Neurobiology of dyslexia
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Introduction
Dyslexia is one of the most common learning disabilities, yet its brain basis and core causes are not yet fully understood. Neuroimaging methods, including structural and functional magnetic resonance imaging, diffusion tensor imaging, and electrophysiology, have significantly contributed to knowledge about the neurobiology of dyslexia. Recent studies have discovered brain differences before formal instruction that likely encourage or discourage learning to read effectively, distinguished between brain differences that likely reflect the etiology of dyslexia versus brain differences that are the consequences of variation in reading experience, and identified distinct neural networks associated with specific psychological factors that are associated with dyslexia.

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Psychological bases of dyslexia
Because reading involves multiple linguistic, visual, and attentional processes, it is probable that variable patterns of weakness may contribute to reading difficulty across children. Although it is unlikely that there is a single causal mechanism of dyslexia, some frequent likely causes have been identified (Table 1). The best understood cause for dyslexia is a weakness in phonological awareness (PA) for spoken (auditory) language that predicts and accompanies dyslexia [11]. Whereas learning a spoken language happens almost effortlessly, learning to read requires explicit knowledge and practice. Children must first become aware of the phonological structure of words, so that they can map those units of sound onto their corresponding printed letters.

A second psychological weakness associated with dyslexia relates to rapid automatized naming or RAN (Table 1). Slowness in naming may reflect difficulty in the integration of cognitive and linguistic processes involved in fluent reading [12]. Often, children who are especially poor readers have weaknesses in both PA and RAN [13], but some children exhibit only one of these weaknesses.

A third category of potential causal explanations for dyslexia relates to basic perceptual processes that may underlie the more proximal PA or RAN weaknesses, such as temporal sampling or processing [14–16], visual–spatial attention [17], or perceptual learning deficits [18]. These explanations are more mechanistic, but perhaps because
they are more distal from reading per se, they are also more debated.

**Functional and structural brain differences in dyslexia**

Meta-analyses of primary research findings have identified broad patterns of functional and structural differences between typical and dyslexic readers. The most common functional brain differences, in children and adults, are reduced activations (hypoactivations) in left temporal, parietal, and fusiform (VWFA) regions [19–22]. In most cases, these hypoactivations arise from comparisons between two tasks or conditions, and thus reflect a lack of differential sensitivity to reading demands rather than a broader dysfunction of those brain regions. Increased activations in dyslexia are sometimes, but not consistently,
observed in left inferior frontal and right-hemisphere regions. Variability across these findings may reflect differences in reading tasks, ages of participants, diversity among dyslexic groups, and other factors. Additionally, structural gray matter differences in dyslexia tend to co-localize with regions that show functional differences [23], but are also observed in the cerebellum, particularly in lobule VI [24,25].

DTI studies often find reduced organization or volume in the left superior longitudinal fasciculus, including the arcuate fasciculus, and corona radiata fibers [26].

Because most neuroimaging studies of dyslexia have been conducted with children or adults who have had years of reading difficulty, it has been impossible to determine whether the brain differences are associated with the underlying neurobiological etiology of dyslexia, or are instead the consequence of years of altered and often vastly reduced reading experience (including compensatory alterations in reading networks). One approach to dissociating the cause and consequence of dyslexia in the brain has been to compare dyslexic children not only to age-matched typically reading children, but also to ‘ability-matched’ children who are years younger than the dyslexic children but read at the same level. Ability-matched children are conceptualized as having approximately the same amount of reading experience as older dyslexic children. In one such study, dyslexic children exhibited reduced left parietal and occipito-temporal activations relative to both age-matched children and ability-matched children, suggesting that these hypoactivations were related to the cause of dyslexia (in contrast, left prefrontal activations tracked ability level) [27].

A similar design challenged another idea about dyslexia, the magnocellular hypothesis of dyslexia. Previously, postmortem evidence from individuals with dyslexia revealed smaller magnocellular neurons in the lateral geniculate body [28], part of the visual pathway that is associated with motion perception. Accordingly, reduced activation for moving gratings in area MT, the cortical region most associated with motion perception, was found in adults with dyslexia [29]. When, however, children with dyslexia were examined, their MT activations were equivalent to ability-matched younger children, suggesting that the MT hypoactivation in dyslexia reflected reading experience [30**]. This conclusion was further supported by evidence that remediation of the reading difficulty also enhanced MT activations in children with dyslexia [30**]. These findings suggest that reduced MT activation for visual motion in dyslexia is a consequence, not a cause, of dyslexia. Similarly, many structural brain differences in dyslexia among age-matched groups were eliminated when a group with dyslexia was compared to ability-matched children [31*].

Another strategy for identifying brain differences that underlie dyslexia has been the study of pre-reading children, typically in kindergarten, for whom brain differences cannot be the consequence of altered reading experience. Although pre-reading children cannot have a formal diagnosis of dyslexia, children can be identified as at-risk for dyslexia because of either a family history of dyslexia, which increases their risk of dyslexia by four times or more [32], or low performance on tests of pre-reading skills that tend to predict future reading difficulty (e.g., PA or RAN). Often, these children are followed longitudinally to determine which at-risk children actually progress to dyslexia.

Several neuroimaging studies have found brain differences preceding formal reading instruction in pre-reading children that resemble those observed in older children and adults. ERP studies of the mismatch negativity (MMN), an automatic response to an oddball auditory stimulus that is reduced in adults with dyslexia, have observed differences between infants with versus without a family history of dyslexia [33], and infants who do or do not develop dyslexia [34,35]. Thus, the MMN may be a promising early endophenotype of dyslexia [36*].

In MRI, pre-reading kindergartners with familial risk for dyslexia exhibited reduced bilateral occipitotemporal and left temporo-parietal activations for PA [37**] and also bilaterally reduced gray matter volumes in similar posterior cortical regions [38]. Decreased gray-matter volumes in prefrontal and parieto-temporal regions were also found in 5- and 6-year-olds with maternal histories of reading difficulty [39]. In a heterogeneous sample of kindergartners, pre-reading children exhibited a positive correlation between measures of PA and both the size and microstructural white-matter organization of the left arcuate fasciculus [40].

Although it is not yet known which of these children will develop dyslexia, these studies support the idea that the most commonly observed functional and structural brain differences characterizing dyslexia are present before significant reading experience and therefore are more likely causes rather than consequences of dyslexia.

**Advances in understanding the brain basis of aspects of dyslexia**

**Brain basis of phonological awareness (PA) deficits**

Impaired PA in dyslexia could reflect either a deficit in representing phonetic sounds and/or a deficit in access to and manipulation of those sounds (e.g., for mapping phonemes to print). Previously, a review of behavioral studies of dyslexia concluded that phonetic representations are intact, but access to those representations may be impaired [41] Recently, a neuroimaging study with adults found that phonetic representations, as measured by multivoxel pattern analysis of activations in bilateral auditory cortices, were intact in dyslexia, but that functional and structural (DTI) connectivity between auditory cortices and left inferior frontal gyrus was reduced [42**]. These findings favor the interpretation of dyslexia as being characterized by weakness in access to otherwise
intact phonetic representations. Consistent with this conclusion is the finding that children with dyslexia exhibited reduced prefrontal activation when engaging in an auditory PA task, but no difference in temporal-lobe activation, as compared with both age-matched children and ability-matched children [43].

Brain basis of rapid automated naming (RAN) deficits
RAN has been partially dissociated from PA as a skill essential for learning to read [12,13], but now there is evidence for a neurobiological distinction between the two skills. A large structural MRI study of typical adult readers of Chinese found that phonological decoding ability was related to gray matter volume in left perisylvian cortex, whereas naming speed was related to volume in a more distributed network across all four lobes [44°]. Further, functional activation to a PA task differed among groups of children with PA and RAN deficits, as predicted by the double deficit hypothesis. Activation in left inferior parietal lobule showed a gradient associated with PA ability, whereas activation in right cerebellar lobule VI showed a gradient with RAN ability [45].

Brain basis of reading fluency deficits
For older children with dyslexia who must read longer texts, slow reading is a major problem. Both the psychological and brain bases of reduced fluency for connected text, such as sentences and paragraphs, have been poorly understood relative to the many studies focusing on single-word reading. Two studies, however, examined reading fluency directly in dyslexia during fMRI by presenting sentences word-by-word at varying rates and testing comprehension, but the two studies reported disparate results [46,47]. Both studies reported that more rapid reading resulted in greater activation of left fusiform cortex in the VWFA region. One study reported that children with dyslexia exhibited reduced activation related to fluency exclusively in left fusiform gyrus despite no significant differences in comprehension accuracy [46]. The other study reported that adults with dyslexia exhibited disproportionately worse comprehension accuracy and lesser activation in left prefrontal and superior temporal regions as a function of reading speed, but found no group difference in the VWFA region [47]. Although the populations and outcomes of the two studies differed, they have initiated the analysis of the brain basis of impaired reading fluency in dyslexia.

Brain basis of basic perceptual processes
Neuroimaging findings have reported neural correlates of atypical basic perceptual processes in dyslexia. Successful parsing of the speech signal depends on the ability of left auditory cortex to selectively amplify phonemic information in the 30 Hz (low gamma) range [48]. MEG revealed reduced entrainment, or synchronization of neural firing, to the 30 Hz frequency range in dyslexia, as well as reduced left-hemisphere specialization for such oscillations [49,50°]. These differences may impede the efficient transfer of acoustic information into more abstract phonemic representations. Individuals with dyslexia also exhibited reduced neural entrainment in response to linguistic stimuli [51,52°], differences in EEG signals that reflect integration of auditory and visual stimuli [53], and greater variability of auditory brainstem responses to speech sounds [54].

An advantage of understanding dyslexia in terms of basic perceptual processes is that the neural mechanisms of those processes can be studied in animals. Animal research has linked dyslexia-associated genes such as KIAA0319 with atypical neural migration [55] and impaired speech sound discrimination [55,56], suggesting that the mechanism by which cortical abnormalities result in behavioral deficits is through the disruption of synchronous firing in response to oral language [57]. In humans, variation in KIAA0319 and two other dyslexia susceptibility genes has been associated with variation in left-hemisphere white matter and reading skill [58]. Such research may integrate findings from the genetic, cellular, cognitive, and behavioral levels in understanding the core deficits in dyslexia.

Conclusion
Progress in understanding the cognitive neuroscience of dyslexia may be approaching translation from basic research to intervention for children who will struggle to read. Remediation is known to be most effective in beginning readers, so early and accurate identification may promote effective intervention for children before they experience prolonged reading failure. Neuroimaging has identified biomarkers that enhance or outperform current behavioral measures in predicting long-term reading outcomes [59,60°,61,62,63°]. With further progress in understanding specific components of dyslexia (e.g., PA, RAN, fluency) it may also become possible to develop personalized interventions that target the specific patterns of weaknesses that undermine learning to read in individual children.

Conflict of interest statement
Nothing declared.

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References and recommended reading
Papers of particular interest, published within the period of review, have been highlighted as:
- of special interest
- of outstanding interest


This review summarized recent task-based and resting-state functional connectivity data from fMRI to address the debate of whether the purported ‘visual word form area’ (VWFA) is specific to reading or general to other visual processes. Understanding the nature of the VWFA could clarify how this region differs in dyslexia.


This study showed how use of a younger, ability-matched control group can revise the interpretation of a brain difference in dyslexia. Abnormal activations in response to visual motion occurred in children with dyslexia relative to age-matched typical readers, but activations were equal to ability-matched typically reading younger children. These findings suggest that activation differences in dyslexic children reflected differences in reading experience and not the etiology of dyslexia.


This paper addressed the question of what brain structure differences in children are a cause versus a consequence of dyslexia. Contrary to the many differences observed between dyslexic and age-matched control groups, differences between dyslexic and ability-matched younger groups included only gray matter in right precentral gyrus, and no white matter differences.


The authors studied children with dyslexia and their unaffected siblings in order to examine genetic effects on the amplitude of the mismatch negativity ERP component. This approach breaks ground on characterizing the variety of phenotypes in dyslexia based on new insights into their biological bases.


This is the first study showing that there are anatomically specific differences in brain function in pre-reading kindergartners at familial risk for dyslexia even before formal reading instruction in school.

Although temporal and oscillatory deficits in dyslexia have been proposed before, the authors trace the problem to a reduced specialization for phoneme-loud rhythms in left auditory cortex.


Examining 4-year-old children, the authors found that the auditory brainstem response to speech sounds was associated with phonological awareness skills. This is a promising potential early biomarker of dyslexia that should be studied longitudinally, and a phoneme window into how neural differences can manifest as reading problems.


This was the first study to combine fMRI and EEG/ERP in kindergarten to predict reading outcomes in 2nd grade. Both fMRI and ERP measures related to visual processing in the left occipito-temporal region predicted 2nd grade reading ability. In this small group of children, results suggest that brain imaging in kindergarten could significantly improve classification of future good versus poor readers.
