

Neuropsychology and Genetics of Speech, Language, and Literacy Disorders

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This article provides an overview of the neuropsychology, neural substrates, and genetics of three disorders of language development: (1) developmental dyslexia, or reading disability (RD); (2) language impairment (LI); and (3) speech sound disorder (SSD). The three disorders are comorbid, and the authors review accumulating evidence for their overlap at the symptomatic, neuropsychologic, neural, and etiologic levels. The overlap is not complete, however, and researchers are still learning why, for example, some children have difficulties with speech sound production but not with reading. Of the three disorders, scientists know the most about RD across all the levels of analysis covered in this review, and the least about SSD. The amount of space dedicated to each disorder in this article reflects the current knowledge base of the field.

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Definitions and epidemiology

Current definitions of RD, LI, and SSD have two parts: (1) a diagnostic threshold and (2) a list of exclusionary conditions, which usually includes a peripheral sensory impairment (eg, deafness), a peripheral deficit in the vocal apparatus, acquired neurologic insults, environmental deprivation, and other more severe developmental disorders (such as autism or mental retardation). The first part of each definition concerns the central problem in the disorder. For RD, this problem lies in fluent or accurate printed word recognition. For LI, the defining problem concerns 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, setting a diagnostic threshold means imposing a somewhat arbitrary cutoff on a continuous variable (eg, Ref. [1]). A further issue has been whether the diagnostic cutoff should be drawn relative to age or IQ expectations for the particular ability involved. The logic of IQ-discrepant definitions is that they identify "pure" cases with a specific deficit, rather than a more general learning difficulty. The research literature generally has not supported the external validity of the distinction between age- and IQ-discrepancy definitions for either the underlying deficit or the kind of treatment that is helpful [2–4]. There is thus a growing consensus that age-referenced definitions are preferable, particularly for clinical purposes. Some research investigations may continue to benefit from an IQ discrepancy definition to identify the purest cases, however [5].

Prevalence estimates, of course, depend on definition. A commonly used cutoff for RD identifies 7% of the population by selecting those whose reading achievement is 1.5 standard deviations below the mean for age. An influential definition of LI requires performance on two language composites to fall below the tenth percentile; this definition identified 7.4% of an epidemiologic sample of kindergartners [6]. The prevalence of SSD declines sharply after the preschool period [7]. In an epidemiologic sample of 6-year-old children, 3.8% met criteria for SSD [8] compared with 15.6% of 3-year-old children [9]. These studies included only children making developmentally inappropriate speech errors; the prevalence is higher if children making errors considered developmentally appropriate that nonetheless interfere with intelligibility are included. All three disorders show a slight male predominance (approximately 1.5:1 [6,8,10]). Although there is widespread agreement that RD, LI, and SSD are all comorbid, specific comorbidity estimates vary widely depending on precise definitions, the age range studied, and the degree to which all three disorders (as opposed to only two) are accounted for. One consistent finding has been that children who have early language impairments are at high risk for later reading problems, with approximately 50% meeting criteria for RD [11,12]. In contrast, fewer children with isolated speech sound production difficulties meet full criteria for RD, although their literacy attainment may still lag behind that of appropriate controls [13,14].

Neuropsychology

Of the disorders considered in this article, researchers know the most about RD. This is largely because dyslexia is so well defined at the cognitive level of analysis. The cognitive analysis of dyslexia has provided both a fairly precise diagnostic phenotype and cognitive components of that phenotype. These cognitive components have proved useful as endophenotypes in genetic and neuroimaging studies. Although it might seem that science should start at lower levels of analysis, such as the etiologic or neural levels, understanding of complex behavioral disorders (including those considered in this article) generally relies on first establishing a sound neuropsychologic theory to define the behavioral phenotypes to tie to any putative neural substrates or genetic causes. Our understanding of SSD and LI across all levels of analysis becomes greatly enriched once we develop more complete neuropsychologic theories of these disorders.

Neuropsychology of reading disability

The ultimate goal of reading is reading comprehension. It turns out that a substantial proportion of the variation in reading comprehension can be accounted for by individual differences in the accuracy and speed of printed word recognition, especially in children [15]. According to the “simple view of reading” [16], reading comprehension (RC) equals the product of single word recognition (WR) and listening comprehension (LC). Empiric evidence has demonstrated that, in children, the product of WR and LC correlates highly with RC (0.84) [16]. The external validity of defining reading disability as characterized by deficits in accurate and fluent word recognition derives partly from the strong relationship of WR to RC. Of course, some children may have reading comprehension difficulties despite good WR skills because of impairments in LC. There is now evidence that such a group of children exists. They have been called “poor comprehenders” and are considered a diagnostically discrete category from RD (see Ref. [17] for a review.) Many poor comprehenders also meet criteria for LI [18], although most children who have LI have difficulties with RC resulting from deficits in both WR and LC. More recent research has also indicated that, as a group, children who have reading disability have problems with LC [19], indicating some phenotypic overlap between RD and LI. Further evidence for this phenotypic overlap comes from longitudinal studies demonstrating that preschoolers who later become RD show early deficits in syntax and semantics (eg, Ref. [20]). The notion that RD arises purely from WR deficits is therefore an oversimplification. This oversimplification allowed for many of the important recent discoveries about RD, however.

Word recognition can itself be broken down into two component written language skills, phonologic coding (PC), and orthographic coding (OC). PC

refers to the ability to use knowledge of rule-like letter–sound correspondences to pronounce words that have never been seen before (usually measured by pseudoword reading), and OC refers to the use of word-specific patterns to aid in word recognition and pronunciation. Words that do not follow typical letter–sound correspondences (eg, *have* or *yacht*) must rely, at least in part, on OC to be recognized, as do homophones (eg, *rows* versus *rose*). A topic of ongoing debate in the adult and developmental literatures has been the extent to which successful PC and OC are achieved by separable cognitive mechanisms [21–23]. One question relevant to that debate is whether there are subtypes of RD that result from impairment to one mechanism or the other. This debate is beyond the scope of this article. The evidence is clear, however, that as a group, children who have RD are impaired at both PC and OC, and a common cause is supported by genetic studies showing that both deficits are linked to the same loci [24,25]. Further, the deficit in PC is generally considered more central because of extensive research documenting that, on the whole, individuals who have RD read pseudowords less accurately than even younger, normal readers matched on real word reading accuracy [26]. We argue that the great majority of children who have RD have difficulties with real word recognition resulting largely from PC deficits.

A complete neuropsychologic theory of RD must also specify the cognitive deficits that lead to phonologic coding difficulties. One family of tasks that has received particular attention measures phoneme awareness, an oral language skill that includes the ability to manipulate and attend to individual sounds in words. As an example of one kind of phoneme awareness task, the child is asked to “say ‘fixed’ without the ‘/k/’” with the correct answer being “fist.” Individuals who have RD perform poorly on phoneme awareness tasks relative to both age-matched controls and younger, typically developing readers. Such tasks are among the best predictors of later reading ability, and phoneme awareness training positively influences later reading skill (see [27] for a recent review). Taken together, the evidence suggests that phoneme awareness plays a causal role in RD. This relationship presumably arises because the ability to map individual sounds onto letters—the defining characteristic of phonologic coding—relies on the ability to break spoken words apart into sounds and to attend to those sounds individually.

It now seems likely that both phonologic coding and phonologic awareness impairments in RD arise from lower-level deficits in the development of phonologic representations (ie, mental representations of individual speech sounds). Evidence for this view comes from the association of RD with poor performance on a wide variety of phonologic tasks, including phonologic memory, confrontational naming, and rapid naming [27]. These are all oral language tasks, buttressing the argument that RD is a language disorder. Further, children who have RD have difficulties with some speech perception tasks that do not require metalinguistic awareness [28,29].

Historical theories of RD postulated a basic deficit in visual processing and focused on the reversal errors commonly made by individuals who had RD, such as writing *b* for *d* or “was” for “saw” [30,31]. The simple visual theory of RD has been discredited for more than 25 years; Vellutino [32] demonstrated that such reversal errors in RD were restricted to print in one’s own language, and were thus really linguistic rather than visual in nature. Several more current hypotheses also propose that RD results from a nonlinguistic, low-level sensory deficit. For example, the magnocellular hypothesis holds that RD results from difficulties with rapidly processing visually presented material [33]. The auditory hypothesis does not deny deficits in phonologic representations in RD, but posits that these deficits result from more basic, nonlinguistic, auditory processing problems [34,35]. (The auditory hypothesis was originally proposed to account for LI and is discussed later.) Indeed, RD participants have shown reliable group deficits on visual and auditory tasks. The argument for causality is damaged by a case-by-case inspection of data, however, which has consistently revealed that many RD participants do not have sensory deficits, whereas some control participants do (see Ref. [36] for a review). One interpretation is that RD sometimes co-occurs with more general sensory difficulties that are not the cause of the central phonologic coding deficit [36,37].

Neuropsychology of language impairment

A challenge to researchers studying the neuropsychology of LI has been the heterogeneity of the phenotype. At the symptomatic level, children’s primary difficulties can range from expressive syntax to receptive vocabulary. Efforts to delineate reliable subtypes of LI have not met with great success, however, partly because subtypes based on symptom descriptions do not show adequate longitudinal stability [38]. The search for a core underlying deficit in LI has led to three competing proposals: the extended optional infinitive hypothesis, the phonologic memory hypothesis, and the auditory hypothesis. These hypotheses differ importantly in the specificity of the proposed impairment, and each is reviewed briefly later. We believe that current evidence best supports the phonologic memory hypothesis. Even this hypothesis is clearly incomplete, however, probably because any single core deficit will be inadequate to account for the full LI phenotype [39].

Of the three hypotheses, the extended optional infinitive proposal of Rice and colleagues [40] is the most specific; it posits that the core deficit in LI lies in the acquisition of a particular aspect of syntax. Evidence for this hypothesis is that children who have LI make characteristic errors in their expressive language. In English, they most notably have difficulties with the past tense, often substituting an unmarked form for a marked one (eg, “He walk there” in place of “He walked there.”) This kind of error is made by typically developing children early in language acquisition, but children

who have LI tend to use unmarked (or infinitive) forms much longer than even younger, typically developing children matched for overall language skill. Despite the elegance of this proposal, it faces two major challenges in trying to account for all cases of LI. First, it does not adequately explain the cross-linguistic data, which have shown that the syntactic forms causing the most difficulty for language-impaired children vary with their perceptual salience in different languages [41]. In English, for example, the past tense may be problematic partly because its marker (“-ed”) is brief and often unstressed. Second, this proposal fails to explain why children who have LI perform poorly on a wide range of language tasks, including those that do not require syntactic competence [38]. The value of this marker may be in its persistence with age, making it an important endophenotype for genetic studies.

The phonologic memory hypothesis of LI holds that the core deficit lies in the ability to hold phonologic forms in working memory [42]. Phonologic memory is most often measured by asking children to repeat spoken lists of real words, such as numbers (digit span) or individual pseudowords (non-word repetition). This proposal is theoretically attractive because work with brain-damaged adults, second-language learners, and typically developing children has converged in highlighting a role for phonologic memory in language learning, particularly vocabulary acquisition [43]. Further, a recent computational model demonstrated that phonologic deficits caused impaired syntax learning [44]. Phonologic memory impairment does seem to be a robust endophenotype for LI. Phonologic memory deficits are heritable and correlate significantly with degree of language difficulty in individuals who have LI [45]. Further, phonologic memory deficits persist even in individuals whose broader language problems have resolved [46]. The phonologic memory hypothesis is unlikely to fully account for LI, however, because children who have RD and SSD also show phonologic memory deficits, often in the face of spared broader language function. To account for this pattern of findings, Bishop and Snowling [47] proposed a two by two classification for developmental language disorders based on the presence or absence of (1) phonologic deficits and (2) broader language deficits, including semantics and syntax. According to this scheme, RD is associated with phonologic deficits only, whereas LI is associated with deficits on both dimensions. Because broader language deficits are the defining symptom in LI, however, this classification scheme remains descriptive. A neuropsychologic theory must specify the cognitive components that underlie these deficits.

Finally, the auditory hypothesis of LI is the least specific because it posits that a nonlinguistic sensory impairment leads to both phonologic and broader language difficulties in LI. This hypothesis was developed in the 1970s by Tallal and Piercy [48] and in more recent years has been extended to RD (see previous discussion). Early studies demonstrated that children who had LI had specific difficulty discriminating rapidly presented

nonspeech sounds, which presumably led to problems processing certain aspects of the speech stream. Later studies found that despite group differences, many children who have LI do not have auditory deficits, whereas many typically developing children do [49]. Further, there is little evidence that the auditory impairments described in these studies are heritable [45]. Because LI is partly heritable, this finding is problematic for the argument that deficits in the discrimination of rapid auditory stimuli are the sole cause of the disorder. It remains possible that auditory deficits of an environmental cause significantly complicate language development in children already at genetic risk for LI [45].

Neuropsychology of speech sound disorder

SSD was originally considered a disorder of generating oral-motor programs, and children who had speech sound impairments were said to have “functional articulation disorder” [38]. A careful analysis of error patterns has rendered a pure motor deficit unlikely as a full explanation for the disorder, however. For example, children who have SSD sometimes produce a sound correctly in one context but incorrectly in another. If children were unable to execute particular motor programs, then we might expect that most of their errors would take the form of phonetic distortions arising from an approximation of that motor program. The most common errors in children who have SSD are substitutions of phonemes, not distortions [41]. Further, a growing body of research is demonstrating that children who have SSD show deficits on a range of phonologic tasks, including phoneme awareness and phonologic memory [50–53]. Although it remains possible that a subgroup of children have speech sound difficulties primarily because of motor impairments, it now seems likely that most children who have SSD have a type of language disorder that primarily affects phonologic development. There is thus a puzzle to be resolved: if RD, LI, and SSD are all associated with phonologic impairments, why is their overlap not complete? One possibility is that phonologic deficits are a shared risk factor for all three disorders, with additional risk factors specific to each disorder [39]. For example, work in our laboratory showed that RD and SSD were associated with similar deficits in phoneme awareness and phonologic memory, but only RD was additionally associated with impairments in rapid naming [51,54].

Neural substrates

Anatomic findings

Evidence for structural abnormalities in the brains of individuals who have RD or LI has come from postmortem studies and MRI. To date, there is little research on the neuroanatomy of SSD. Interpretation of the RD and LI results is complicated because definitions of the disorders vary across

studies, and many studies have not adequately addressed the question of comorbidity. This confound can be seen in the pioneering work of Galaburda and colleagues, who reported a series of postmortem findings in individuals who had severe reading difficulties. One group of findings concerned histologic anomalies, including abnormally-sized cells, and ectopias and dysplasias presumed to result from failures of neural migration. Overall, these anomalies were more common in RD than control brains, particularly in perisylvian regions and in parts of the thalamus. A second group of postmortem findings related to the planum temporale, a region of the superior temporal gyrus (STG) implicated in auditory and language processing. Most typically developing individuals show an asymmetry of this structure, with larger left hemisphere than right hemisphere volumes, whereas brains of several reading-disabled individuals showed symmetry [55,56]. Although this result has most often been assumed to relate to RD, it is likely that many of the individuals studied by Galaburda and colleagues would have also met criteria for language impairment [47]. In fact, symmetric plana temporale and perisylvian histologic anomalies have since been associated with LI [57,58].

More recent MRI studies have suggested that reduced or reversed planum temporale asymmetry is indeed more likely to be associated with LI than with RD. Although two early MRI studies supported the absence of a normal leftward asymmetry in RD, there have since been numerous failures to replicate this finding and some reports of greater leftward asymmetry for individuals who have RD than controls [59]. In contrast, abnormal asymmetry of the planum temporale (or of the STG, which includes this structure) has been reported somewhat more consistently in the LI literature [57,60–63] (but see [64,65]). In one study that directly compared children who had RD to children who had LI, only the group that had LI had symmetric plana temporale [62].

Another brain region that has garnered attention in the RD and LI literatures is the inferior frontal gyrus (IFG), which includes Broca's area, long known as a critical region for language production. This structure also shows a leftward asymmetry in most typically developing individuals, whereas studies have reported reduced or reversed asymmetry in LI [60,64]. De Fosse and colleagues [64] found that reduced leftward asymmetry correlated with lower verbal IQ. Findings for RD have been similar. For example, Brown and colleagues [66] reported gray matter decreases in the left IFG in individuals who had RD, whereas Robichon and colleagues [67] found an abnormal rightward asymmetry of the IFG in RD that correlated with pseudoword reading performance. It is thus possible that IFG abnormalities confer risk for language impairment and reading disability.

Both disorders have also been associated with more widespread neural differences. RD researchers have reported abnormalities in many parts of the temporal lobes, in perisylvian regions of the parietal lobes, and in the cerebellum (see Ref. [68] for a review). LI researchers have reported

differences across frontal, temporal, parietal, and subcortical regions [47]. Further, there have been some reports of total cerebral volume reduction in both RD [69,70] and LI [62,71]. In a direct comparison of children who had RD to children who had LI, however, volume reduction seemed specific to LI [62]. Furthermore, another study by the same research group reported that cerebral volume did not correlate with symptom measures that are central to RD (eg, pseudoword reading) but did correlate with measures more central to LI, such as oral comprehension [72].

Two exciting recent studies of RD participants used diffusion tensor imaging and reported disturbances in the white matter tracts connecting anterior and posterior perisylvian regions [73,74]. Similar techniques have yet to be used in LI samples and should be fruitful for future research.

In summary, structural findings in RD and LI have most often implicated left hemisphere perisylvian regions involved in skilled reading and language, although findings are by no means limited to these regions. The commonalities in structural findings for LI and RD are likely to be both meaningful (because some brain differences are probably shared by the disorders) and artifactual (because studies have not carefully controlled for comorbidity). Future studies should compare children who have only one of the disorders, both disorders, or neither (controls).

We are not aware of any studies that have specifically examined neuroanatomic correlates of SSD using a precisely defined phenotype. In-depth study of one British family, referred to as the KE family, has produced findings that could help guide future research. About half the KE family members are affected with a general language deficit impacting grammar and expressive language and a severe speech production disorder that significantly impairs intelligibility [75,76]. Affected members of the KE family thus meet criteria for LI and SSD, although it is not clear that they are representative of the larger population of individuals who have speech and language disorders. Their speech difficulty is often described as a verbal apraxia, a label that implies their articulation difficulties arise from impairments in sequencing oral-motor movements. It is possible that verbal apraxia is a subtype of SSD that is etiologically distinct from a more common, phonologically based subtype. MRI findings in the KE family indicated bilateral abnormalities in the basal ganglia, especially the caudate nucleus, and in the left IFG and premotor areas of affected family members [77]. Left caudate volume correlated with performance on a task of oral praxis, suggesting that this brain region in particular may relate to affected family members' articulation difficulties.

Functional findings

Several investigations have attempted to further elucidate the neural bases of RD by examining brain function during reading and language tasks using positron emission tomography (PET) and functional MRI (fMRI).

A smaller body of literature has investigated brain function in LI, and again there is almost no work on SSD. As in the anatomic literature, the comorbidity of these disorders has rarely been carefully addressed. Interpretation of functional results is further limited in studies that use a case-control design but do not equate performance across the two groups (see Ref. [78]). In these cases, it is not clear whether the neural differences are a cause or a result of impaired performance.

Functional neuroimaging studies of reading and language tasks have identified aberrant activation patterns in RD participants across a distributed set of left hemisphere sites, including many of the same regions implicated by the anatomic literature (see [78,79] for reviews). The most common findings have been reduced activation of left occipitotemporal and temporoparietal regions. Findings in the region of the left IFG have been mixed, with several studies reporting increased activation in RD, whereas others have reported decreased activation. Both task and participant characteristics likely contribute to the variability in findings. For example, increased IFG activity in RD has most often emerged in the context of reading aloud [78]. In silent reading or other language tasks, decreased activity in this region is more likely among the most impaired readers [80]. A common interpretation of the full pattern of results is that decreased occipitotemporal activity corresponds to deficits in word recognition processes (ie, OC), decreased temporoparietal activity corresponds to phonologic processing difficulties, and increased IFG activity relates to compensatory processes. Notably, few studies have equated performance across RD and control groups. This limitation particularly complicates the interpretation of temporoparietal findings, which (to date) have emerged only in the context of group performance differences [78].

Fewer studies have investigated the functional brain correlates of LI. One PET study compared brain activation in two affected members of the KE family to four normal controls [76]. The nature of the task used (word repetition minus a baseline articulation condition) meant that the results may relate more to the family's language impairment than to their speech difficulties. Affected family members showed aberrant activation patterns (some overactivation and some underactivation) across a widely distributed set of left hemisphere sites, including IFG, angular gyrus, motor and premotor areas, and caudate nucleus. Two more recent studies have used fMRI to examine brain function in LI outside the KE family. Hugdahl and colleagues [81] used a passive listening task that activated bilateral superior temporal gyrus (STG) and middle temporal gyrus (MTG) in control subjects. Activation for five individuals who had LI (all from one Finnish family) were similar to the control group, but smaller and weaker, particularly in the region of the superior temporal sulcus and MTG. Using a verbal working memory task, another research group found that children who had LI tended to have reduced activation across several left hemisphere sites, including the IFG, parietal regions, and the precentral sulcus [82]. One of the most exciting

findings from this paper relied on a correlational analysis to examine the extent to which groups tended to coactivate different brain regions (possibly relating to their degree of anatomic connectivity.) Compared with the control group, the LI group showed less coactivation between STG and IFG, but more parietal–frontal and parietal–STG coactivation. Unfortunately, however, this study did not equate in-scanner performance across groups.

Taken together, the structural and functional neuroimaging literatures in RD and LI are beginning to implicate many of the brain regions involved in skilled reading and language—notably including the STG, the IFG, and temporoparietal regions. Researchers have just begun to explore how differences in the connectivity among these regions may relate to reading and language problems. To date, we have little understanding of how the neural substrates of RD and LI relate to each other and virtually no knowledge of the brain bases of SSD.

Genetics

Genetics of reading

There is convergence across different genetic methodologies that all three of the disorders considered in this article are partly heritable. Again, our knowledge of RD is deeper and has a longer history than our knowledge of the other two disorders, particularly SSD. The cognitive dissection of RD described previously proceeded hand in hand with decades of work demonstrating that RD and its cognitive components are familial and heritable [83] and are linked to several quantitative trait loci (QTLs) across the genome [84]. Seven replicated QTLs have been identified on 1p34-p36 (DYX8), 2p11-16 (DYX3), 3p12-q13 (DYX5), 6p21.3-22 (DYX2), 15q15-21 (DYX1), 18p11 (DYX6), and Xq27.3 (DYX9). Two additional genetic loci for RD are included on the most recent Human Gene Nomenclature Committee list (www.gene.ucl.ac.uk/nomenclature/). These are on 6q13-q16 (DYX4 [85]) and 11p15 (DYX7 [86]). There are currently nine genetic risk loci for RD, but two of these need additional replication to be convincing. This linkage work has now been followed by the initial identification of four candidate genes in three of these linkage regions: 3p12-q13 (ROBO1), 6p21.3-22 (DCDC2 and KIAA0319), and 15q15-21 (DYX1C1, initially labeled as EKN1) (see [87,88] for reviews).

The first candidate gene to be identified was DYX1C1 [89], so it has been the target of the most replication attempts (six so far). Five of these failed to find any association between DYX1C1 variants and RD phenotypes [90–94], but one study by Wigg and colleagues [95] found an association in the opposite direction, such that the more common, non-risk alleles of the haplotype proposed by the original work of Taipale and colleagues [89] were associated with the phenotype. They also found a significant association with an additional SNP that was not tested by Taipale and colleagues [89]. More work is needed to confirm or reject this candidate gene.

The other three candidate genes, *ROBO1* [96], *DCDC2* [97], and *KIAA0319* [98], were identified more recently and thus have been tested less for replication. The *DCDC2* candidate was replicated by Schumacher and colleagues [99] and *KIAA0319* by Paracchini and colleagues [100].

One of the most exciting aspects of the work on all four candidate genes is that the role of each in brain development has been studied in animal models. Research using RNAi technology found that shutting down the expression of *DCDC2* [97], *KIAA0319* [100], and *DYX1C1* [101] interferes with neuronal migration, consistent with Galaburda's discovery of ectopias in the brains of individuals who had RD. *ROBO1* is also known to be involved in brain development, specifically in axon pathfinding. Andrews and colleagues [102] genetically modified mice so that they were lacking *ROBO1* completely (a *ROBO1* knockout). Although the knockout mice died at birth, they demonstrated prenatal axonal tract defects and neuronal migration defects in the forebrain.

These results from animal models indicate that alterations in *DYX1C1*, *DCDC2*, *KIAA0319*, and *ROBO1* could disrupt human brain development in a way that is consistent with what little is known about the neuropathology of RD [103]. But to really prove causation requires several more steps: (1) the functional or regulatory mutations in these particular genes have to be identified, (2) it has to be demonstrated that these particular mutations disrupt brain development in animal models, and, most difficult of all, (3) it has to be shown that humans who have a dyslexic phenotype and these mutations have similar disruptions in brain development. Thus far, no mutations have been identified in coding regions of any of the candidate genes, so it is likely that mutations involve regulatory regions that control the level of gene product produced, rather than a faulty protein. This theory is consistent with the milder impairment of RD compared with more severe cognitive deficits that typically result from absent or defective gene products. In sum, the identification of candidate genes for RD has taken us all the way from cognitive dissection to developmental neurobiology, so that we are now able to test specific hypotheses about how brain development is disrupted in this prevalent disorder. This work is now developing rapidly, so new insights about brain development in RD are likely. One particular issue for future research is that each gene has been implicated in global brain developmental processes, such as neural migration and axonal guidance. There is a puzzle to be unraveled: how can a disruption in global brain development result in a relatively specific phenotype?

Genetics of language impairment and speech sound disorder

One striking example of the role of genes in language development comes from the KE family. About half the members of this family are affected with a general speech and language impairment impacting, most notably, expressive language and articulation. Pedigree analysis revealed that the

inheritance pattern was consistent with a single gene, autosomal dominant trait [104]. The gene responsible for this disorder was eventually localized to the long arm of chromosome 7 in the 7q31 region and subsequently identified as the FOXP2 gene [75,105]. The simple Mendelian transmission of this disorder in the KE family is a unique example, which is probably not representative of the larger population of individuals who have speech and language disorders [106].

Analysis of LI outside the KE family indicates that although the disorder is significantly heritable, its cause is typically more consistent with a complex disease model, in which multiple causative risk factors (genetic and environmental) interact to produce an eventual phenotype. Genomewide scans of multiple families affected by LI have not identified FOXP2 as a candidate gene. Instead, significant linkage has been reported to 13q21 (using various language phenotypes), 16q (using a phonologic memory phenotype), and 19q (again, with various phenotypes) [107–109]. None of these loci overlap with those identified for RD, but some of the positive linkage results with LI individuals used reading phenotypes [107,109]. At this point, it is unclear if the lack of overlap between RD and LI risk loci is attributable to a lack of power or a true null finding.

The etiology of SSD outside the KE family also seems consistent with the complex disease model, and we are accumulating knowledge about specific genetic risk factors involved. Again, the FOXP2 gene does not seem to be implicated in most cases, although mutations in this gene may play a role in the development of SSD in a small minority of cases—notably, among individuals who seem to fit a verbal apraxia subtype [110]. Two independent studies have investigated whether SSD shows linkage to known RD risk loci [111,112]. These studies reported possible linkage of SSD to chromosome 1p36 and significant linkage to 3p12-q13 (where ROBO1 is located), 6p21.3-22 (where DCDC2 and KIAA0319 are located) and 15q21 (where DYX1C1 is located). Recent attempts to replicate the 1p36, 6p21.3-22 and 15q21 loci in an independent SSD sample have been partially successful. There is preliminary evidence of replication of the 1p36 [113] and 6p22 loci (S Iyengar, personal communication, 2006). There is evidence for a possible replication of the 15q21 locus, although these results are ambiguous because the linkage peak is closer to genes associated with autism and Prader-Willi/Angelman Syndrome than the region associated with dyslexia/SSD [114].

That SSD and RD seem to share genetic risk factors is consistent with these disorders being comorbid and associated with impairments in phonologic processing. The failure (to date) to find clear evidence for shared genetic risk factors for LI and RD is puzzling—these disorders are also comorbid, and as we have seen, they overlap at the symptom, neuropsychologic, and brain levels. Further, longitudinal studies have demonstrated that children who have early language impairments are at much higher risk for later RD than are children who have isolated speech sound difficulties,

a finding that suggests that the overlap between RD and SSD is partly attributable to the third variable of LI. A goal of future research will be to identify shared etiologic risk factors for RD and LI and to clarify the etiologic relationship of all three disorders.

Etiologic interactions

The heritability of all three disorders considered in this chapter is significantly less than 100%, a factor that points to the importance of environmental variables in their development. Such variables are likely to include home language and literacy environments and instructional quality (especially for RD), along with environmental events that have a more direct effect on biology (eg, lead poisoning or head injury). Unfortunately, few studies investigating main effects of such environmental variables on language development have used genetically sensitive designs. In addition to main effects of environment, it is likely that the disorders considered here are influenced by gene by environment ($G \times E$) interactions. A recent study in our lab investigated $G \times E$ using measures of the home language and literacy environment in a sample of children who had SSD and their siblings. We tested for $G \times E$ at the two SSD/RD linkage peaks with the strongest evidence of linkage to speech phenotypes, 6p22 and 15q21. The interactions were tested using speech, language, and preliteracy phenotypes. Results showed four significant and trend-level $G \times E$ interactions at both the 6p22 and 15q21 locations across several phenotypes and home environmental measures [115]. The direction of the interactions was such that in enriched environments genetic risk factors substantially influenced the phenotype, whereas in less optimal environments genetic risk factors had less influence on the phenotype. This directionality of the interactions is consistent with the bioecological model of $G \times E$ [116]. This work is preliminary because these linkage-based methods are a step away from the ideal of using identified risk alleles to test for $G \times E$ [117,118]. As molecular genetics identifies specific risk alleles for RD, SSD, and LI, the field will be able to more rigorously test etiologic models that include $G \times E$ interactions.

Summary

We have provided a brief overview of the symptoms, neuropsychology, brain bases, and genetics of three common disorders of language development: reading disability, language impairment, and speech sound disorder. Across levels of analysis, our understanding of RD is the most advanced, but it is by no means complete. For all three disorders, future work is required to precisely identify etiologic risk factors (ie, specific risk alleles, specific environmental conditions) and to discover how these interact to produce particular brain differences and behavioral phenotypes. Because there is partial, but not complete, overlap of the three disorders, this work is likely to

produce findings that are common to all three disorders along with findings unique to each. Ultimately, our understanding of typical and atypical language development will be enriched by research that investigates not only RD, LI, or SSD alone but also the relationships of these disorders to each other.

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