal gyrus, middle temporal gyrus, and medial and lateral extrastriate areas. On each anatomic and functional image the positions of the anterior commissure and posterior commissure and the direction of the midline were found manually. These reference points and the edges of the brain let us define the standard Talairach coordinate system⁶⁸ for each subject. Each brain (anatomic image and activation map) was then rescaled to the standard Talairach form using cubic proportional fitting for each block, a piece-wise warping algorithm. Each anatomic region of interest was identified in the Talairach coordinate system and approximated by a set of squares.

The activated pixels in each region of interest were detected for each pair of activation tasks using a split Student's *t*-test. The split *t*-test divides the data into two parts and performs a separate *t*-test on each half. If the *t*-value for a given pixel from both *t*-maps was more than 2 (nominal $P < 0.05$ on each, nominal $P < .0025$ for both), the pixel was considered to be activated. The number of significantly activated pixels in each region was then used as a measure of the level of activation for any given subtraction condition. The dependent variable was the number of pixels within these regions of interest that demonstrated significant changes in MR image intensity (by split *t*-test) between tasks being compared. For example, pixels activated during the rhyme task minus pixels activated during the letter case task yield activations related to phonologic processing, since, by the logic of the subtraction strategy (see Table 1) rhyme minus case isolates phonologic processing. Data were analyzed by region of interest and for each subtraction condition by hemisphere and gender.

Figure 2 illustrates activations in three subtraction conditions (representing orthographic, phonologic, and semantic processing) in two regions of interest (inferior frontal gyrus [IFG] and extrastriate [ES]). In the IFG, activations during phonologic processing were significantly greater than activations during either orthographic or semantic processing. These findings are consonant with previous functional imaging studies that show activation in this region in speech-production tasks,⁶⁷ in complex discriminations of speech tokens,^{14, 15, 95} in phonologic judgments on visually presented single-letter displays,⁷⁹ and in word/nonword discriminations on visual stimuli.⁶⁹ Our findings are also consistent with studies

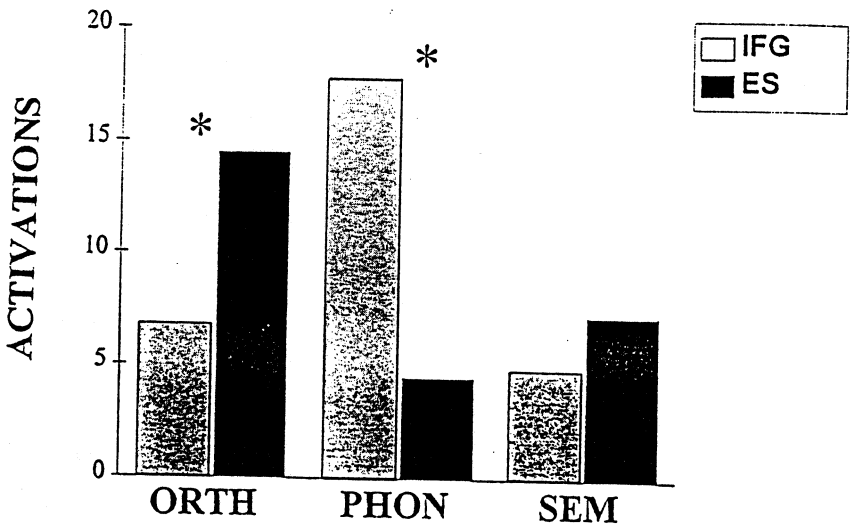


Figure 2. Brain regions activated by tasks that tap orthographic (ORTH), phonologic (PHON), and semantic (SEM) processing. The ordinate represents mean activations for case, rhyme, and SEM subtractions in the inferior-frontal gyrus (IFG) and extrastriate (ES) regions, respectively. ES regions are activated significantly, more by the orthographic task than during either PHON or SEM processing. In contrast, IFG was activated more significantly during PHON processing.

of patients with lesions in this region who show evidence of problems with phonetic discriminations.⁶ In contrast, the ES had activations during orthographic processing that were significantly greater than during either phonologic or semantic processing. That orthographic processing makes maximum demands on ES sites is consistent with claims made by Petersen and colleagues^{66, 67} using different tasks in several PET studies.

Activation during phonologic processing was also observed at sites in both the superior temporal gyrus and middle temporal gyrus, areas that fall within traditional language regions.^{14, 67, 92} Semantic processing, however, activated both of these areas significantly more than did phonologic processing, suggesting that these regions subserved both phonologic and lexical semantic processing. We conclude that the temporal sites examined are multifunctional, relevant for both phonologic and lexical semantic processing, an interpretation supported by previous PET studies^{14, 67, 92} as well as by a previous fMR imaging study.⁸³ Lesion studies have also suggested that damage to temporal and temporoparietal sites results in semantic deficits.³⁴

Men and women have different brain activation patterns during phonologic processing. This is illustrated in Figure 3, which shows activation in men and women for each hemisphere during phonologic processing. In the ES region, no significant hemisphere differences in activations are seen for either men or women. In the IFG, however, women had similar amounts of activation in right and left hemispheres but men had significantly more activation in the left hemisphere than in the right. We examined the ratio of right hemisphere (RH) to left hemisphere (LH) activation in the IFG. Eleven of 19 women but no men had an RH-to-LH ratio ≥ 0.70 . For nine of these 11 women the RH-to-LH ratio

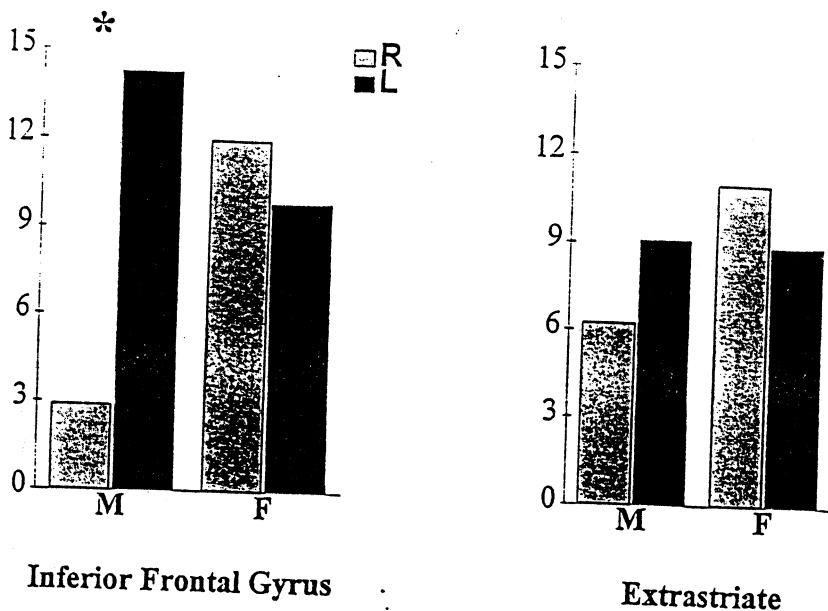


Figure 3. Relationship between region of interest, hemisphere, and gender during phonologic processing. Ordinate represents mean activations across tasks for inferior-frontal gyrus (IFG) and extrastriate (ES) regions. In the ES region, both men and women activated both hemispheres equally. In the IFG, activations for left and right hemispheres were not significantly different for women, but men activated the left hemisphere significantly more than the right.

was ≥ 1.0 . This pattern of activation is also illustrated in Color Plate 2, Figure 4, which demonstrates that activation during phonologic processing in men was lateralized to the left IFG; activation during this same task in women resulted in bilateral activation of this region.

These findings provide evidence of gender differences in the functional organization of the brain for language at the level of phonologic processing. They support a long-held hypothesis that suggests that language functions are more likely to be highly lateralized in men but are more likely to be represented in both cerebral hemispheres in females.^{31-33, 37, 39, 42, 60, 93} Based on these results, we can make a tentative sketch of the anatomic sites associated with the component processes engaged by reading. Initial visual processing presumably makes demands on primary and secondary occipital sites. Mapping these visual features onto orthographic representations seems to engage medial and lateral extrastriate networks irrespective of whether the letter string is pronounceable or nonpronounceable. From this point, assembling a phonologic representation engages primarily inferior frontal sites, largely lateralized in men but bilateral in women. Lexical-semantic information engages aspects of the middle and superior temporal gyri and prefrontal sites. Phonologic processing also appears to engage sites within the temporal gyri, though not uniquely. Activation of the IFG during the performance of a rhyming task may provide a neural signature for phonologic processing, the core cognitive component in reading and reading disability.

This initial study indicates that it is possible to link cognitive function and

brain organization in nonreading-impaired individuals. Recently, we have used these same tasks in men and women with a life-long history of severe reading difficulty and are now analyzing our results. To address questions about the relationship between the functional organization of brain and reading strategies, we have used individual differences in word recognition, as measured by spelling-to-sound regularity effects on lexical decision latencies, and we have related them to brain activation patterns during the four tasks described previously. These relations imply systematic links between neurobiologic measures of brain activation and reading strategies.⁷¹

CONCLUSIONS

Dyslexia represents a deficit of the language system related to phonologic processing. Recent advances in imaging technology and the development of tasks that isolate component processes of reading make it possible to localize phonologic processing in brain, and provide the potential for elucidating a biologic signature for reading and dyslexia. At the basic research level, it is now possible to investigate specific hypotheses regarding the neural substrate of dyslexia and to test cognitive models. From a clinical perspective, a potential biologic signature for dyslexia provides a more sensitive and precise diagnosis of reading disability and offers a parameter to assess the effects of interventions on neuroanatomic systems serving the reading process.

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