Developmental Dyslexia

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reading disability, etiology, neuropsychology, language, genetics

Abstract

This review uses a levels-of-analysis framework to summarize the current understanding of developmental dyslexia's etiology, brain bases, neuropsychology, and social context. Dyslexia is caused by multiple genetic and environmental risk factors as well as their interplay. Several candidate genes have been identified in the past decade. At the brain level, dyslexia is associated with aberrant structure and function, particularly in left hemisphere reading/language networks. The neurocognitive influences on dyslexia are also multifactorial and involve phonological processing deficits as well as weaknesses in other oral language skills and processing speed. We address contextual issues such as how dyslexia manifests across languages and social classes as well as what treatments are best supported. Throughout the review, we highlight exciting new research that cuts across levels of analysis. Such work promises eventually to provide a comprehensive explanation of the disorder as well as its prevention and remediation.

Contents

INTRODUCTION

This review uses a levels-of-analysis framework (Pennington 2002) to summarize current knowledge regarding developmental dyslexia (henceforth, dyslexia). The guiding principal behind this framework is that a complete explanation of any disorder—or indeed, of any typical developmental phenomenon—requires understanding the phenomenon across multiple levels: its defining symptoms or behaviors; its neuropsychology (underlying cognitive, emotional, or other psychological processes that are not directly observable and not part of the disorder's definition); its pathophysiology (for cognitive disorders, changes in brain structure and function); its etiology, or distal causes, including genetic and environmental risk and protective factors; and its social context. No level is fully reducible to a "lower" level because of the emergence of new phenomena as systems become increasingly complex, and no level has priority over the others in terms of scientific value. For example, obtaining comprehensive knowledge regarding all the genetic and environmental risk factors that contribute to poor reading skills would be extremely valuable but could not replace a thorough understanding of the cognitive processes involved in reading words aloud. The sections below cover dyslexia's definition and epidemiology (with discussion focusing on both behavioral and social context levels), neuropsychology, brain bases, etiology, and treatment. We particularly highlight exciting recent research that cuts across levels of analysis—for example, from etiology to brain bases, brain bases to neuropsychology, or social context to etiology.

DEFINITION OF DYSLEXIA

Individuals with dyslexia have difficulties with accurate or fluent word recognition and spelling despite adequate instruction and intelligence and intact sensory abilities (Lyon et al. 2003). The ultimate goal of reading is comprehension, which is a function of both decoding ability and oral language comprehension (Hoover & Gough 1990). Dyslexia is defined by difficulties with

decoding, whereas by comparison, listening comprehension is typically more intact. Thus, although individuals with very limited decoding abilities (i.e., young children or individuals with severe dyslexia) have poor reading comprehension, individuals with milder decoding problems can still support adequate reading comprehension with intact oral language skills (Bruck 1993). So-called poor comprehenders show the opposite profile of adequate decoding but poor understanding of what is read. Not surprisingly, poor comprehenders tend to have deficits in oral language comprehension, and this profile is sometimes considered a type of language disorder (Nation et al. 2010).

SES: socioeconomic status

Phonological processing: umbrella term for oral language tasks emphasizing processing of sounds

Although some previous diagnostic systems have grouped dyslexia and poor reading comprehension together (e.g., Am. Psychiatr. Assoc. 2000), this review is about dyslexia only. Many researchers use the terms "dyslexia" and "reading disability" interchangeably, although as the preceding discussion makes clear, other learning disorders (e.g., language disorder) can affect reading.

Some disorders, such as cystic fibrosis, are categorical (you either have the disorder or you do not), and these categorical disorders often have a discrete etiology, such as a mutation in a single gene, as is true for cystic fibrosis, phenylketonuria, and Huntington's dementia. Many other disorders (such as hypertension) do not represent categories, but just extremes on a continuous distribution that ranges from optimal outcomes to poor outcomes, with the underlying causal mechanisms being similar across the whole distribution. Essentially all behaviorally defined disorders, including dyslexia, are such continuous disorders. Dyslexia is mainly defined as the low end of a normal distribution of word reading ability (Rodgers 1983, Shaywitz et al. 1992). Thus, in order 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. Specifically, it has been assumed that IQ sets a limit on achievement across domains, and thus children with low IQ are likely to be poor readers because of general learning difficulties rather than a specific decoding problem. Genetic differences contribute more to high-IQ dyslexia than to low-IQ dyslexia (Wadsworth et al. 2010). A related finding is that dyslexia is more genetically based in children from higher socioeconomic status (SES) families than in children from lower SES families (Friend et al. 2008). Together, these results suggest that advantaged children with strong cognitive abilities are likely to be good readers unless they have specific genetic risk factors for poor decoding. There are myriad reasons why other children will struggle with reading. These reasons include environmental influences associated with low SES, and those influences will account for more of the variance in poor reading in children from lower SES families than in children from higher SES families. Although the same risk genes are likely important across the range of SES, they contribute less to poor reading in the presence of environmental risk factors associated with lower IQ. We do not yet know which proximal environmental factors are most likely to contribute to low reading ability, though some reasonable possibilities are discussed later in the sections titled Socioeconomic Status and Environmental Influences.

Despite this evidence for a different weighting of genetic and environmental risk factors in the etiologies underlying dyslexia in children with high versus low IQ, 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. Specifically, poor readers of all general ability levels typically have disproportionately poor skills in phonological processing (processing sounds in language), as discussed further below in the Neuropsychology of Dyslexia section. As a group, children with dyslexia respond best to treatment emphasizing phonics-based reading instruction. Although there are individual differences in how well children with dyslexia respond to such intervention, these differences do not appear to be solely or even primarily a

function of IQ (Jimenez et al. 2009, Stuebing et al. 2009). The two definitions overlap, but 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). The previous version of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (version IV-TR; Am. Psychiatr. Assoc. 2000) required that reading achievement be below the level expected for both age *and* IQ. The most recent revision of the DSM (DSM-5; Am. Psychiatr. Assoc. 2013) now requires that reading be below age expectations in every case. Although the updated definition should facilitate the identification and remediation of reading problems in children with broader cognitive difficulties, it unfortunately continues to exclude those of high ability who nonetheless have clinically impairing difficulties and could benefit from reading intervention. Indeed, as the above discussion makes clear, the new definition ironically means that fewer children with a stronger genetic etiology will be classified as dyslexic. Thus, for both research and clinical purposes, we think it is more appropriate to identify children who meet either age- *or* IQ-discrepancy criteria as having dyslexia.

ADHD: attention-deficit/hyperactivity disorder

EPIDEMIOLOGY

Prevalence estimates, of course, depend on definition. A common definition sets the cutoff for reading achievement to 1.5 standard deviations (SD) below the mean for age and identifies 7% of the population; a similar IQ-achievement discrepancy definition identifies a comparable proportion (Shaywitz et al. 1990). There is a relatively small but significant male predominance (from 1.5:1 to 3.1:1; Rutter et al. 2004). However, the gender difference in referred samples is even higher (from 3:1 to 6:1; Smith et al. 2001). Boys with dyslexia come to clinical attention more often than girls apparently because they have higher rates of comorbid externalizing disorders, including attention-deficit/hyperactivity disorder (ADHD) (Willcutt & Pennington 2000).

Socioeconomic Status

As mentioned above, SES is associated with reading skill, as with virtually all other measures of achievement. The effects of SES on literacy are part of the so-called achievement gap that has garnered considerable attention in public policy and education circles. For example, in 2011, the overall reading level of a national sample of fourth graders eligible for free lunch was 0.83 SD lower than that of students not eligible for free or reduced lunch, a large effect size (Natl. Cent. Educ. Stat. 2011). Lower SES is associated with both poorer word reading and poorer reading comprehension, though the effect is larger for reading comprehension, particularly at older ages (MacDonald Wer 2014). The SES–word-reading link means that by definition, a disproportionate number of children from lower SES families will meet diagnostic criteria for developmental dyslexia. Lower SES predicts both poorer early reading skills at the onset of formal literacy instruction and a slower trajectory of literacy growth over the early school years (Hecht et al. 2000).

Systematic reviews and meta-analyses have consistently shown that SES accounts for approximately 10% of the variance in reading outcome (Scarborough & Dobrich 1994, Sirin 2005, White 1982). Although this effect is statistically significant and moderate, it also means that approximately 90% of the variance in reading outcome is independent of SES and thus that many children from disadvantaged backgrounds will be strong readers while many weak readers will come from advantaged families.

SES probably serves as a proxy for several environmental variables that adversely affect literacy development. However, SES is not solely an environmental construct, at least in societies that allow for a degree of social mobility, since there are genetic influences on individual differences that impact people's ability to achieve higher levels of education, income, and occupational status

(Baker et al. 1996). Thus, some of the SES–reading association may be due to a third variable: genes shared by parents and children that influence reading or cognitive abilities more broadly. Adoption studies suggest that of the 10% of reading variance that is related to SES, approximately half is mediated by environmental factors and half by genetic factors (Petrill et al. 2005, Wadsworth et al. 2001). So, about 5% of overall reading outcome can be linked to environmental factors that fall under the SES umbrella. Two important caveats are that (*a*) existing samples may not have included the very low tail of poor environments for reading development and (*b*) as discussed previously, there is evidence for a bioecological gene-by-environment interaction in reading development, such that the balance of genetic and environmental influences is not constant across SES levels.

What are the specific environmental variables that directly influence reading development? Methodologically rigorous research on this question is still at an early stage of development, but the causal factors are probably many and act at the child, family, neighborhood, school, and broader community levels. In terms of family factors, research indicates that the quality and nature of language interaction between parents and children vary across SES levels (Hoff 2003), including around specific preliteracy and literacy activities (Phillips & Lonigan 2009, Robins et al. 2014).

We return to the question of genetic and environmental influences on dyslexia in the Etiology section. Importantly, although this research tells us about the distal causes of individual differences in reading, it does not tell us about the extent to which particular environmental treatments (such as providing evidence-based reading instruction) can shift the average score for a group with poorer-than-average reading, such as children from lower SES backgrounds. This issue evokes the Flynn effect that has been demonstrated for IQ, in which the mean IQ of the whole distribution increases over time, and this effect appears to be carried disproportionately by improvements in the low tail of the distribution (perhaps because of basic public health improvements, such as better nutrition; Lynn & Hampson 1986). There probably has been a Flynn effect for reading as well over the last century. Despite these group-level changes, which are driven by environmental factors, the etiology of individual differences may well have remained the same, and these differences include substantial genetic influence.

Bioecological gene-by-environment interaction: type of G × E interaction shown in dyslexia in which genes have greater influence in more favorable environments

Rapid serial naming: type of neuropsychological task requiring speeded naming of a matrix of familiar objects, color swatches, letters, or numbers

Cross-Cultural Findings

Although research on dyslexia initially focused primarily on reading difficulties in English, recently a good deal of attention has been paid to the nature of dyslexia across languages. Here, we briefly summarize what is known about how dyslexia manifests across languages showing two different types of variability: first, among alphabetic orthographies that vary in the degree of consistency of letter-sound correspondences; and second, in alphabetic versus logographic orthographies.

Children at the low end of reading ability distribution in languages with more consistent mappings between letters and sounds (e.g., Italian or Finnish) have less severe reading problems than those learning to read less consistent languages (i.e., English), at least in terms of accuracy (Landerl et al. 1997). Difficulties with reading fluency (speed of reading connected text) seem similar across languages (Caravolas et al. 2005). 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), in 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 less consistent than in 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 (Ziegler et al. 2010).

LI: language impairment

SSD: speech sound disorder

Cross-cultural similarities appear to extend in large part to logographic languages as well, such as Chinese. By contrast with alphabetic languages, in which letters represent phonemes, 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, and skilled readers of the language show phonological effects on word recognition (Pollatsek 2014). Phonological awareness is a key correlate and predictor of reading skill in Chinese just as in alphabetic orthographies. However, in contrast to alphabetic languages in which awareness of phonemes is critically important, morphological and syllabic awareness play a large role in learning to read Chinese (McBride-Chang et al. 2005). This finding is not surprising given the differences in how the orthographies represent language.

Comorbidities

In addition to its comorbidity with ADHD, dyslexia is comorbid with two other disorders of language development: language impairment (LI) and speech sound disorder (SSD) (Nittrouer & Pennington 2010). LI is defined by problems in the development of structural language, including syntax (grammar) and semantics (vocabulary), whereas for SSD the defining problem is in the ability to accurately and intelligibly produce the sounds of one's native language. In each case, evidence indicates that the comorbidity with dyslexia is mediated by shared etiologic and neurocognitive risk factors (Pennington & Bishop 2009, Willcutt et al. 2010). The comorbidities are clinically significant because dyslexia is not diagnosed until after a child has been exposed to formal literacy instruction, but ADHD, SSD, and LI are all likely to be apparent earlier and can thus indicate a child's risk for later reading problems. Children with dyslexia are also at increased risk for learning disabilities affecting other academic skills, including those impacting reading comprehension (Christopher et al. 2012), math (Landerl & Moll 2010), and writing (Berninger et al. 2001). Thus, many students with dyslexia have more than a "specific" reading disability and can be expected to struggle broadly in school. The most recent revision of the DSM (version 5) acknowledges these high levels of comorbidity by grouping all learning disabilities under a single umbrella diagnosis ("Specific Learning Disorder") and allowing the clinician to select a modifier(s) describing the particular academic skill(s) affected (Am. Psychiatr. Assoc. 2013). This approach has the advantage of explicitly recognizing the overlap among learning disorders that again arises from shared risk factors. However, equally strong evidence does not support the validity of all learning disorders. Although many decades of work have elucidated the causes, neurobiology, neuropsychology, and appropriate treatments for dyslexia, the scientific study of difficulties in written expression or mathematical problem solving is at a much earlier stage of development.

NEUROPSYCHOLOGY OF DYSLEXIA

History

Reading disabilities in children were first described more than a century ago by Pringle-Morgan (1896) and Kerr (1897) and were labeled dyslexia because of the parallels with the loss of reading ability following brain injury in previously skilled adult readers. In the first part of the twentieth century, Samuel Orton (1925, 1937) focused on the letter and word reversal errors commonly seen in children with dyslexia (such as b/d confusions or reading "was" for the word saw) and hypothesized that a visual problem arose because of a hemispheric dominance failure in which mirror images of visual stimuli were not inhibited. Vellutino (1979) demonstrated that such reversal errors were restricted to processing print in one's own language and were thus really linguistic

rather than visual in nature. Unfortunately, the perception that dyslexia primarily reflects a visual problem persists among many in the lay public and continues to form the basis of therapies for the disorder that lack empirical support (Pennington 2011). Although it remains possible that some sorts of visual processing problems correlate with dyslexia, the scientific consensus for the last several decades has been that dyslexia is a language-based disorder whose primary underlying deficit involves problems in phonological processing (processing of sounds in oral language) that lead to later problems processing written language (Vellutino et al. 2004). Despite this long history, this and other fundamental controversies about the neuropsychology of dyslexia have been recapitulated several times over the years, as discussed further below.

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. Phonological processes are important not only for learning to read alphabetic orthographies (in which the script represents phonemes, or individual speech sounds) but also for learning to read logographic orthographies (in which the script represents language at the morpheme/syllable level), although the phonological grain size most important for skilled reading varies across scripts (Perfetti et al. 1992).

Phonological grain size: size of the linguistic unit most informative in the mapping between spoken and written language (i.e., phonemes, morphemes, or syllables)

Phoneme awareness: meta-linguistic awareness of individual speech sounds (phonemes)

Issues in the Phonological Theory of Dyslexia

Access versus representations. One old controversy in the phonological theory of dyslexia that has recently been revisited concerns the nature of the phonological deficit. The initial assumption was based on a Chomskyan view (Chomsky & Halle 1968) and held that the ability to discriminate phonemes was innate and universal, and so implicit phonological representations should be intact in dyslexia. Early investigations into the phonological deficit thus focused on metacognitive awareness of phonemes (e.g., Liberman 1973). Phoneme awareness develops over several years and is strongly correlated with literacy skill, making it an attractive initial core deficit candidate for dyslexia. However, research on early language development eventually demonstrated that phonemic representations are not innate and instead develop in response to linguistic input. A detailed review of early phonological development is beyond the scope of this article, but briefly, it appears that for all children, phonological representations start out as fairly holistic and become gradually more detailed or segmented over time. Babies likely represent most words as single entities. With language development, phonological representations begin to emphasize syllables, then subsyllabic distinctions, and ultimately individual phonemes (e.g., Metsala & Walley 1998). In a seminal paper, Fowler (1991) argued that this implicit phonological development underlies parallel development in metaphonological awareness (Treiman 1985) and helps account for the fact that preschool children generally cannot perform tasks that require explicit manipulation of individual phonemes, although they can perform phonological awareness tasks at a larger grain size (e.g., rhyming).

Through the 1990s and first decade of the 2000s, empirical evidence accrued highlighting faulty implicit phonological representations in dyslexia (Boada & Pennington 2006, Elbro et al. 1998, Manis et al. 1997). More specifically, children with dyslexia show deficits on phonological processing tasks that do not require explicit attention to or manipulation of phonemes, including categorical speech perception, priming, and lexical gating tasks. Various research groups have described the implicit phonological deficit in different ways, including that phonological representations in dyslexia are imprecise, poorly segmented, or otherwise degraded.

Recently, the debate about the nature of the phonological deficit and whether it involves phonological representations themselves or only metacognitive access to those representations has been

rekindled. Proponents of the updated "access-only" argument point out that adults with dyslexia perform normally on many implicit phonological tasks, including those emphasizing phonotactics and stress perception (Dickie et al. 2013, Ramus & Szenkovits 2008). Furthermore, findings on some other implicit tasks (particularly categorical speech perception) have been inconsistent, with some scientists arguing that speech perception problems are more clearly linked to LI than to dyslexia (Joanisse et al. 2000). Most of the studies in support of the access-only view have used behavioral methods, although recently Boets and colleagues (2013) published a neuroimaging study showing that brain response to phonetic contrasts in primary and secondary auditory cortex was similar in adults with and without dyslexia, but structural and functional connectivity between auditory cortex and left inferior frontal gyrus were reduced in those with dyslexia. Boets et al. (2013) argued that these findings were consistent with "intact but less accessible phonetic representations in dyslexia" (p. 1251; see also Ramus 2014).

This rekindled argument has garnered a good deal of attention, with some of the papers in favor of the access-only view being published in top journals and gaining numerous citations. Certainly, many of the experiments showing intact aspects of phonological processing in dyslexia have been elegantly designed and have yielded important results for the field to integrate into current explanations of reading difficulties. However, we think this argument faces a number of challenges that its proponents have not yet adequately addressed. First, the history of the access-only view and its basis in a nativist, Chomskyan account of phonology have not been explored. Second, there is a striking lack of consensus regarding which tasks are most appropriate to measure implicit phonological representations. The fact that dyslexia appears to be associated with atypical performance on lexical gating tasks (Boada & Pennington 2006) but not stress perception (Dickie et al. 2013, Mundy & Carroll 2012) is probably meaningful, especially if these results could be replicated in a within-subjects design. Third, we disagree with the conclusion that normal brain response to phonemes in auditory cortex implies normal phonological representations. In fact, phonological representations can be thought of as emerging from the mappings between acoustic inputs and motoric outputs (Plaut & Kello 1999). Given this view, deficient connectivity between more posterior auditory regions and left inferior frontal gyrus is exactly what we would expect to find in children with poor phonological representations.

Causal direction. A second issue in the phonological theory of dyslexia concerns the direction of effect between phonological development and reading (Castles et al. 2011). Because written language is parasitic on oral language, and formal literacy instruction does not begin until children have mastered most of the fundamentals of a spoken language, it seems reasonable that the causal direction flows from phonology to reading rather than vice versa. Several lines of evidence support this conclusion. First, preschool children who will later develop dyslexia show deficits on various phonological tasks, with phoneme awareness being particularly predictive of later literacy attainment by around kindergarten age (Pennington & Lefly 2001, Scarborough 1991, Snowling et al. 2003). Furthermore, children with dyslexia underperform even younger, typically developing children matched on reading level on phoneme awareness tasks (Wagner & Torgesen 1987), and these deficits tend to persist in adults with dyslexia who have otherwise compensated well for the disorder (Bruck 1992, Hatcher et al. 2002).

The conclusion that phoneme awareness deficits have a unidirectional causal link to reading problems is oversimplified for several reasons, however. Speech scientists complain about the tyranny of the phoneme (Greenberg 2004) because these idealized representations have become reified and likely mislead us about what dimensions in the speech stream are important in development and how those dimensions are flexibly integrated to recover linguistic structures, such as words. There are longstanding controversies about the units of speech perception (Goldinger &

Azuma 2003), and recent evidence demonstrates that speech representations preserve much more than 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 (Port 2007). Related work with adult natural illiterates (who are cognitively normal but have no formal schooling) confirms that phoneme-level representations do not arise automatically in language development (Castro-Caldas et al. 1998, Morais et al. 1979). In other words, as literate adults we think that individual phonemes exist in the speech signal like beads on a string, but this is an illusion that arises from our extensive experience with an alphabetic script. Thus, difficulties in phonological development in dyslexia are probably not restricted to phonemic or segmental representations and must lie in other dimensions of the speech stream, at least initially. Despite this evidence that learning to read changes phonological development, methodologically rigorous work demonstrates that phoneme awareness training, when combined with direct reading instruction, improves literacy in early school-age children (Hulme et al. 2012). The most accurate conclusion therefore appears to be that the relationship between phonology and literacy is bidirectional.

Orthography: written system for a language. Alphabetic orthographies represent individual sounds with letters; logographic orthographies represent words or morphemes with symbols

Orthographic learning. In recent years there has been burgeoning interest in an orthographic learning account of reading problems, which emphasizes not phonological representations themselves but rather the ability to establish mappings between phonemes and graphemes, or letters and sounds (e.g., Aravena et al. 2013). This explanation has strong face validity to explain dyslexia, which is essentially defined by problems decoding print. Good neurophysiological evidence indicates that skilled readers treat letters as single audiovisual objects (Blau et al. 2010), and the orthographic learning hypothesis states that problems developing such integrated representations interfere with the emergence of fluent reading. Limited behavioral support for this hypothesis comes from research comparing the performance of children with and without dyslexia when they were asked to learn associations between sounds in their native language and an unfamiliar orthography. Although both groups learned the associations, the children with dyslexia performed more poorly than controls under time pressure (Aravena et al. 2013).

In addition to its face validity, the orthographic learning hypothesis has a number of strengths. It represents an admirable attempt to integrate across the brain and neuropsychological levels of analysis to explain reading development and difficulties. Furthermore, it avoids some of the reductionistic errors of other accounts that have been put forward as alternatives to the dominant phonological view, such as auditory and visual explanations. However, this hypothesis also faces some serious problems. Most critically, it does not account for the early language development of predyslexic children, who have subtle difficulties with spoken language long before they encounter a written script. Babies who will become dyslexic show a brain response to speech stimuli that differs from that of babies who will not become dyslexic (Guttorm et al. 2005). As toddlers, these children lag behind their peers in vocabulary and syntax (grammar) development, and in preschool, they have difficulties with phonological awareness (Scarborough 1991, Torppa et al. 2010). Notably, this same criticism can be applied to the access-only phonological view.

A related point is that it is difficult to test a pure integration account of phoneme-grapheme binding because we know that children with dyslexia are not equivalent to their typically developing peers in processing phonemes of their native language. So, the meaning of the fact that they are slower in learning phoneme-grapheme mappings is ambiguous; it could arise directly from the unimodal phonological deficit. To show that there is an additional contribution of cross-modal letter-sound processing over and above the well-established phonological processing problem in dyslexia, we will need behavioral studies that can somehow control for unimodal phonological and orthographic processing across groups. This will be an important issue to be addressed by future research.

Single Versus Multiple Deficit Accounts

Processing speed: speeded neuropsychological task emphasizing information processing (e.g., visual perception; learning a new symbolic code). Graphomotor output often required

Despite the large body of evidence supporting the phonological theory of dyslexia, it is now clear that a single core phonological deficit is insufficient to explain reading difficulties. As we and others have discussed elsewhere (Bishop & Rutter 2009, Pennington 2006), the etiology of dyslexia (like all behavioral disorders) is complex and multifactorial, so it should not be surprising that the underlying neuropsychology also involves several interacting risk and protective factors. Consistent with a multiple deficit hypothesis, results of family-risk designs (which follow children who are at genetic risk for dyslexia based on their family history but who are too young to have been diagnosed with the disorder) and longitudinal studies of children with early speech/language disorders consistently indicate that many children develop normal-range literacy skills despite preschool phonological deficits similar in magnitude to those of children who ultimately develop dyslexia (Bishop et al. 2009, Peterson et al. 2009, Snowling et al. 2003). These children appear to be protected from dyslexia because of relative strengths in other cognitive skills associated with reading. Conversely, children with multiple cognitive deficits are at much higher risk for dyslexia. Across countries and languages, many cognitive-linguistic constructs predict later dyslexia. The constructs that are most consistently implicated include phonological awareness, rapid serial naming, verbal short-term memory, vocabulary and other aspects of broader oral language skill, and graphomotor processing speed (McGrath et al. 2011, Pennington et al. 2012, Scarborough 1998, Wolf & Bowers 1999). The most powerful individual predictor varies with developmental stage. In toddlers and young children, broader language development is most strongly linked to later reading; by age 4 or 5 years, phonological awareness is the dominant predictor; and tasks emphasizing speed (i.e., rapid serial naming and processing speed) become increasingly important as literacy development progresses, probably because they are more linked to reading fluency than to single- word reading accuracy (Pennington & Lefly 2001, Puolakanaho et al. 2008, Scarborough 1990, Snowling et al. 2003, Torppa et al. 2010). Longitudinal research suggests that these deficits make a causal contribution to reading problems and are not fully accounted for by comorbidities or the cumulative effects of reading difficulties.

Research has made clear for many years that dyslexia does not result from disturbances in basic visual perception (Ramus 2003, Vellutino 1979). However, recently there has been renewed interest in the possible role of visual attentional deficits in reading difficulties (Facoetti et al. 2010). Visual attention is measured through serial search, orienting/cueing paradigms, or crowding paradigms that require participants to recognize pictures amid varying degrees of visual clutter; some of these skills probably contribute to performance on nonlinguistic processing speed tasks known to be correlated with reading. A recent study demonstrated that performance on visual attention tasks in preschool significantly predicted reading ability two years later, after accounting for the influence of reading-related phonological processing skills (Franceschini et al. 2012). Initial evidence suggests a similar pattern of results across writing systems with varying degrees of consistency in letter-sound relationships (i.e., Italian and French) (Zorzi et al. 2012). Although a deficit in visual attention does not easily account for the early speech-language phenotype in predyslexic children, it might represent an additional cognitive difficulty that interacts with language problems to cause reading failure. Further research is needed on this question.

BRAIN BASES OF DYSLEXIA

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 (see **Figure 1**). Indeed, functional

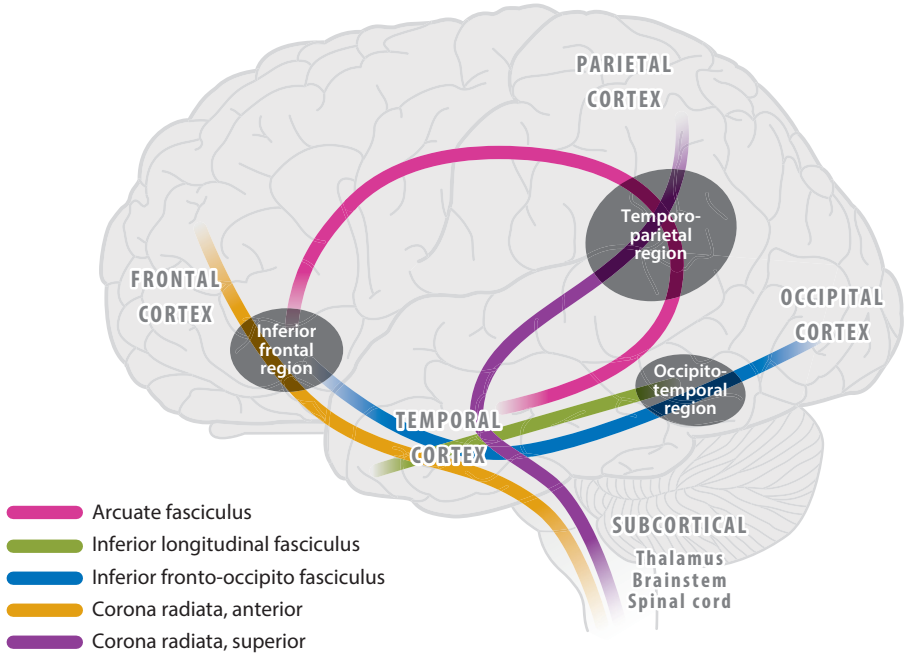

Figure 1

Schematic representation of grey matter regions (*dark grey ovals*) and white matter tracts (*colored lines*) that might be relevant for reading. Given the sagittal view of the figure, the corpus callosum is not depicted. Figure adapted with permission from Vandermosten M, Boets B, Wouters J, Ghesquière P. 2012. A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neurosci. Biobehav. Rev.* 36:1532–52.

imaging studies have consistently revealed that individuals with dyslexia show abnormal activations of a distributed left hemisphere language network (Demonet et al. 2004, Richlan et al. 2009). Underactivations 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, that is thought to participate in whole-word recognition. Abnormal activation of the left inferior frontal gyrus is also commonly reported. Structural imaging studies have revealed grey matter decreases in this same network. A recent family risk study demonstrated that these grey matter decreases predate literacy instruction and are thus not only a consequence of reading failure (Raschle et al. 2011).

Because individuals with dyslexia show functional abnormalities in both posterior and anterior language networks, it has been hypothesized that dyslexia is a disconnection syndrome. Accordingly, much research has used diffusion tensor imaging to explore white matter correlates of dyslexia. 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 (Deutsch et al. 2005, Klingberg et al. 2000, Rimrodt et al. 2010). Studies have consistently reported correlations between white matter integrity and phonological skills. This work is beginning to be integrated into neuropsychological theories of dyslexia, and this area should be a continued focus of future research. For example, as discussed above, a disconnection between posterior auditory processing areas and anterior motor planning areas is potentially consistent with disrupted development of phonological representations. Because of its emphasis

on letter-sound binding, the orthographic learning hypothesis also aligns with a disconnection account.

The neural correlates of dyslexia appear remarkably consistent across alphabetic languages with varying degrees of consistency (Paulesu et al. 2001, Silani et al. 2005) and even across alphabetic and logographic orthographies (Hu et al. 2010) despite the fact that the neural basis of skilled reading in Chinese is at least partly different from the neural basis of skilled reading in English. However, learners of consistent alphabetic orthographies are less likely to display clinically significant reading problems compared to learners of inconsistent orthographies (probably because those with reading vulnerabilities can still read accurately, even if slowly, in consistent languages). In summary, cross-cultural work suggests universality in the neurobiological and neurocognitive causes of dyslexia, but there is cross-cultural specificity in the manifestation of these underpinnings, with the same biological liability more likely to cause substantial impairment in some languages than in others.

ETIOLOGY

Scientific progress concerning the etiology of dyslexia has been built on a fairly mature understanding of its neuropsychology. It turns out that the neuropsychological deficits associated with a developmental disorder are often more stable and heritable than the defining symptom itself, and the deficits are frequently present in family members who do not meet full diagnostic criteria for the disorder. In the case of dyslexia, relatives of affected family members can have reading skills in the normal range despite deficits on some specific phonological processing tasks. In other words, neuropsychological constructs can serve as endophenotypes for behaviorally defined disorders. Most of what we know about the genetics of dyslexia has depended on decades of research on its neuropsychology, research that has allowed for the use of optimal endophenotypes in etiologic studies. The relationship is reciprocal: As scientists discover links from etiology to pathogenesis, that knowledge will further constrain the neuropsychological level of analysis and will particularly help inform which brain and cognitive changes may be causal in a disorder (as opposed to associated with the disorder for other reasons).

Behavioral Genetics

Main effects of genes and environment. Behavioral geneticists have documented moderate heritability (often around 0.50) for individual differences in most dimensions of human cognition and personality (Plomin et al. 2013), including both typical reading and dyslexia. It is important to understand what the technical term "heritability" means and does not mean. Heritability refers to the proportion of variance in a given population that is attributable to genetic influences; other variance components are attributable to environmental influences, gene-environment interplay, or just error of measurement. Heritability estimates do not tell you about the cause of an individual's outcome, and, because they are population specific, they can vary across populations. Like all behaviorally defined disorders, the cause of dyslexia is multifactorial and is associated with multiple genes and environmental risk factors. Both dyslexia and normal variations in reading skill are familial and moderately heritable (Christopher et al. 2013, Harlaar et al. 2005, Logan et al. 2013, Pennington & Olson 2005), with the caveat that the heritability of reading skill changes with age. For instance, Logan et al. (2013) demonstrated that the heritability of individual differences in reading skill steadily increases from 0.22 at age six years to 0.82 at age twelve years. These increases in heritability likely reflect both (*a*) a narrowing of environmental influences on reading produced by a fairly standard reading curriculum once children enter formal education and (*b*) an increasing correlation between genotype and environment (i.e., G-E correlation) as children increasingly are

able to pick niches that fit their level of reading skills (e.g., good readers read more on their own and become even better readers, whereas poor readers avoid reading). Both of these explanations are examples of G-E interplay, which is discussed below. Because these results come from mainly middle-class twin samples in developed countries, it is important to remember that they may not generalize to other populations [but see Hensler et al. (2010), who found moderate heritability (>0.50) both for dyslexia and typical reading skill in a more ethnically and economically diverse sample].

Gene-environment interplay. Beyond the main effects of genes and environment is the question of how genetic and environmental risk factors act together in the development of abnormal behavior, including dyslexia. As discussed above, Friend et al. (2008) found evidence for a bioecological gene-by-environment (G × E) interaction in dyslexia. Specifically, the heritability of dyslexia increases as parent education increases. This result suggests that the child's literacy environment is, on average, both more favorable and less variable as parent education increases, resulting in genetic risk factors playing a bigger role in a child's dyslexia. Conversely, as parent education decreases, the child's literacy environment is on average less favorable and more variable, resulting in environmental risk factors playing a bigger role in a child's dyslexia.

There is also increasing evidence for the importance of transactional processes in atypical development, in which the child and environment mutually alter each other over time. G-E correlation is an example of such a transaction. These transactions occur because children evoke different kinds of reactions from their environments (Scarr & McCartney 1983) and select different kinds of environments for themselves. Not surprisingly, the individual characteristics that influence such reactions and selections are genetically influenced. There are three subtypes of G-E correlation: passive, evocative, and active (Scarr & McCartney 1983). In the case of reading development, an example of a passive G-E correlation is the relation between parents' reading skill and the number of books in the home. Parents' reading skill is partly due to genes, and parents who are better readers on average have more books in their home. Without any action on the part of their biological children, their literacy environment is correlated with their reading genotype, on average. In contrast, an evocative G-E correlation occurs when adults in a given child's environment notice their interests and talents and seek to foster them. In the case of reading development, an example of an evocative G-E correlation would be a parent or relative taking a child who likes to read to the library. Finally, an active G-E correlation occurs when children, on their own initiative, seek or avoid environments as a function of their genotype. Dyslexia provides a clear example of an active G-E correlation. Even before formal literacy instruction, children at genetic risk for dyslexia who will later develop the disorder avoid being read to and spend less independent play time looking at books than do their siblings who do not develop dyslexia (Scarborough et al. 1991). As they get older, school-age children with dyslexia read dramatically fewer words per year than do typically developing children (Cunningham & Stanovich 1998), such that this reduced reading experience negatively influences both their reading fluency and their oral vocabularies (Stanovich 1986, Torgesen 2005).

Active gene-environment (G-E) correlation: type of gene-environment interplay thought to operate in dyslexia in which children select environments for themselves based on their genotypes

Single-neucleotide polymorphism (SNP): single DNA nucleotide whose base (A, T, C, or G) varies across individuals at a specific location in the genome

Molecular Genetics

Dyslexia has been linked to nine risk loci (DYX1–DYX9, with DYX standing for dyslexia and the number indicating the order of discovery) identified through replicated linkage studies that used molecular methods (Fisher & DeFries 2002, McGrath et al. 2006), although not every study has replicated these results (Ludwig et al. 2008, Meaburn et al. 2008). For instance, Meaburn et al. (2008) used DNA pooling and over 100,000 single-nucleotide polymorphisms to identify loci that

distinguished a high- from a low-reading group. Their few significant hits each accounted for very small amounts of the variance and did not include the best-replicated dyslexia loci.

Genome-wide association study: study testing the association between a given phenotype and many SNPs (often a million or more) across the entire genome

More precise mapping methods have led to the identification of six candidate genes (termed C for candidate and followed by a number, again indicating the order of discovery) in some of the nine replicated risk loci [a risk locus is specified by its chromosome number out of the 23 human chromosomes, by which of the two arms—short (p) or long (q)—the risk locus is on, and by an "address" on that arm, indicated by a number]. These six candidate genes are *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. Studies of their role in brain development (Kere 2011) in rodents has shown that *DYX1C1*, *DCDC2*, *KIAA0319*, and *ROBO1* affect prenatal processes of brain development, specifically neuronal migration (the movement of immature neurons from where they are first formed to their final destination in the brain) and the formation of connections once neurons reach their final destination (e.g., neurite—axon and dendrite—outgrowth and guidance). More generally, these two processes of early brain development are genetically controlled by a family or network of genes that interact with each other through molecular signals. In contrast, very little is known about the functions of the two DYX3 candidate genes. Two other studies have identified new candidate genes for dyslexia, three on chromosome 18 (*MC5R*, *DYM*, and *NEDD4L*) (Scerri et al. 2010) and one on chromosome 16 shared with LI (*CMIP*) (Scerri et al. 2011), but these results need to be replicated. **Table 1** summarizes the nine dyslexia candidate genes as well as four additional genes that were initially identified in comorbid disorders (SSD or LI) and have since been associated with dyslexia.

Gialluisi and colleagues (2014) recently published the first genome-wide association study of dyslexia and related disorders. This work identified some novel candidate genes, but previously identified candidates did not reach significance, possibly because of low power. This pattern has been fairly common in genome-wide association studies of other traits, especially with smaller *N*s. Hence, confirmation of current candidate genes for dyslexia awaits larger samples and testing for their roles in molecular signaling networks.

Exciting new research using animal models is beginning to integrate knowledge about the development of dyslexia across the etiologic, brain, neurocognitive, and behavioral levels of analysis. The rat homologue of human dyslexia candidate gene *KIAA0319* is known as *Kiaa0319*, and

Table 1 Dyslexia candidate genes[1]

Locus	Location	Gene
DYX1	15q21.1	*DYXC1*
DYX2	6p22.2 6p22	*KIAA0319* *DCDC2*
DYX3	2p15-16	*MRPL19*, *C20RF3*
DYX5	3p12-q13	*ROBO1*
DYX6	18p11.2	*MC5R*, *DYM*, *NEDD4L*
SPCH1	7q31.1	*FOXP2*
SLI4	7q35-36	*CNTNAP2*
SLI1	16q23-24	*CMIP*, *ATP2C2*

[1]This table summarizes candidate genes for dyslexia in some of the best-replicated linkage regions for the disorder [DYX1–DYX6 (DYX stands for dyslexia; the number indicates the order of discovery)] as well as candidate genes that were initially identified in comorbid speech/language disorders [i.e., speech sound disorder (SPCH1) and specific language impairment (SLI1 and SLI4)] and have since been associated with dyslexia.

neuroscientists have created a knockdown in the rat model via in utero RNA interference, which causes reduced expression of *Kiaa0319*. This knockdown probably yields changes in gene expression that are more severe than those associated with dyslexia in humans but are hypothesized to lie along the same continuum as the dyslexia risk in humans. Rats with the *Kiaa0319* knockdown are largely developmentally and behaviorally normal but show subtle changes in brain development and auditory processing of speech sounds (Szalkowski et al. 2013). At a structural level, knockdown leads to focal disruptions of neuronal migration (Platt et al. 2013), similar to those first described in the brains of adult humans with dyslexia many years ago by Galaburda and colleagues (1985). Furthermore, these rats show an atypical neurophysiological response to speech sounds in auditory cortex (Centanni et al. 2013) and are less effective than typical rats at discriminating phonemes (Centanni et al. 2014). Of most direct clinical relevance, intensive behavioral training using speech sounds normalizes the rats' behavioral performance (Centanni et al. 2014).

Another strategy for linking candidate dyslexia genes to brain structure and function is to conduct a genetic neuroimaging study in humans, in which the association between risk genotypes for dyslexia and established brain phenotypes for dyslexia can be tested. As reviewed above, reductions in left hemisphere white matter volume are a well-replicated brain phenotype in dyslexia. Darki and colleagues (2012) tested whether this brain phenotype was associated with genetic markers for variants in each of three established risk genes for dyslexia—*DYX1C1*, *DCDC2*, and *KIAA0319*—in a sample of typical adults and found a significant association for all three risk genes. The fact that these associations were found in a typical population is consistent with the fact that dyslexia is a continuous rather than a categorical disorder, such that individuals without diagnosed dyslexia may nonetheless have some of the risk factors for dyslexia. More work is needed to replicate and extend both the animal and human findings, but the emerging picture is that risk genes for dyslexia alter brain development differentially in the left hemisphere, thereby altering speech and language development so as to make the acquisition of written language more difficult.

In a recent review of the molecular genetics of dyslexia, Carrion-Castillo et al. (2013) discuss the two molecular signaling networks already implicated in the development of dyslexia—neuronal migration and neurite outgrowth and guidance—as well as a third one, ciliary biology. Cilia are microscopic hair-like structures on the surface of cells, as in a paramecium, and their rhythmic movement turns out to play a role in the patterning of early brain development. Carrion-Castillo et al. (2013) also discuss in detail the sometimes inconsistent evidence found across samples for the various candidate genes for dyslexia. This inconsistency is due to the fact that (*a*) the mutations found in dyslexia are not in the coding regions of genes that directly code for the structure of proteins but rather in noncoding regions that affect expression levels of structural genes, sometimes with small and subtle effects, and (*b*) many of the samples in these studies are too small, as discussed above.

Nonetheless, the knowledge that these candidate genes interact with each other and act on the same molecular signaling pathways is a promising beginning for eventually discovering the many more genes that are likely involved and for working out the early developmental biology of dyslexia.

Environmental Influences

Because the heritability of dyslexia is substantially less than 100%, we know that environmental factors contribute to the development of the disorder. However, limited methodologically rigorous work has investigated which specific environments causally influence reading development. Possible candidates include the language and preliteracy environments that parents provide for their children, but, unfortunately, much of the research on these topics has used correlational

rather than genetically sensitive designs (such as twin and adoption studies). Thus, parents with a genetic risk for dyslexia may provide less literacy exposure to their children because of the G-E correlations discussed above, and so it is not clear that the environment plays a causal role in the child's reading outcome. This limitation is avoided in treatment studies that use random assignment. The results of such research suggest that training parents in various home literacy activities promotes young children's vocabulary (a reading precursor; Lonigan & Whitehurst 1998) and early reading skills (Sénéchal 2014, Sylva et al. 2008). This work is broadly consistent with findings from twin studies demonstrating that, during the preschool years, individual differences in vocabulary and some other literacy precursors are more influenced by family environment than by genes (Byrne et al. 2009, Hayiou-Thomas et al. 2012). However, this work has also shown that over time, the relative importance of etiologic influences shifts, and by later school age, genetic influences on oral language and literacy predominate. Thus, further work is needed to know whether the effects of home literacy environment on word reading persist beyond the beginning stages of literacy instruction.

Related research has used randomized controlled trials to study the effects of instructional type on reading development in alphabetic systems. This research has consistently shown that phonologically based instruction, which emphasizes explicit knowledge about letter-sound correspondences, is superior to other forms of literacy instruction that emphasize sight word recognition (e.g., whole-word instruction) or listening comprehension (e.g., whole-language instruction) in promoting word-level reading skills, particularly for children who are at risk for reading difficulties (Brown & Felton 1990, Snowling & Hulme 2011, Vellutino et al. 2006). Because literacy curricula vary across and sometimes within countries, instructional type can influence the risk of an individual child meeting standard diagnostic criteria for dyslexia.

TREATMENT

The development of evidence-based treatments for dyslexia has benefitted from our understanding of the neuropsychology of the disorder, and the best interventions provide intensive, explicit instruction in phoneme awareness, the alphabetic principle and phonics, word analysis, reading fluency, and reading comprehension (Natl. Read. Panel 2000, Snow et al. 1998). Much more is known about effective remediation of reading problems in younger than in older children. In addition, it appears to be easier to treat accuracy than fluency problems, perhaps in part because fluency is so dependent on reading experience, which varies dramatically by reading level. It may be nearly impossible for poor readers to close the gap in print exposure once they have accumulated several years of reading failure, but there is some evidence that fluency problems can be prevented with appropriate intervention in kindergarten and first grade, at least over the short term (Torgesen 2005). An important conclusion is that professionals should not wait until children are formally diagnosed with dyslexia or experience repeated failures before implementing reading treatment, given that remediation has been shown to be less effective than early intervention (Vaughn et al. 2010).

Recent work on treatments for reading failure (Scammacca et al. 2007) supports the following conclusions: (*a*) intervention is most effective when provided in a one-to-one or small group setting (Vaughn et al. 2003); (*b*) successful interventions heavily emphasize phonics instruction; and (*c*) other valuable treatment elements include training in phoneme awareness, supported reading of increasingly difficult connected text, writing exercises, and comprehension strategies. Many effective treatments are relatively low cost, further highlighting the importance for public health of early identification, prevention, and treatment of dyslexia.

There are individual differences in how well individuals with dyslexia respond to treatment, with about half of successfully treated children maintaining gains for at least one to two years. The well-documented preschool predictors of later reading skill (i.e., phoneme awareness, letter name and sound knowledge, and rapid serial naming) also predict treatment response, although more research is needed on this question (Mathes et al. 2005). Regarding long-term prognosis independent of treatment, language skill is a known protective factor for both children and adults with dyslexia (Shaywitz et al. 2003).

A growing number of intervention-imaging studies are investigating how remediation of dyslexia alters brain activity. This research has been reviewed in more detail elsewhere (Gabrieli 2009). Briefly, effective intervention appears to promote normalization of activity in the left hemisphere reading and language network, which has been shown to reduce activity in dyslexia. In addition, increased right hemisphere activation has been reported following dyslexia treatment, which is sometimes interpreted as reflecting compensatory processes.

Although there is a solid evidence base for treatments emphasizing direct instruction in reading and phonological training, several alternative therapies either lack sufficient evidence or have been shown to be ineffective for dyslexia and thus should not be recommended to children and families (for a review, see Pennington 2011). Most of these therapies are based on sensory-motor theories of dyslexia and include training in rapid auditory processing (e.g., the Fast ForWord program), various visual treatments (colored lenses, vision therapy), and exercise/movement-based treatment (e.g., vestibular training).

CONCLUSIONS

Among developmental disorders, dyslexia is one of the most extensively studied and best understood. As we hope this review has made clear, real progress in our scientific understanding of dyslexia has benefitted from a highly interdisciplinary approach drawing on numerous fields and subfields including developmental psychology, neuroscience, cognitive science, speech science, behavioral and molecular genetics, and clinical psychology. The answers to some basic questions about the disorder, particularly those confined to a single level of analysis, have been reasonably clear for many years. This work laid the foundation for current cutting-edge research that should ultimately lead to a complete understanding of dyslexia by making links across levels of analysis—from genetic and environmental risk and protective factors, to changes in brain development, to cognitive profiles, and ultimately to applied issues such as early identification and treatment. Of course, this description is an oversimplification because effects between levels of analysis are not unidirectional. As we have discussed above, research with rats and humans makes clear that effective behavioral interventions reach backward to change cognitive processes and brain functioning, and although such treatments cannot change DNA sequences, they do have the potential to impact etiology by altering the environments that children select for themselves and perhaps even to influence gene expression.

Will this work eventually lead to a cure for dyslexia? The answer to that question depends in part on how we define the disorder. Our current behavioral definition simply captures the lower tail of the reading distribution. Thus, a "cure" at the individual level means moving one child up in the distribution, ahead of others who would then meet the behavioral criteria. Since eradication of all individual differences is not realistic (or desirable), behaviorally defined disorders can be eliminated only in the fictional location of Lake Wobegon. However, it is seems reasonable that scientific progress will continue to point toward educational and policy changes that could move

the mean of the reading distribution as a whole and in particular could continue to move up the lower bar for basic literacy attainment in our society.

SUMMARY POINTS

1. Dyslexia is a prevalent neurodevelopmental disorder, and in recent decades much progress has been made in understanding its etiology, brain bases, neuropsychology, comorbidities, and sociocultural context.
2. Dyslexia is moderately heritable, and several candidate genes known to play a role in brain development have been identified.
3. Environmental risk factors, including those associated with lower socioeconomic status, also influence children's risk for dyslexia.
4. The most consistent brain findings include aberrant structure and function of left hemisphere reading and language networks.
5. The neurocognitive causes of dyslexia are also multifactorial and include phonological processing, broader oral language skill, and processing speed.
6. Common comorbidities include attention deficit/hyperactivity disorder, speech/language disorders, and other learning disabilities, all of which are mediated by shared etiologic and cognitive risk factors.
7. Although there are some differences in the manifestation of dyslexia across various languages and orthographies, there is also evidence for impressive universality of the disorder's underlying brain bases and neuropsychology.
8. Evidence-based treatments for dyslexia emphasize intensive, explicit instruction in phoneme awareness, phonics, word analysis, reading fluency, and reading comprehension.

FUTURE ISSUES

1. The total effect size of the candidate genes identified to date is small and does not account for most of dyslexia's heritability. More work is needed to identify additional genetic risk factors and to understand the role of individual risk genes within molecular signaling networks.
2. Future studies using genetically sensitive designs should help identify specific environmental factors that increase children's risk for dyslexia.
3. Although evidence supports substantial universality across countries and languages, we know less about how the manifestation of dyslexia may vary across levels of socioeconomic status and ethnic/racial groups within countries.
4. The field of neuroimaging is evolving rapidly and increasingly emphasizing whole-brain/connectivity analyses, but the application of these approaches to dyslexia has been limited to date.

5. Although the orthographic learning hypothesis has several strengths, further work is needed to demonstrate that letter-sound binding problems are greater than those expected on the basis of unimodal phonological processing problems alone.
6. Available treatments can successfully remediate reading problems in many young children with dyslexia, but less is known about successful treatment of older children, of reading fluency, and of the subset of children who do not respond well to existing interventions.

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