

# Developmental dyslexia

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Dyslexia is a neurodevelopmental disorder that is characterised by slow and inaccurate word recognition. Dyslexia has been reported in every culture studied, and mounting evidence draws attention to cross-linguistic similarity in its neurobiological and neurocognitive bases. Much progress has been made across research specialties spanning the behavioural, neuropsychological, neurobiological, and causal levels of analysis in the past 5 years. From a neuropsychological perspective, the phonological theory remains the most compelling, although phonological problems also interact with other cognitive risk factors. Work confirms that, neurobiologically, dyslexia is characterised by dysfunction of the normal left hemisphere language network and also implicates abnormal white matter development. Studies accounting for reading experience demonstrate that many recorded neural differences show causes rather than effects of dyslexia. Six predisposing candidate genes have been identified, and evidence shows gene by environment interaction.

## Definition

Individuals with developmental dyslexia have difficulties with accurate or fluent word recognition and spelling despite adequate instruction and intelligence and intact sensory abilities.<sup>1</sup> The ultimate goal of reading is comprehension. Dyslexia is defined by difficulties with decoding, whereas by comparison comprehension is more intact. So-called poor comprehenders show the opposite profile of adequate decoding but poor understanding of what is read.<sup>2</sup> Although some previous nosologies have grouped the two categories together (eg, the fourth edition of the diagnostic and statistical manual of mental disorders [DSM-4]), this Seminar is only about dyslexia. Many researchers use the terms “dyslexia” and “reading disability” interchangeably, although as the preceding distinction makes clear, other forms of learning disability can affect reading. Research suggests that dyslexia represents the low end of a normal distribution of word reading ability.<sup>3,4</sup> Thus, to diagnose the disorder a somewhat arbitrary cutoff must be set on a continuous variable.

Should the diagnostic threshold for dyslexia be relative to age or intelligence quotient (IQ)? The logic behind IQ-discrepancy definitions is that the cause of poor reading might differ between low-IQ and high-IQ individuals. Genetics contributes more to high-IQ dyslexia than to low-IQ dyslexia.<sup>5</sup> However, published work does not support the external validity of the distinction between age-referenced and IQ-referenced definitions in terms of underlying neuropsychology or appropriate treatments.<sup>6–8</sup> Although the two definitions overlap, some people with clinically significant reading problems meet only IQ-discrepancy criteria (high ability, weaker-than-expected word reading), whereas others meet only age-discrepancy criteria (low ability, poor word reading). Thus, for clinical purposes, children who meet either definition should be identified and treated.

## Epidemiology

### Prevalence

Prevalence estimates depend on the definition of dyslexia. A common definition sets the cutoff for reading achievement 1.5 standard deviations below the mean

for age and identifies 7% of the population as dyslexic; a similar IQ–achievement discrepancy definition identifies a similar proportion.<sup>9</sup> A small but significant male predominance exists (1.5–3:1),<sup>10</sup> however, the sex difference in referred samples is higher (3–6:1).<sup>11</sup> Boys with dyslexia come to clinical attention more often than girls, seemingly because they have higher rates of comorbid externalising disorders, including attention-deficit hyperactivity disorder.<sup>12</sup>

### Comorbidities

In addition to comorbidity with attention-deficit hyperactivity disorder, dyslexia is also comorbid with two other disorders of language development—language impairment and speech sound disorder.<sup>13–15</sup> Language impairment is defined by difficulties in the development of structural language, including syntax (grammar) and semantics (vocabulary), whereas the defining characteristic of speech sound disorder is trouble with the accurate and intelligible production of the sounds of one’s native language. In each case, evidence suggests that comorbidity with dyslexia is mediated by shared causative and neurocognitive risk factors.<sup>16,17</sup> These comorbidities are clinically significant because dyslexia is not diagnosed until after a child has been exposed to formal literacy instruction, but attention-deficit

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### Search strategy and selection criteria

We searched PubMed under the medical subject heading “dyslexia” and also searched PsycInfo with the terms “dyslexia” and “reading disability” in conjunction with the terms “developmental”, “genetics”, “treatment”, “brain imaging”, and “cross-linguistic”. We largely selected publications published in the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy and selected any we judged relevant. Several review articles or book chapters were included because they provide comprehensive overviews that are beyond the scope of this Seminar.

hyperactivity disorder, speech sound disorder, and language impairment are all likely to be apparent earlier and can thus predict a child's risk for later reading problems. In one study, the comorbidity between reading and mathematical disabilities in a population sample of schoolchildren (age range 7–12 years) was roughly 25%.<sup>18</sup> Thus, many children with dyslexia can be expected to struggle broadly in school and have more than a specific reading disability.

### Cross-cultural findings

Historically, research on dyslexia has focused mainly on the English language. Reading problems in other languages are now receiving increased attention, and pronounced cross-cultural differences were initially expected (panel 1). Among alphabetic languages, English is especially difficult to learn because the mapping between letters and sounds is less consistent than in most other languages. Thus, the historical emphasis on English could have biased our understanding of universal issues in normal and disordered reading development.<sup>19</sup> In population samples, consistency of orthography strongly predicts reading accuracy among school-age children (panel 2).<sup>20</sup> Children at the low end of reading ability distribution in languages with more consistent mappings between letters and sounds have less severe reading problems than their English-speaking counterparts, at least in terms of accuracy.<sup>21</sup> Difficulties with

reading fluency, or speed of reading connected text, seem similar across languages.<sup>22</sup> Spelling problems can also persist in individuals with dyslexia who have good reading accuracy in highly consistent orthographies.<sup>23</sup> Several studies have noted important universal features in normal and disordered reading across cultures, despite linguistic differences. Cognitive predictors of early reading were similar for five European orthographies (Finnish, Hungarian, Dutch, Portuguese, and French) that fall along a consistency continuum, with good agreement with previous results in English. Particularly, phonological awareness was the main predictor of reading in each language, although it had more of an effect in consistent than in less consistent orthographies. Other predictors, such as rapid serial naming, vocabulary knowledge, and verbal short-term memory made smaller contributions than did phonological awareness, except in Finnish (the most consistent language), in which vocabulary had at least as large an effect on reading.<sup>24</sup>

Cross-cultural similarities extend to Chinese—a logographic language. By contrast with alphabetic languages, in which letters represent phonemes (individual sounds), the smallest written units in Chinese are characters representing monosyllabic morphemes (units of language that convey meaning). However, phonology is not irrelevant to reading in Chinese. Chinese characters have phonological elements,<sup>25</sup> and skilled readers of the language show phonological effects on word recognition.<sup>26</sup> Moreover, these cross-cultural similarities extend to the perception of auditory cues important for speech perception—namely, auditory rise time, as measured by a beat perception task. Individuals with dyslexia who were native speakers of English, Spanish, or Chinese<sup>27</sup> did poorly on auditory rise time tasks. In all three languages, this task predicted both phonological awareness and reading skill. This finding converges with reports of deficits in amplitude envelope tasks, in which auditory rise time is an important cue.

The neural correlates of poor reading seem to be very consistent across cultures. A neuroimaging study showed that weak readers in English, French, and Italian had similar patterns of aberrant neural activation (underactivation in left temporal and occipital regions) during a reading task.<sup>28</sup> The reading accuracy of the Italian participants (the language in which orthography is most consistent) was superior to that of the English and French participants. The Italian participants were least likely to have had clinically significant reading problems, although they still presented with poor fluency. Another study compared Chinese and English dyslexic and typical readers in a functional MRI framework.<sup>29</sup> Some language-specific differences in neural activations for typical reading were noted. However, the effect of dyslexia was very similar in both languages (ie, reduced activation in posterior and anterior left hemisphere regions) and agreed with work on the neurobiological basis of dyslexia in English. Thus, this study updates

#### Panel 1: Cross-linguistic findings in dyslexia

##### Past

- Dyslexia exists in every language studied, but clinically significant difficulties are less common in languages with consistent orthographies than in languages with inconsistent orthographies.
- Reading problems in consistent orthographies are characterised more by fluency problems than by accuracy problems.
- Phonological awareness is the main predictor of reading skill in inconsistent orthographies, whereas rapid serial naming is the main predictor in consistent orthographies.
- The neural basis of dyslexia is similar across alphabetic languages and includes disruption of posterior and anterior language regions in the left hemisphere
- The neural basis of dyslexia in Chinese is somewhat different and includes disruption of the left middle frontal gyrus.

##### Update

- Phonological awareness is a key predictor of reading skill in both more and less consistent orthographies. Rapid serial naming predicts reading speed across languages.
- Similar syllable processing deficits characterise dyslexia in English, Spanish, and Chinese.
- The neurobiological basis of dyslexia in Chinese seems to be more similar to that of alphabetic languages than previously believed.

##### Future directions

- Replication of findings indicating neurocognitive and neurobiological similarity across alphabetic and logographic languages, and extension to logographic languages other than Chinese and to lower socioeconomic-status groups.
- Exploration of cross-cultural similarities and differences at the causative level of analysis.

previous research that had suggested partly distinct neural signatures for dyslexia in Chinese compared with alphabetic languages,<sup>30</sup> but did not vary both language and disorder status within the same study. In sum, cross-cultural work suggests universality in the neurobiological and neurocognitive causes of dyslexia. However, cross-cultural specificity exists in the manifestation of these underpinnings, with the same biological liability more likely to cause substantial impairment in some languages than in others.

### Neuropsychology

Early theories of dyslexia postulated a basic deficit in visual processing and focused on the reversal errors commonly made by individuals with the disorder—such as writing ‘b’ for ‘d’ or ‘was’ for ‘saw’.<sup>31</sup> Vellutino<sup>32</sup> reported that such reversal errors in dyslexia were restricted to print in a person’s own language, and thus were linguistic rather than visual in nature. Since then, much research has made clear that dyslexia is a language-based disorder whose primary underlying deficit involves problems in phonological processing (processing of sounds in language; panel 3). Historically, several alternatives to the phonological theory have been proposed, and there has been renewed interest in a visual explanation for dyslexia. However, many relevant studies include limitations similar to earlier work—eg, measurement of visual attention with linguistic stimuli.<sup>33</sup> Overall, the phonological explanation remains the most probable, although questions remain.<sup>34</sup>

In the phonological theory of dyslexia, the ability to attend to and manipulate linguistic sounds is crucial for the establishment and automatization of letter–sound correspondences, which in turn underlie accurate and fluent word recognition through the process of phonological coding. An important caveat is that the relation between phonological skills (particularly phonological awareness) and reading is bidirectional; over time, poor reading can cause poor phonological awareness.<sup>35,36</sup> The general consensus is that the phonological deficits of dyslexia result from faulty development of phonological representations, which are characterised as poorly segmented, imprecise, or otherwise degraded.<sup>37–39</sup> However, not all investigators agree with this explanation.<sup>40</sup>

How does the phonological theory of dyslexia relate to developments in speech science about the nature and development of speech perception? Speech scientists complain about the so-called “tyranny of the phoneme” or “tyranny of the orthography”.<sup>41</sup> Because letters in an alphabetic orthography represent phonemes, a common assumption is that each phoneme is represented by a discrete part of the speech stream. However, speech representations are not that simple. The acceptance of these so-called tyrannies probably misleads us about what dimensions in the speech stream are important in development and how those dimensions are flexibly integrated to recover linguistic structures (eg, words).

### Panel 2: Glossary of psycholinguistic terms

#### Orthography

The written system for a language. Alphabetic orthographies use letters to represent sounds, whereas logographic orthographies use pictorial symbols to represent units of meaning. Alphabetic orthographies vary in their consistency, or in the degree of regularity of their letter–sound mappings across different words.

#### Phonological awareness

The ability to attend to and manipulate sounds in words.

#### Rapid serial naming

A type of neuropsychological task in which individuals are required to quickly name a matrix of familiar items, such as common objects, colour swatches, letters, or numbers.

#### Verbal short-term memory

The ability to keep verbal information, such as lists of words, in conscious awareness for brief periods of time.

#### Phoneme

The smallest unit of sound that makes a difference in meaning and thus distinguishes words from one another. For example, the word “bat” differs in one phoneme from the word “bit”. Both words have three phonemes, whereas the word “flock” has four.

#### Morpheme

A linguistic unit that conveys meaning. Morphemes can be words (eg, shoe) or parts of words (eg, the past tense marker -ed).

#### Allophonic variation

Phonetic differences in a phoneme that do not contribute to differences in meaning. For example, the p sound in “pin” and “spin” show allophonic variation, but native English speakers collapse across these differences and categorise both as examples of the same sound.

#### Auditory rise time

The length of time an audible stimulus takes to reach its maximum intensity. Also called onset rise time.

#### Amplitude envelope

Relatively slow changes in amplitude structure of an auditory speech signal that remain when the signal is low-pass filtered. Even though the amplitude envelope does not have the temporal detail (ie, formant transitions) judged to be crucial for distinguishing phonemes, it is surprisingly comprehensible.

#### Phonological coding

The use of knowledge of letter–sound relations to retrieve the pronunciation of a letter string.

#### Alphabetic principle

The understanding that words are composed of letters that represent sounds in a systematic fashion.

Controversies about the units of speech perception are longstanding,<sup>42</sup> and evidence shows that speech representations preserve much more of the speech signal than do phonemes. This work has led to a proposal that phonemes are not the targets of speech perception, and are mainly important in the context of learning an alphabetic written language.<sup>43</sup> Since children who develop dyslexia have trouble with spoken language long before they encounter a written alphabet,<sup>44–46</sup> difficulties in their phonological development are probably not restricted to phonemic or segmental representations and must lie in

**Panel 3: Neuropsychology****Past**

- Dyslexia is caused by an underlying deficit in phonological representations, which causes poor performance on various oral language tasks and is the source of the phonological coding deficit.
- The phonological deficit impairs language processing at the level of the phoneme, and thus interferes directly with the establishment of phoneme–grapheme mappings.
- Many alternative theories have garnered substantially less support than the phonological theory, such as low-level sensory theories (auditory and visual), the cerebellar theory, and the magnocellular theory. Convergent evidence shows that sensorimotor problems are correlated with dyslexia but are not causal.
- Another set of theories emphasises the importance of subtypes in developmental dyslexia (eg, phonological vs surface subtypes; phonological awareness vs rapid serial naming subtypes). Children with dyslexia can be subtyped according to various criteria, but most are best described by the phonological account.

**Update**

- A single phonological deficit does not seem to be sufficient to cause dyslexia. Many children with other disorders of language development (eg, speech sound disorder, language impairment) have normal-range reading abilities despite phonological deficits.
- Phonological difficulties are very important in the development of dyslexia, and they probably interact with other neurocognitive risk factors and protective factors.
- Interest remains in alternative accounts, and visual attention has been a particular focus. Much of the relevant research has important limitations, such as use of linguistic stimuli to measure visual attention. However, visual attention weaknesses could be an additional risk factor that interacts with a phonological deficit.
- Problems in speech perception and phonological development are not limited to phonemes.

**Future directions**

- Further clarification of which linguistic and non-linguistic risk factors interact with phonological problems in the development of reading problems.
- Direct testing of the hypothesis that visual attention problems underlie difficulties with rapid serial naming and reading fluency.
- Further information about the nature of the phonological deficit.

other dimensions of the speech stream. Identification of syllables in speech is important early in development and various results suggest that children with dyslexia have trouble with recovery of syllables from the speech stream. Investigators have noted that children with dyslexia have difficulties with the use of an amplitude envelope to recover spoken words<sup>47</sup> and with the integration of various cues in word perception.<sup>48</sup> In the amplitude envelope task, a speech signal is filtered to remove brief acoustic cues that have traditionally been viewed as necessary for speech perception (especially the speech segmental cues that distinguish phonemes). These findings converge with the previously discussed<sup>27,49</sup> deficits in dyslexia across languages in auditory rise time—an important component of what is preserved in an amplitude envelope speech signal.

Related evidence comes from a study that noted impaired voice identification in dyslexia.<sup>50</sup> The cues for voice identification are not phonemic (we distinguish different speakers saying the same sentence) and instead include allophonic variations in how individual phonemes

are produced. Taken together, the auditory rise time, amplitude envelope, and voice identification results draw attention to the fact that difficulties with speech perception and phonological development in dyslexia are not exclusively phonemic. Although more research is needed to fully understand the phonological issues in dyslexia and related language disorders (such as speech sound disorder and language impairment), to focus only on phonemes would be a mistake.

For many years, a single-deficit phonological theory of dyslexia was most prominent. However, mounting evidence shows that, although phonological deficits are standard in individuals with dyslexia, a single phonological deficit is probably not sufficient to cause the disorder. Other deficits could relate to phonological problems in several ways: the additional deficit could be independent of the phonological issue, with several deficits needed to cause the full clinical phenotype;<sup>51</sup> there could be phonological and non-phonological subtypes of dyslexia;<sup>52,53</sup> the phonological deficit could arise from a sensory or general learning problem;<sup>54,55</sup> or the phonological deficit might cause the reading trouble, whereas other deficits are associated for other reasons.<sup>56</sup>

Consistent with a multiple deficit hypothesis, we noted that a lot of children with a history of speech sound disorder developed normal literacy despite persistent deficits in phonological awareness. Furthermore, phonological awareness alone predicted literacy outcome less well than did a model that also included syntax and non-verbal IQ.<sup>13</sup> Similarly, Bishop and colleagues<sup>57</sup> classified children on the basis of whether they had language impairment only, dyslexia only, language impairment and dyslexia, or typical development. Many children with language impairment did not develop dyslexia even though their early phonological skills had been as poor as those of the language impairment and dyslexia group. At age 9–10, the language impairment only and language impairment and dyslexia groups both continued to have impaired phonological awareness, but only the latter group had deficits in rapid serial naming.

Rapid serial naming has long been hypothesised to be a risk factor for reading failure independent of phonological awareness.<sup>58</sup> Cross-cultural work confirms that children with phonological awareness and rapid serial naming deficits have particularly poor literacy outcomes.<sup>59,60</sup> Debate remains about how distinct rapid serial naming is from other aspects of phonological processing.<sup>61</sup> Although rapid serial naming tasks certainly require lexical phonology, they also correlate strongly with non-verbal measures of processing speed, which in turn predict reading fluency.<sup>62,63</sup> As mentioned previously, there has been renewed interest in the role of visual attention in dyslexia.<sup>52,54,64–68</sup> Although some of this research has included serious flaws, well controlled studies noted a link between visual deficits and dyslexia that cannot be fully accounted for by other factors.<sup>54,69,70</sup> One specific hypothesis that has yet to be tested



empirically is that trouble with visual attention could underlie rapid serial naming deficits and associated problems with reading fluency.<sup>54</sup> This proposal is attractive because the phonological theory readily explains the reading accuracy issue in dyslexia but does not fully account for difficulties with reading fluency, which have been shown to be more persistent developmentally, more universal across languages, and harder to remediate.<sup>71</sup>

The studies discussed previously that support a multiple deficit view generally used correlational designs. Thus, some deficits might not relate directly to word reading, but instead could explain comorbidities or brain dysfunction. The clearest data on this question come from longitudinal studies of children at family risk for dyslexia. Across countries and languages, many cognitive–linguistic constructs—including semantics, syntax, phonological awareness, verbal short-term memory, and rapid serial naming—consistently predict dyslexia later in life. The most powerful individual predictor varies with developmental stage.<sup>45,46,72–74</sup> Verbal short-term memory and phonological awareness seem to act as endophenotypes, because deficits in each are reported in individuals with a family risk of dyslexia who do and do not develop the disorder. Difficulties with rapid serial naming and letter knowledge are more specific to dyslexia, because individuals at family risk who do not have dyslexia perform almost normally in these domains (Snowling MJ, University of York, personal communication). Thus, although results vary as to which additional deficits interact with phonological awareness issues to cause dyslexia, convergent evidence suggests that: many children with weak phonological awareness nonetheless develop normal-range literacy skills; children with phonological awareness troubles and other language deficits are at high risk for dyslexia; and rapid serial naming deficits in dyslexia cannot be fully accounted for by comorbidity with attention-deficit hyperactivity disorder or other developmental disorders.

## Neural substrates

### Functional findings

Because reading is a linguistic skill, we would expect it to involve activation of brain structures used in oral-language processing and some additional structures associated with visual-object processing and establishment of visual–linguistic mappings. A large number of functional imaging studies have shown aberrant activation patterns in these regions in dyslexia. The most common findings, as described in several qualitative reviews, encompass abnormalities of a distributed left hemisphere language network.<sup>75,76</sup> Consistent under-activations have been reported in two posterior left hemisphere regions; a temporoparietal region believed to be crucial for phonological processing and phoneme–grapheme conversion, and an occipitotemporal region, including the so-called visual word form area, which is thought to participate in whole word recognition.

Abnormal activation of the left inferior frontal gyrus is also commonly reported.

There have been several important advances in this area of research since the previous *Lancet* Seminar<sup>75</sup> about dyslexia (panel 4). First, a quantitative meta-analysis<sup>77</sup> of imaging studies—in which participants did reasonably similar tasks while their brains were scanned—has been published, and confirmed the primary findings of qualitative reviews. Second, most early imaging studies did not equate in-scanner performance or did not control for reading experience, and thus whether recorded activation differences were a cause or result of dyslexia was not clear. Several studies have attempted to control for reading experience in various ways. In general, findings support the view that characteristic brain changes are associated with dyslexia from an early age.

The direction of the relation between imaging findings and reading experience has been clarified through use of reading-age control groups and family risk studies. One research group has compared individuals with dyslexia both with chronological-age and with reading-age controls on visual rhyme tasks.<sup>78,79</sup> The reading-age control

### Panel 4: Neural substrates in dyslexia

#### Past

- Dyslexia is associated with anatomical and functional abnormalities in left hemisphere language and reading areas (more widespread abnormalities are also reported).
- Anatomical abnormalities include histological abnormalities thought to result from failures of neural migration.
- The most commonly reported functional abnormalities include underactivation of left hemisphere temporoparietal and occipitotemporal regions. Aberrant activation of the left hemisphere inferior frontal gyrus is also commonly reported.
- Some studies reported overactivation of left inferior frontal gyrus or of right hemisphere sites, which were thought to show compensatory processes.

#### Update

- Quantitative meta-analysis confirms underactivation of left hemisphere temporoparietal regions that is believed to show deficient phonological processing; left hemisphere occipitotemporal region (ie, visual word form area) believed to be important in word recognition.
- Studies controlling for reading experience confirm that temporoparietal abnormalities are more likely a cause than a result of reading failure. Findings about the visual word form area are complicated and could show failure of this region to tune appropriately over time.
- Convergent evidence implicates white matter disruption, particularly in left hemisphere perisylvian regions.

#### Future directions

- Studies controlling for reading experience across a range of participant and task characteristics.
- Further evidence about the developmental course of neural abnormalities, particularly occipitotemporal underactivation.
- Examination of neural signature predicting differential treatment response.
- Genetic neuroimaging studies to test the link between candidate genes for dyslexia and structural and functional neuroimaging findings.

design (ie, inclusion of young, typically developing children matched on reading ability to participants with dyslexia) is often used in behavioural research as a test of whether noted group differences contribute to dyslexia. Overall, results showed abnormal activation in people with dyslexia, with underactivation in left temporoparietal regions relative to both chronological-age and reading-age controls. Several other areas of underactivation relative to both control groups were also reported. These areas differed somewhat by study, however, one of which included school-age children aged 8–12 years, whereas the other included children and adolescents aged 7–16 years. This research group has also compared neural activation in dyslexic and typically-developing children on a visual sentence comprehension task, and treated reading ability continuously rather than categorically.<sup>80</sup> The main finding was that poor reading was associated with a reduction in activation in the bilateral temporoparietal cortex; no effects were found in occipitotemporal regions.

A related approach is to investigate neural correlates of reading and reading-related tasks among young children at risk for dyslexia or who have just begun to experience reading difficulties. Compared with same-age controls, 6-year-old children at risk for dyslexia showed activation abnormalities across a widely distributed set of bilateral cortical and bilateral subcortical regions.<sup>81</sup> With regard to the regions most commonly reported in published work, bilateral temporoparietal activation was increased in high-risk children during an easy reading task, whereas occipitotemporal activation was reduced on a more difficult task. Another study compared young (mean age 8 years) readers with dyslexia and normal-ability readers in a reading task designed to emphasise phonological processing.<sup>82</sup> Children were equated on in-scanner performance (though, by definition, not on reading ability). The left inferior and middle-frontal gyri were underactivated in poor readers, whereas many bilateral frontotemporal sites showed overactivation. Furthermore, children with dyslexia showed reduced left-sided specialisation for the phonological task compared with children with normal reading ability.

Other imaging technologies support the conclusion that characteristic brain differences are a cause rather than a result of dyslexia. Particularly, event-related potential studies in several languages have noted that infants at family risk for dyslexia show aberrant neural response to speech sounds from as early as the first week of life,<sup>83</sup> and that infant event-related potential response predicts language learning and dyslexia risk over several years.<sup>44,84,85</sup>

Overall, results from studies attempting to control for reading experience are only partly consistent with each other and with functional MRI published work. However, not all reported neural abnormalities in dyslexia result from an absence of reading experience, with convergent evidence that temporoparietal abnormalities are more

likely a cause than a result of reading failure. Findings for the visual word form area are complicated. Whereas underactivation of the visual word form area in adolescents with dyslexia cannot be attributed solely to reading experience, this relation is less clear in children. Possibly occipitotemporal regions fail to tune appropriately to word stimuli over time in dyslexia, consistent with a functional MRI study of 11-year-old children.<sup>86</sup> This explanation attributes abnormalities of occipitotemporal regions to an interaction between the disorder itself and exposure to print, and could be tested empirically by examination of a group with little reading experience for reasons other than dyslexia.

### Structural findings

That individuals with dyslexia show functional abnormalities in both posterior and anterior language networks has led to the hypothesis that dyslexia is a disconnection syndrome. Accordingly, much research has explored white matter correlates of dyslexia by use of diffusion tensor imaging. The most consistent findings have included local white matter changes (as indexed by fractional anisotropy) in children and adults with dyslexia in left temporoparietal regions and in the left inferior frontal gyrus.<sup>87–98</sup> Studies have consistently reported correlations between white matter integrity and reading skill.

Work has clarified the relations between structural and functional neuroimaging findings in dyslexia. First, Paulesu and colleagues<sup>28</sup> international study has been followed up with grey matter and white matter structural analyses by Silani and co-workers.<sup>99</sup> This follow-up investigation is the first to examine associations between functional and structural findings in dyslexia in the same sample. These investigators noted a grey matter density decrease in people with dyslexia that corresponded to the key area of functional underactivation in the left medial temporal gyrus reported in their previous study. Consistent with other diffusion tensor imaging studies, the researchers recorded white matter decreases in the left frontal and parietal portions of the arcuate fasciculus and other left hemisphere sites. These structural differences were replicated across the three countries and languages in the study (Italy [Italian], France [French], and the UK [English]).

Consistent with the functional imaging findings, a family risk study<sup>100</sup> reported that grey matter decreases are present before the onset of reading instruction, and thus do not seem to be a result of reading failure. The family risk group had selective grey matter decreases in left hemisphere regions (occipitotemporal, temporoparietal, and lingual gyrus) previously associated with dyslexia. Furthermore, evidence that genetically based brain abnormalities can cause reading problems is provided by syndromes such as periventricular nodular heterotopias,<sup>101,102</sup> XXY syndrome in male populations,<sup>103</sup> and Rolandic epilepsy.<sup>104</sup> The neuropathology of periventricular

nodular heterotopias—a cortical malformation in which nodules of heterotopic grey matter line the ventricles bilaterally—is similar to that reported in autopsy studies of dyslexia by Galaburda and colleagues.<sup>105,106</sup> Those studies found increased numbers of grey matter heterotopias in individuals with reported histories of poor reading, although these findings were stronger in male patients<sup>105</sup> than in female patients.<sup>106</sup>

An emerging and still speculative hypothesis for the pathogenesis of dyslexia is that risk genes disrupt neuronal migration mainly in the left hemisphere, which leads to grey matter and white matter changes in parts of the language–reading network. However, white matter tracts could also possibly be disrupted in other ways (Appel B, University of Colorado School of Medicine, personal communication; Rosen G, Beth Israel Deaconess Medical Center, personal communication). Altered connectivity in the white matter tracts of the left superior longitudinal fasciculus compromise the acquisition of language and cognitive skills important for reading. Direct evidence is needed to support this hypothesis. Perhaps most crucially, we need genetic neuroimaging studies that test the link between candidate genes for dyslexia and the structural and functional neuroimaging findings. We also need to replicate the small study<sup>100</sup> documenting grey matter decreases (and test for white matter changes) in children at family risk for dyslexia before the onset of reading instruction.

Even though causation in dyslexia seems to flow, partly, from brain to reading skill, reading unquestionably changes the brain, as documented by neuroimaging studies of dyslexia treatments<sup>107</sup> and of adults who are illiterate.<sup>108</sup> Thus, the neuroimaging phenotype in dyslexia probably includes a mix of both kinds of effects and separating these will require longitudinal work, starting with very young children.

## Causes

Like all behaviourally defined disorders, the cause of dyslexia is multifactorial and is associated with multiple genes and environmental risk factors (panel 5). Dyslexia is familial and moderately heritable<sup>109</sup> and has been linked to nine risk loci (DYX1–DYX9) through replicated linkage studies,<sup>110,111</sup> although not every study has replicated these results.<sup>112,113</sup>

The main advance in the genetics of dyslexia since the previous *Lancet* Seminar<sup>75</sup> has been the identification of six candidate genes (*DYX1C1* in the DYX1 locus on chromosome 15q21; *DCDC2* and *KIAA0319* in the DYX2 locus on chromosome 6p21; *C2Orf3* and *MRPL19* in the DYX3 locus on chromosome 2p16–p15; and *ROBO1* in the DYX5 locus on chromosome 3p12–q12) and studies of their role in brain development.<sup>114</sup> Work in animals has shown that *DYX1C1*, *DCDC2*, *KIAA0319*, and *ROBO1* affect neuronal migration and axon guidance and coregulate each other. Very little is known about the functions of the two DYX3 candidate genes. Two other

### Panel 5: Causes of dyslexia

#### Past

- Dyslexia is familial and moderately heritable, with nine replicated linkage sites.
- Because the heritability of dyslexia is substantially less than 100%, environmental risk factors must also play a part, but little is known about their effects.

#### Update

- Six candidate genes have been identified (*DYX1C1*, *DCDC2*, *KIAA0319*, *C2Orf3*, *MRPL19*, and *ROBO1*) in four of the nine linkage regions.
- Four of the candidate genes are known to participate in neuronal migration and axon guidance.
- Genetic contribution to dyslexia in families increases with a high level of parent education (a bioecological gene by environment interaction).

#### Future directions

- Identification of additional risk loci to account for missing heritability.
- Clarification of which risk loci are unique to dyslexia and which overlap with comorbid disorders.
- Investigation of newly discovered genetic mechanisms, such as copy number variations, parent-of-origin effects, and epigenetic effects.
- Genetically controlled studies investigating environmental contributions to the development of reading problems.

studies have identified three new candidate genes for dyslexia (*MC5R*, *DYM*, and *NEDD4L*)<sup>115</sup> on chromosome 18 and one shared with language impairment (*CMIP*),<sup>116</sup> but these results need to be replicated.

Despite this important progress, much remains to be done to fully understand the causes of dyslexia. First, a genome-wide association study of dyslexia has not been done, and the known loci do not account for most of the heritability of dyslexia reported in twin studies—a so-called missing heritability problem. Second, although our understanding of the causes of the comorbidities of dyslexia has progressed, much remains to be done to identify loci that are shared and not shared with the comorbid disorders attention-deficit hyperactivity disorder, language impairment, and speech sound disorder. Third, whether dyslexia shows any of the newly discovered genetic mechanisms found in other neurodevelopmental disorders—eg, copy number variations, parent of origin effects, and epigenetic effects—is unknown. Fourth, much remains to be learned about the role of the environment in the cause of dyslexia. We know that the heritability of dyslexia declines linearly with decreasing parental education (a bioecological gene by environment interaction),<sup>117</sup> but we do not know which proximal environmental factors mediate this interaction. Possible candidates include the language and pre-literacy environments that parents provide for their children, but direct tests of these hypotheses are needed. Finally, although cross-cultural research on dyslexia is robust, dyslexia has been less studied in lower socioeconomic status groups than in people from more privileged backgrounds, in non-white ancestry groups than in white populations, and in children with a

bilingual background (eg, Hispanic-American children) than in monolingual children. A universal account of normal and abnormal reading development needs to encompass these understudied groups.

### Treatment

The development of evidence-based treatments for dyslexia has benefited from our understanding of the neuropsychology of the disorder, and the best interventions provide intensive, explicit instruction in phonological awareness, the alphabetic principle and phonics, word analysis, reading fluency, and reading comprehension.<sup>118,119</sup> Much more is known about effective remediation of reading problems in younger than in older children. Accuracy difficulties seem to be easier to treat than issues with fluency, perhaps partly because fluency is so dependent on reading experience, which varies substantially by reading ability. For poor readers to close the gap in print exposure once they have accumulated several years of reading failure might be nearly impossible, but some evidence shows that fluency problems can be prevented with appropriate intervention in kindergarten and first grade (age range 5–7 years), at least in the short term.<sup>120,121</sup> Professionals should not wait until children are formally diagnosed with dyslexia or experience repeated failures before implementation of reading treatment because remediation is less effective than early intervention.<sup>122</sup>

Work on treatments for reading failure<sup>123</sup> supports the following conclusions: intervention is most effective when provided in a one-to-one or small-group setting;<sup>124</sup> successful interventions heavily emphasise phonics instruction; and other important treatment elements include training in phonological awareness, supported reading of increasingly difficult connected text, writing exercises, and comprehension strategies. Many effective treatments are low cost, which further draws attention to the importance of early identification, prevention, and treatment of dyslexia for public health.

Individual differences exist in how well people with dyslexia respond to treatment, with about half of successfully treated children maintaining gains in reading ability for at least 1–2 years. The well documented pre-school predictors of later reading skill (ie, phonological awareness, letter name and sound knowledge, and rapid serial naming) also predict treatment response.<sup>125</sup> With regard to long-term prognosis independent of treatment, language skill is a known protective factor for both children and adults with dyslexia.<sup>74,126,127</sup>

The number of intervention–imaging studies investigating how remediation of dyslexia alters brain activity is increasing.<sup>75,107</sup> Briefly, effective intervention seems to promote normalisation of activity in the left hemisphere reading and language network that has shown reduced activity in dyslexia. Additionally, increased right hemisphere activation has been reported after dyslexia

treatment, which is sometimes interpreted as showing compensatory processes.

Although a solid evidence base emphasises direct instruction in reading and phonological training, several alternative therapies either do not have sufficient evidence or have been shown to be ineffective for dyslexia and thus should not be recommended to children and families.<sup>128</sup> Most of these therapies are based on sensorimotor theories of dyslexia and include training in rapid auditory processing (eg, Fast ForWord), various visual treatments (eg, coloured lenses, vision therapy), and exercise or movement-based treatment (eg, vestibular training).

### Conclusion

Of all the neurodevelopmental disorders, dyslexia has been the most studied and is the best understood. The specialty continues to benefit from reciprocal relations between basic and clinical neuroscience, and there has been considerable progress over the past 5 years in understanding dyslexia's cross-cultural manifestation, causes, neuropsychology, and neurobiology. Much of the most exciting work includes an interdisciplinary focus across these different specialties. This research has helped to promote scientific knowledge and public health and draws attention to the complexity of the development of reading difficulties. Future research will address important questions both within and across different levels of analysis. For example, we still need to learn more about the nature of the phonological deficit and how this problem interacts with other linguistic and non-linguistic risk factors, the developmental course of neural abnormalities and how these predict treatment response, and which environmental risk factors contribute to the development of poor reading and whether these are the same across demographic groups. If we find the answers to these questions we can improve the lives of children who struggle to learn to read.

#### Contributors

Both authors contributed equally to the overall conceptualisation and planning for the article and to the writing of the definition, neuropsychology, neural substrates, and conclusion sections of the report. RLP took primary responsibility for doing the literature search and for writing the epidemiology and treatment sections. BFP took primary responsibility for writing the section on causes.

#### Conflicts of interest

We declare that we have no conflicts of interest.

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