CHAPTER

40

Language Impairment

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OUTLINE

40.1 INTRODUCTION

Language represents a complex and unique aspect of human neurocognitive processing and, as such, is vulnerable to disturbance through disruption of or damage to underlying neural systems. Such disruption is generally divided into two types: developmental (encompassing pre- and perinatal brain injury) and acquired.

Acquired disturbances of language generally present as deficits in the comprehension (reception) and/or production (expression) of language following traumatic injury to *established* neural language systems, generally in the left cortical hemisphere (although a minority of individuals seem to have language functions in the right cortical hemisphere; Figure 40.1). These language regions include interconnected areas, such as a left perisylvian posterior lateral temporal (auditory) region called Wernicke's area. This region is believed to mediate the perception and processing of spoken language. Another key language area is Broca's area, found in the left inferior frontal/motor cortex, which generally is thought to mediate production of oral speech. Additional areas routinely activated during neuroimaging measures of language tasks include left parietotemporal and occipitotemporal areas implicated in reading. Damage to these regions results in a range of language deficits collectively termed *aphasias*, with symptoms reflecting the functions mediated by the damaged regions. For example, Wernicke's aphasia presents as a loss in receptive language processing, whereas Broca's aphasia presents as a general deficit in language production (but not comprehension). More recent evidence suggests that these disorders are not as circumscribed as once believed (e.g., Blank et al., 2002), but the terms continue to be used in clinical diagnosis. More global forms of aphasia, encompassing both expressive and receptive language deficits, may also be seen after more extensive damage affecting multiple brain regions. Acquired language disorders may also include deficits in reading skills, termed *acquired dyslexia* or *alexia*. Importantly, all of these disorders are – by definition – confined to the assessment of acquired injury in previously language-competent individuals (older children and adults) and reflect a loss in language skills due to damage of *already-developed* neural systems subserving these processes (see Jordan and Hillis, 2006, for review). Interestingly, language functions do seem to reorganize to the right hemisphere after left-hemisphere damage in young children, evidencing a

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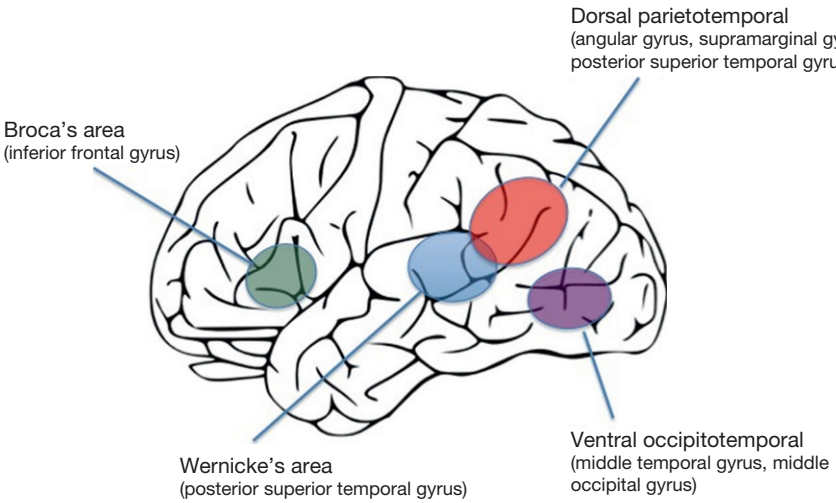

FIGURE 40.1 Left-hemisphere cortical regions implicated in language processing.

high degree of plasticity in language systems during early development. Indeed, young children who undergo left temporal lobectomy because of intractable epilepsy show a surprisingly normal course of language development (Vargha-Khadem et al., 1997). However, comparable injuries in older children and adults with established language functions lead to more permanent language function loss and substantially less reorganization (less plasticity). These early plasticity effects parallel evidence that a second language is acquired more quickly and effortlessly in young children compared with adults.

In contrast to acquired aphasias, *developmental* disruptions to language systems occur as a result of early factors influencing the *initial* establishment of neural systems needed to support emergent language. These disruptions may occur as one component of a more global neural disruption, resulting in overall degradation of cognitive processing (e.g., mental retardation, learning disorders, or pervasive developmental disorders; Broman and Grafman, 1994; Pennington, 1991), or may be *specific* to language systems (meaning overall intellect or IQ is within the normal range). The latter condition is most commonly associated with the term *language impairment* (LI), and therefore the rest of this chapter addresses behavioral features and underlying factors implicated in the developmental disruption of language systems.

40.2 SPECIFIC LANGUAGE IMPAIRMENT AND RELATED DISABILITIES

The ability to understand and produce spoken words represents a profoundly complex process that most young children acquire with remarkable ease, despite a lack of formal instruction (i.e., most young children are not explicitly taught how to speak). Such evidence of innate predisposition toward language skill has fueled debates about intrinsic 'preadaptations' in the human brain for language, particularly compared with neural substrates underlying other species-specific use of communicative vocalizations or even learned communicative systems (such as sign or computer use in nonhuman primates; see Fischer and Marcus, 2006; Hauser, 1996). Despite the language-ready predisposition seen in most typically developing human children, a subset nonetheless experiences delays in the achievement of language milestones in the absence of known causal factors. That is, even when potential underlying impairments such as epilepsy or other neurologic abnormalities, disorders of vision or hearing, psychiatric impairments, or environmental deprivation are excluded, about 5–10% of children exhibit unexplained deficits/delays in language development (Beitchman et al., 1986; Leonard, 1998; see Heim and Benasich, 2006, for review). These problems are specific to language and occur despite a nonverbal IQ in the normal range. Such language-specific developmental disorders are termed either (LI) or *specific language impairment* (SLI), and deficits associated with SLI can be further subdivided into receptive (*SLI-R*, comprehension), expressive (*SLI-E*, production), or combined deficits.

What is implied by SLI being defined, in part, by the *exclusion* of other impairments and disabilities? One example of this 'exclusionary criteria' would be applied when fetal lead or fetal alcohol exposure (FAS) results in generalized cognitive impairments that include impaired language skills. A young child with language delays related to FAS would *not* likely be diagnosed as having SLI, based on the more generalized underlying cognitive deficit. A diagnosis of SLI also requires the exclusion of other related disorders with similar or overlapping symptoms. For example, a subset of exclusively

expressive language difficulties specific to articulation, phonology, and/or oral-motor skills are thought to represent a related but separate disability termed *speech-sound disorder* (SSD; Pennington and Bishop, 2009; Peterson et al., 2007). *Receptive* deficits in language processing may also overlap with central auditory processing disorder (CAPD or APD). However, CAPD generally presents as a broad-based difficulty in listening to and processing sounds that include, but are not limited to, speech sounds. Moreover, CAPD has been characterized by the American Speech & Hearing Association to include deficiencies in 'blocking out' noise and acoustic distracters (Bamiou et al., 2001), which are not diagnostic features of SLI. Therefore, CAPD may be a contributing factor in the development of SLI, but the two disorders are, at least at the present time, considered clinically different.

SLI can also be diagnosed as *comorbid* with other co-occurring developmental disabilities. For example, SLI might co-occur with attention difficulties, as seen in attention deficit disorders with or without hyperactivity (ADD/ADHD) (see Chapter 22). SLI might also be comorbid with SSD or CAPD. From a diagnostic perspective, SLI might further 'overlap' with characteristics of related disorders. For example, autism spectrum disorder (ASD; see Chapter 34) encompasses substantial communicative disabilities, and ASD individuals presenting with significant LI have even been designated as ASD-LI (e.g., Williams et al., 2008). While these overlaps may lead to complications and difficulties in individual diagnosis, when taken from a research perspective, the existence of overlapping phenotypic deficits across SLI and ASD-LI populations presents an opportunity to study potential commonalities in underlying etiology. Such studies have revealed some evidence of phenotypic similarity between ASD-LI and SLI populations (e.g., evidence of common neuroanatomic abnormalities, and similarities in anomalous information processing; Herbert and Kenet, 2007), but others suggest that the underlying etiology (i.e., genetics) leading to language disruptions in these two disorders may follow different neurodevelopmental routes and that ASD-LI versus SLI are in fact likely to stem from very different causes (Williams et al., 2008). Ongoing research in this area will be critical in ascertaining whether common mechanisms across these disorders may account for the similarities in phenotypic language disturbance or whether perhaps differing vectors of disruption to early brain development might exert such fundamental (core) effects on information processing that they ultimately lead to seemingly similar phenotypes in higher-order language processing ('phenocopies').

Overall, the most common comorbidity seen with SLI is the subsequent diagnosis of *dyslexia* or *reading disability* (*RD*, also called *specific reading disability* or *developmental dyslexia*). Dyslexia is defined by exclusionary criteria (much like SLI), but in this case represents an unexpected delay or deficit in the acquisition and performance of reading, despite an overall nonverbal IQ in the normal range. This prevalent comorbidity between SLI and dyslexia likely reflects the fact that, while most children with SLI do eventually reach normal language milestones (i.e., they learn to understand and produce speech), the subsequent milestones in reading require the translation of learned phonemes (letter sounds) onto orthographic representation (written letters). Since deficits in phonemic representation and/or phonologic processing comprise a core and persisting component of SLI (see below for more discussion), it is not surprising that a large portion (>50%) of children with SLI go on to be diagnosed as dyslexic/RD (Bishop and Snowling, 2004; Catts et al., 2005; Schuele, 2004; Sices et al., 2007). It is a matter of ongoing debate whether those children who are initially diagnosed as SLI but overcome their disorder without further reading difficulties may, in fact, comprise a different subtype of the SLI population as compared to those who go on to be comorbid for dyslexia/RD. Moreover, another subgroup may be comprised of older children/adults diagnosed with dyslexia/RD in the *absence* of any prior history of SLI (see Bishop and Snowling, 2004; Pennington and Bishop, 2009, for discussion). In fact, it has been suggested that the latter subset of dyslexics, generally thought to correspond to a subcategory termed orthographic, or surface, dyslexics, exhibit primarily visual and higher-order reading deficits but lack the core phonological deficits characteristic of SLI. Conversely, the remaining dyslexics do show core phonological deficits and are accordingly designated phonologic dyslexics. Many or most of the dyslexics in this category do have some history of SLI or language-related difficulties.

Ongoing assessment of these various subgroups appears likely to support the existence of core functional components that characterize both SLI and dyslexia/RD, and may speak to the fact that some of these core deficits show a large amount of overlap across the two disorders (Figure 40.2). For this reason – and recognizing the obvious underlying heterogeneity inherent to the term – some researchers have begun to use combined terms such as *language disabilities* (*LD*), *language-learning disabilities*, or *language-learning impairments* to refer to this set of language-related developmental disabilities (Peterson et al., 2007; Tallal et al., 1993; but see Bishop and Snowling, 2004, for an opposing view). The remainder of this chapter will discuss the phenotypic features and underlying genetics for this *common* category of *LD*, inclusive of both SLI and dyslexia/RD. This grouping reflects the fact that much of the pertinent neuroimaging and genetic research has been performed using adult dyslexic and/or combined LD populations, with

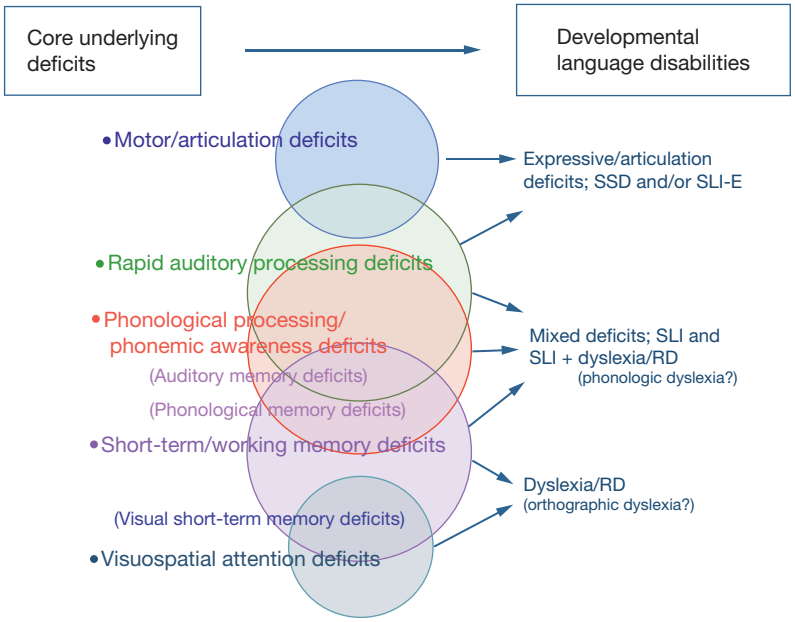

FIGURE 40.2 A proposed schematic diagram relating identified core function deficits associated with developmental language disability, and clinically defined populations evidencing those underlying deficits. SSD, speech sound disorder; SLI, specific language impairment; SLI-E, specific expressive language impairment; RD, reading disability.

a comparatively limited amount of research performed exclusively on SLI children (but see Webster and Shevell, 2004 for data specific to SLI).

40.3 BEHAVIORAL FEATURES OF LD

Behavioral profiles in clinically defined language-disabled groups vary, but are typically characterized by deficits in both lower-order (e.g., sensory/motor) and higher-order (e.g., grammatical, syntactic, and verbal memory) processes (e.g., Menghini et al., 2010). In fact, the LD population appears to be a heterogeneous mix of individuals with an assortment of deficits corresponding to some subset of the following functional core areas (along with other possible deficits not listed here). (1) Oral-motor skills and articulation, as required for tasks such as rapid naming. (2) Rapid auditory processing, as required to discriminate rapidly changing acoustic sounds such as consonant–vowel syllables. (3a) Phonemic awareness, as required to distinguish and identify phonemes, or subunits of words, and (3b) phonological processing, as required to manipulate phonemes within words and perform mapping to-and-from sounds and letters, as required for non-word reading. (4) Short-term and/or working verbal memory and the related auditory and phonological memory, required for nonword repetition. (5) Visuospatial processing, visual memory, and/or visuospatial attention, required for specific reading tasks. Evidence further suggests that unique patterns of these core deficits may characterize specific subsets of individuals (i.e., SLI/SSD only, SLI+dyslexic/RD, and dyslexic/RD only; see Figure 40.2). Thus, dyslexic/RD-only individuals (orthographic dyslexics) are less likely to show motor/articulation deficits. Conversely, SLI-E populations are less likely to show visual-processing and memory deficits. However, both groups, as well as the comorbid overlapping population, share evidence of *common* deficits in rapid auditory processing (Farmer and Klein, 1995; Fitch and Tallal, 2003), phonemic and phonological processing (Pennington and Bishop, 2009; Schuele, 2004; Shankweiler et al., 1995), and aspects of short-term/working memory (Briscoe and Rankin, 2009; Montgomery et al., 2010). Each of these core functional features of LD (including SLI and dyslexia/RD) is discussed in greater detail below.

40.3.1 Motor/Articulation Deficits, SSD, and the KE family

As young children learn to speak, it is not unusual to hear substitutions of letter sounds (e.g., /w/ for /r/, as in 'wabbit'), lisps, or stutters. Normally, children outgrow these charming but immature articulation patterns. Some children, however, persist with articulation difficulties (lisp, stutter, and other oral mispronunciations) that may reflect chronic defects in oral musculature, vocal apparatus, palate formation, or general oral-motor 'weakness.' When evidenced in the absence of any delays in language comprehension or reductions in vocabulary, these articulation deficits tend to be less predictive of long-term language and literacy

problems, although the chronic incorrect encoding of certain letter sounds may, in fact, lead to some difficulties in the orthographic translation of those same sounds. On the other hand, children with expressive language difficulties characterized by *multiple* speech-sound errors (phonemic omissions, substitutions, and distortions characterized as phonological processing difficulties) exhibit more marked impairment of articulation and expressive language. (In a phonological (or phonemic) disorder (PD), a child has difficulty learning the sound system of the language, and, specifically, fails to recognize and identify specific sounds as unique. For example, the sounds /k/ and /t/ may not be recognized as different and may therefore be substituted for each other). Children exhibiting language difficulties characterized by such deficits in the oral production or expression of language are, depending on other deficits, likely to be diagnosed with *specific expressive language impairment* (*SLI-E*), *PD*, *SSD*, or some combination of these (Fischer and Scharff, 2009; Pennington and Bishop, 2009). Concurrent research also aims to examine a putative role for more generalized motor deficits associated with SLI, and to separate these features from related overlapping disorders such as developmental coordination disorder (e.g., Archibald and Alloway, 2008).

An intriguing series of studies have been performed on a single extended family with an inherited form of expressive LI (also called 'verbal dyspraxia'; Alcock et al., 2000). Half the members of the patient KE's family (so named for anonymity) show this disorder, exhibiting severe impairments in phonology and syntax, as well as oral praxis. Ongoing studies of this family have led to the isolation of a gene termed *FOXP2* that may be associated with the expressive and oral language deficits evidenced in the KE family. Interestingly, animal studies of the *Foxp2* homolog have shown that disruptions of this gene lead to defects in motor learning, including the acquisition of birdsong and the production of vocalizations in mice (reviewed in Fischer and Scharff, 2009; see below for further discussion).

Ongoing research will continue to assess the specific role of articulation and motor-specific deficits in defining subtypes within the heterogeneous LD population.

40.3.2 Rapid Auditory Processing Deficits

A key series of studies by Tallal and colleagues showed that SLI children were unable to discriminate two sequential tones when the interval between the tones fell below a threshold interval and were also impaired in the identification and discrimination of consonant–vowel syllables characterized by short, rapidly changing formant transitions (e.g., /ba/, /da/, /pa/, /ta/; see Tallal, 1977, 1980; Tallal and Newcombe, 1978; Tallal and Piercy, 1973a,b, 1975; Tallal and Stark, 1981; reviewed in Fitch and Tallal, 2003). Additional studies showed that performance on these auditory tasks was correlated not only with speech perception indices, but also with nonword reading scores (Tallal, 1980). Thus, it was posited that basic defects in low-level auditory processing may be associated with deficits in speech perception and phonology and thus could represent a core factor in the development of LD.

This suggestion of a low-level auditory processing deficit as a possible causal factor in developmental LD has elicited some controversy (e.g., Mody et al., 1997; Ramus, 2003; Rosen and Manganari, 2001). However, ongoing behavioral and psychophysical studies of language-disabled subjects appear to support the notion of an auditory processing deficit that may underlie (or at least be related to) some deficits in speech perception and subsequent language development (Au and Lovegrove, 2007; Cardy et al., 2005; Cohen-Mimran and Sapir, 2007; Corbera et al., 2006; Edwards et al., 2004; Farmer and Klein, 1995; Gaab et al., 2007; Hari and Kiesla, 1996; King et al., 2007; Kraus et al., 1996; McAnally and Stein, 1996, 1997; McCrosky and Kidder, 1980; Neville et al., 1993; Reed, 1989; Renvall and Hari, 2002; Robin et al., 1989; Sutter et al., 2000; Watson, 1992; Witton et al., 1998; Wright et al., 1997). Again, while it remains to be determined whether these auditory deficits represent causal or comorbid (parallel but noncausal) deficits (see McArthur and Bishop, 2001; Ramus, 2003; Rosen and Manganari, 2001), an early deficit in auditory processing could reasonably precede observable LI, in which case assessment of auditory processing in at-risk infants would be extremely useful in identifying those likely to develop later language problems. In fact, Benasich et al. (2002) found that infants with a family history of LI or dyslexia (and thus at an elevated risk of developing language problems themselves; Tallal et al., 1991) were impaired relative to controls in their ability to discriminate two-tone sequences when there was a short interval between the tones, but not with a longer interval. Prospective follow-up of these children revealed a predictive relationship between the threshold at which rapidly presented auditory stimuli could be processed in infancy and language outcomes at 12–24 months (Benasich et al., 2006; Choudhury et al., 2007). More recently, a comparable relationship was seen between early auditory-evoked response potential and electroencephalogram (AERP/EEG) scores using these same stimuli and later language outcomes (Choudhury et al., 2007). In addition, predictive associations between early auditory processing skills have been related to language performance later in life in normally developing samples. Trehub and Henderson (1996) found that children who had performed above the median on a variety of

acoustic gap detection tasks at 6 or 12 months were found to have larger productive vocabularies, use longer, more complex sentences, and produce more irregular words compared with children who had scored below the median. Such findings are also supported by evidence from studies recording evoked response potentials (ERPs) to auditory stimuli in infancy. Molfese and Molfese (1997) found that ERPs to consonant–vowel syllables recorded from infants within 36 h of birth differed between children whose verbal IQ was above, versus below, the norm at 5 years of age. Similarly, infants with a family history of dyslexia showed different patterns of ERPs to consonant–vowel stimuli as compared with matched controls when recorded at 1 week and at 6 months (Leppänen and Lyytinen, 1997; Leppänen et al., 1999; Pihko et al., 1999). Importantly, evidence indicates that these group differences do in fact relate to emergent language skills, based on longitudinal analysis (Benasich et al., 2006; Choudhury et al., 2007).

Collective data thus support the notion that the ability to make fine auditory discriminations (rapid auditory processing) is strongly correlated with later language development and that deficits in this basic function may impair subsequent language development, with ultimate implications for higher-order processes seemingly distal to basic acoustic processing (e.g., reading). Ongoing research will continue to evaluate the role of basic auditory processing deficits in the later emergence of language deficits.

40.3.3 Phonemic and Phonological Processing Deficits

A wide variety of language-based developmental disorders appear to encompass a central deficit in the ability to learn to identify and discriminate individual speech sounds as unique (phonemic awareness). Studies of both SLI and dyslexic/RD populations have consistently shown deficits in phonemic awareness, as well as phonological processing (i.e., using and manipulating phonemes and translating them to and from print) within these populations. Tasks that tap such processes include asking individuals to remove phonemes from words (e.g., /slid/ to /lid/), substitute phonemes (e.g., /bat/ to /hat/), map phonemes from or onto letters (phoneme to grapheme), and/or decode phonemes during nonword reading tasks. The consistency of profound deficits observed in such tasks within both SLI and dyslexic populations has led to some speculation that phonological deficits may form a critical core deficit spanning diverse language disorders (e.g., Bradley and Bryant, 1983; Catts et al., 2005; reviewed in Vellutino et al., 2004). However, speculation still continues regarding the putative etiological underpinning of core phonemic and phonological difficulties. For example, many studies suggest that difficulties with phonological processing in LD populations may reflect underlying deficits in sound processing and identification (or rapid auditory processing deficits, as described above), while others suggest that phonological deficits may arise in parallel with separate auditory problems, but remain specific to linguistic systems (e.g., Ramus, 2003). Still others ascribe core phonological deficits in LD to primary difficulties with phonological memory (e.g., Gathercole and Baddeley, 1990). In fact, a plausible explanation would suggest that the core demands of phonological processing in language development may be such that disruption from a variety of *different* routes or causes (bottom-up or top-down) might lead to impairments in this key process of language development and reading and lead in turn to shared or overlapping phenotypes of language disruption.

Again, ongoing research into the role of core deficits in phonemic awareness and phonological processing will continue to inform the diagnosis, treatment, and etiologic understanding of developmental LD as a whole.

40.3.4 Short-Term/Working Memory Deficits

Evidence has shown consistent evidence of deficits in language processing using working and/or verbal *short-term memory* (*STM*) to process sentence morphology, syntax, and/or semantics in LD populations (Brady et al., 1983; Shankweiler and Crain, 1986; Shankweiler et al., 1995; Smith et al., 1989). Clearly, the effective use of language requires the use of STM to hold letter sounds in memory during word processing (prior to combining the sounds into a meaningful word), as well as in processing complex semantic meaning within sentences, paragraphs, and narratives (e.g., the meaning of later parts of a sentence may be modified by early sentence structure that must be held in STM to fully interpret the complete sentence). Tasks that tap these underlying capacities include digit-span recall tasks, word-memory tasks, and more complex assessments of active narrative comprehension during reading (see Montgomery et al., 2010, for review). Evidence for STM deficits specific to processing phonological information, such as is required for repeating nonwords, has also been reviewed (Gathercole and Baddeley, 1990; see also Catts et al., 2005). In a recent review by Briscoe and Rankin (2009), the authors discuss data dissociating deficits specific to the 'phonological memory loop' versus more generalized deficits in executive working memory systems in SLI subjects, concluding that evidence more strongly supports a deficit in core phonological memory processes (phonological loop) as opposed to overall executive memory. However, these assertions are counted by findings such as those of

Smith-Spark and Fisk (2007), who demonstrated deficits in cross-modal executive working memory, as well as phonological memory, in dyslexics.

An intriguing family-based genetic association study has also shown a genetic–behavioral linkage within a subset of dyslexic individuals, with deficits in STM appearing to correspond to variations in a segment of the dyslexia-risk gene *DYX1C1* (Marino et al., 2007). Specifically, a significant linkage was observed between single-letter backward-span scores and a genetic variant within this segment of the *DYX1C1* gene. Further evidence suggests associations between memory and/or attentional difficulties and anomalies in other dyslexia-risk genes such as *DCDC2* (Berninger et al., 2008). These collective results support the view that ongoing genetic research into LD may eventually reveal a correspondence between specific genes (out of multiple LD risk genes that have been, and are likely yet to be, identified) and specific core functional deficits contributing to LD (e.g., STM).

40.3.5 Visuospatial Processing, Visuospatial Memory, and/or Visuospatial Attention Deficits

A series of studies in the 1990s suggested that, in addition to rapid auditory processing deficits, adult dyslexics might also be characterized by deficits in processing rapidly changing, but not slowly changing (or static), visual information. This assertion was based on evidence of impairments in processing visual rapid change in human dyslexics and led to suggestions that LD may include a core deficit in 'magnocellular' system processing, since rapidly changing visual information is processed in the magnocellular (rather than parvocellular) subsystem of the visual thalamic nucleus (Lehmkuhle et al., 1993; Livingstone et al., 1991; Lovegrove et al., 1990; Slaghuis et al., 1992). Evidence of a 'magnocellular theory' of dyslexia continues to be explored (e.g., Stein, 2001). With regard to visual memory, a recent study of adult dyslexics and age/IQ-matched controls reported evidence of working memory deficits in dyslexics for both verbal and nonverbal (visuospatial) working memory span tasks that encompassed simple, complex, and dynamic span assessments (Smith-Spark and Fisk, 2007). These latter studies were of particular interest in showing that STM deficits in dyslexic populations are *not* seen exclusively in the phonological domain and may therefore reflect a more fundamental defect in neurological memory systems that in turn impacts on language processing (as well as other functions; but see Briscoe and Rankin, 2009). Ongoing research also continues to explore the role of visual memory and/or attention as a feature of LD populations. For example, Shaywitz and Shaywitz (2008) have shown that attentional processing plays a key role in reading for dyslexic individuals as measured by fMRI, further suggesting that this component of LD may even be amenable to pharmacological remediation, similar to treatment for ADHD.

Clearly, research has shown a range of core functional deficits associated with SLI and/or dyslexia/RD (Figure 40.2), and research continues to refine these behaviorally established criteria for reliable subtyping within the LD population. Thus, a very strong impetus exists to establish markers of genetic or neural features that could be used to segregate this heterogeneous LD population. Unfortunately, what are needed first are reliable markers by which to identify homogeneous subgroups for testing, which will in turn yield significance in genetic linkage and neuroimaging studies. This makes the task circular and very difficult. Recognizing these limits, studies have proceeded nonetheless by using heterogeneous populations (i.e., both SLI and dyslexic/RD) with *post hoc* analysis of subgroups, by separating groups based on core behavioral features (e.g., those with/without phonologic deficits), by correlating one putative marker with another (e.g., memory scores and genetic mapping), by using longitudinal analyses of emergent language measures to segregate groups, and by assessing distinctions and overlaps with related disorders (such as ASD-LI and SLI). Each of these approaches (as well as others) moves us forward in understanding the underlying etiology of LD. The following sections will review some of the anatomic, neuroimaging and genetic data that have resulted from these approaches.

40.4 NEUROPATHOLOGY OF LD

To date, structural neuroimaging and *postmortem* studies performed on clinically defined childhood and adult LD populations (SLI and dyslexic/RD) have, by and large, failed to reveal consistent neurological factors as markers for developmental language and reading disabilities. Some evidence of reduced cortical and subcortical volume in children with LD (e.g., Jernigan et al., 1991) has been reported. Others have reported evidence of anomalous hemispheric asymmetry in language-disabled subjects as measured by *postmortem* anatomical analysis (e.g., Galaburda, 1991; Galaburda et al., 1985; Humphreys et al., 1990) and MRI (Hynd et al., 1990, 1991; Jancke et al., 1994; Larsen et al., 1990; Leonard et al., 1993, 2006; Robichon et al., 2000; Schultz et al., 1994). Generally, these studies report greater evidence of abnormal (increased) symmetry in affected populations, specifically in the *planum temporale*, an area between Heschl's gyrus and the sylvian fissure and including Wernicke's area, and, more recently, in the

inferior frontal gyrus (with both regions showing a left greater than right asymmetry in typical populations). Interestingly, these effects appear to be larger and more reliable for SLI subjects, as compared to dyslexics. In fact, recent work by Leonard et al. (1993, 2006) specifically compared cortical asymmetry for SLI and dyslexic populations and found evidence for smaller cerebral volume and greater temporal symmetry only in SLI children. Some evidence also shows reductions in cerebellar volume, as well as in the cortex and caudate nucleus, in individuals with a speech/language disorder (Watkins et al., 2002). The cerebellar deficits are postulated to relate more specifically to motor component deficits in LD. Clearly, more research is needed using homogeneous subtypes of the LD population in order to gain information about the biological underpinnings of identified functional deficits associated with LD.

Notably, failure to identify a consistently observable, gross anatomical neural feature of LD does *not* imply a normal brain, which has led some to investigate more subtle, but no less deleterious, mechanisms of neural disruption in developmental disabilities of language. For example, key neurodevelopmental processes may be disrupted early in life, leading to anomalous neurocircuitry not necessarily evident at the gross anatomical level. Such complex and subtle effects, however, could have potentially severe behavioral consequences. One scenario that could lead to such effects involves a confluence of genetic and/or environmental factors that occurs in the perinatal period, during key periods of neural development that disrupt the cascade of normal developmental events. One such example is neuronal migration disorders (Barth, 1987). Neuronal migration disorders occur when control mechanisms regulating the final positioning of newly generated migrating neural cells are disrupted and can result in permanent cellular/structural anomalies including agyria/pachygyria, microgyria, dysplasia, and neuronal and leptomeningeal heterotopias and focal ectopias (see Barth, 1987 for review). In fact, Galaburda and Kemper (1979) reported the presence of such focal cellular anomalies in the *postmortem* brain of an adult dyslexic male. This subject was characterized by delayed speech development in the preschool period, and difficulties with reading and spelling soon after entering elementary school, despite normal intelligence and special tutoring. These neuroanatomical findings, including the presence of cortical dysplasias and polymicrogyria in the left temporal lobe and cortical dysplasias throughout the left hemisphere, provided one of the first suggestions that language and reading impairments may represent behavioral manifestations of an underlying neuroanatomical disorder. Subsequently, Galaburda et al. (1985) published an account of three additional brains obtained at *post mortem* from adult male dyslexics. One of these subjects exhibited delayed speech development followed by reading difficulties in school, and the others exhibited early childhood learning disabilities followed by reading difficulties. Again, numerous neuronal ectopias and cortical dysplasias were observed, primarily in left perisylvian/temporal (language) regions. The authors ascribed these cellular anomalies to focal disruption of neocortical neuronal migration, which probably occurred during the prenatal period (see also Chang et al., 2005, 2007; Preis et al., 1998; Rocha de Vasconcelos Hage et al., 2006). This assertion is supported by developmental studies of animal models exhibiting similar neuronal migration disorders.

In addition to neocortical neuronal migration disorders, fMRI studies have revealed clear evidence of abnormal cortical activation in LD subjects during language tasks, which is thought to reveal abnormal cortical connectivity and/or circuitry in these subjects (e.g., Hoeft et al., 2006; Shaywitz et al., 1998, 2002; Temple et al., 2001). In general, these results correspond to anatomic findings, with evidence of reduced activation in left perisylvian, occipitotemporal, and temperoparietal regions during phonological and reading tasks in dyslexic/RD individuals (see Figure 40.1). Abnormalities in white matter tracts connecting anterior and posterior perisylvian regions have also been reported in subjects with impaired reading ability (Klingberg et al., 2000). Anomalous patterns of activation could in turn stem from a common underlying etiology relating to processes involved in neuronal migration, *or* they could reflect aspects of LD largely orthogonal to focal anomalies. An improved understanding of how these disruptions in neural functioning may underlie, or relate to, expressed behavioral deficits would further our understanding of the relationships among and between the behavioral deficits that characterize LD overall (as well as within various subtypes). In other words, the ambiguity in our understanding of the etiology and interrelation of *neural* anomalies characterizing LD parallels clinical controversies regarding the role of core characteristic *behavioral* deficits that define human LD (as discussed above). Are neural anomalies – perhaps with a common underlying etiology – expressed in a variety of interrelated structures and in turn expressed as a cascade of interwoven functional deficits defining the fabric of 'language disability'? Alternatively, can multiple and semi-orthogonal anomalies simultaneously arise in neural development (both cortical and subcortical), leading in turn to semi-orthogonal functional deficits that contribute (in varying degrees) to a heterogeneous behavioral expression of LD (with some features more pronounced in certain subtypes than others)?

As an interesting aside, histopathological analysis of sections from the same *postmortem* brains that had previously shown focal cortical anomalies (Galaburda

et al., 1985) also subsequently revealed abnormalities at the thalamic level, specifically, in the lateral geniculate (visual) nucleus (LGN; Livingstone et al., 1991). The dyslexic brains showed significantly smaller magnocellular LGN cells (28% smaller in surface area), but no size differences in parvocellular LGN neurons, as compared to controls. Concurrent electrophysiological evidence showed that healthy adult dyslexics exhibited anomalies in neural activation during performance of visual tasks known to depend on the magnocellular system. Livingstone and colleagues suggested that the focal cortical anomalies seen in dyslexics were linked to disruptions of thalamic development, including the visual pathways of the LGN responsible for transmission of low spatial frequency, low luminance contrast, and high temporal rate of change of information (magnocellular pathways; see also Lehmkuhle et al., 1993; Lovegrove et al., 1990; Slaghuis et al., 1992). Subsequent analysis of the same brains showed a similar type of anatomical change in the auditory (medial geniculate) nucleus (MGN). Specifically, dyslexics exhibited a significant shift toward more small and fewer large cells in the left MGN as compared to controls (Galaburda et al., 1994). The latter findings have been viewed in light of concurrent data demonstrating that language-disabled subjects also exhibit fundamental defects in the processing of rapidly changing auditory information (discussed above).

40.5 CANDIDATE LD AND DYSLEXIA SUSCEPTIBILITY GENES

Another approach to understanding the basic etiology of language disorders derives from epidemiological and family studies designed to draw linkages between the incidence of specific genetic variants and the incidence of language disorders (including dyslexia/RD). Studies have examined the incidence of LD in families in order to determine estimates of heritability, used linkage analysis to assess genetic 'markers' shared at above-chance levels among affected individuals from the same family, and used genetic association studies to examine correspondence between variations in regions of genes and specific phenotypes within a group (generally a clinically defined group, such as dyslexics). Such studies have revealed that language disorders are characterized by a degree of heritability, but do not conform to any single-gene models. Moreover, a degree of environmental influence seems to exist as well, since affected individuals can appear in families with no history of LD. The etiology of these 'nonheritable' incidences *could* reflect factors such as chronic ear infections (which impair hearing and thus may disrupt language acquisition), perinatal birth incidents, or the cumulative effects multiple 'risk' genes inherited from parents with subthreshold expression, but expressed in offspring due to recombination or environmental exacerbation.

Cumulative studies appear to implicate a role for regions on chromosomes 1, 3, 6, and 15 for SSD; 13, 16, and 19 for SLI; and 1, 2, 3, 6, 15, 18, and X for dyslexia/RD (reviewed in Bishop, 2009; Gibson and Gruen, 2008; Pennington and Bishop, 2009). Studies honing in on specific genes have further revealed a role for the *FOXP2* gene in the KE family, as associated with the incidence of an expressive language disorder (Fischer and Scharff, 2009). Researchers have also reported on evidence for six candidate dyslexia susceptibility genes. These include *DYX1C1*, *KIAA0319*, *DCDC2*, *ROBO1*, *MRPL19*, and *C2ORF3* (see Anthoni et al., 2007; Brkanac et al., 2007; Cope et al., 2005; Francks et al., 2004; Hannula-Jouppi et al., 2005; Harold et al., 2006; McGrath et al., 2006; Meng et al., 2005; Paracchini et al., 2006; Schumacher et al., 2006; Taipale et al., 2003, see Fischer and Francks, 2006, for review).

Of these genes, *KIAA0319* and *DCDC2* are located on chromosome 6, *FOXP2* is located on chromosome 7, *ROBO1* is located on chromosome 13, and *DYX1C1* is located on chromosome 15. *MRPL19* and *C2ORF3* are coregulated genes on chromosome 2, the function of which is not yet known. Research suggests that each of the remaining genes appears to be involved in early cortical development, including neuronal migration, axon growth, and synaptic plasticity (Wang et al., 2006). Since neurodevelopmental processes such as neuronal migration and axon growth share several common features and requirements, including dependence upon coordinated changes in cell adhesion and cytoskeletal restructuring, the overlapping functions implicated for these genes is not surprising. For example, *ROBO1* has well-understood roles in axon growth and neuronal migration. The proteins in the *DCX* family, of which *DCDC2* is a member, play well-documented roles in neuronal migration to neocortex and may also play a role in the development of the corpus callosum (LoTurco et al., 2006; Miller, 2005; Rosen et al., 2007; Wang et al., 2006). In addition, *KIAA0319* appears to play a role in cortical cell adhesion and migration, as does *FOXP2* (possibly via regulation of contactin-associated protein). Moreover, *FOXP2* appears to specifically modulate cortical synaptic plasticity, and acts as a transcriptional factor (transcriptional repressor) that may further regulate the expression of other genes important to brain development (Fischer and Scharff, 2009). Indeed, research has revealed very minor changes to a promoter sequence in the *FOXP2* gene when comparing humans and nonhuman primates, and this evolutionary change may modulate some aspects of the development of unique human language-processing capabilities (Konopka et al., 2009).

In terms of functional implications, studies using animal models have provided a unique insight into the role of these various genes by linking individual gene actions with core functional deficits characteristic of human LD populations. For example, studies have demonstrated that knockdown of the avian ortholog to *FOXP2* in birds leads to an impairment in the motor learning of birdsong, and also that *Foxp2* knockout mice show anomalous vocalizations (Gaub et al., 2010; Shu et al., 2005). Similarly, recent research has used rodent models to knock down the actions of identified dyslexia-risk genes transiently, specifically through the transfection of 'interference RNA' (RNAi) into the cerebral ventricles of fetal rats. This RNAi is taken up by new neurons in the ventricular zone, thus deactivating the target genes in these specific cells. Behavioral testing of rodents treated using this technology shows that male rats with embryonic cortical RNAi of the homolog *Dyx1c1* exhibit deficits in complex auditory processing later in life (Threlkeld et al., 2007). These results have intriguing implications for the possible role of *DYX1C1* in modulating auditory processing deficits, and perhaps even associated phonemic/phonological deficits. More recent research has extended these findings to rodent models using another dyslexia-risk gene, *KIAA0319*. Specifically, rats with embryonic RNAi for the homolog *Kiaa0319* also showed significant deficits in rapid auditory processing for fast frequency-modulated (FM) sweep stimuli as compared to sham controls (Szalkowski et al., 2012). Again, these effects are interpreted to parallel evidence of rapid auditory processing deficits in LD populations. As an aside, it is important to note that neither group of RNAi animals was categorically impaired in sound processing tasks, and both groups performed quite normally on discrimination tasks with easier/slower stimuli (e.g., single tones). This point is important when developing animal models for clinical conditions, since a genetic defect resulting in comprehensive learning and cognitive impairments would provide a poor model for the relatively specific pattern(s) of deficits seen within the LD phenotype.

More recently, another study examined STM performance on a delayed match to sample radial arm maze task in male rats with or without embryonic RNAi of *Dyx1c1* (Szalkowski et al., 2011). In this study, results showed persistent STM deficits in *Dyx1c1* knockdown rats, as indicated by higher numbers of errors, paralleling evidence of cross-modal STM deficits in human dyslexics (Smith-Spark and Fisk, 2007). These effects were seen despite parallel evidence that *Dyx1c1* RNAi rats do *not* show deficits on basic spatial maze learning (Morris maze) unless migrational anomalies specifically extended into the hippocampus (as was seen in a small subset of subjects; Threlkeld et al., 2007). Interestingly, similar working memory deficits were *not* seen in a sample of *Kiaa0319* knockout rats, suggesting that these genetic risk factors may exert dissociable effects on core behavioral deficits related to dyslexia (Szalkowski et al., 2012). Again, this pattern of behavioral–genetic associations provides a relatively specific profile to model deficits seen in LD (i.e., deficits in STM). Future work will continue to explore a role for animal models in evaluating these gene–brain–behavior relationships.

40.6 CONCLUSIONS

As will by now be readily apparent from the current chapter, research in the field of language-related disabilities represents one of the most comprehensive and complex cross-disciplinary research fields currently confronting the scientific and clinical community. On the one hand, the breadth of expertise and approaches brought to bear on the issue has led to a vast database concerning the behavioral, neural, and genetic features of LD. On the other hand, the field also suffers from the challenge inherent to processing and integrating the enormous amount of information that now exists. These difficulties are reflected in the fact that different researchers have created conflicting acronyms for what appear to be the same terms, that substantial disagreements exist regarding the distinctions and overlap between subgroups as a function of behavioral criteria (leading to studies that use differently defined populations as subjects for assessment and experimentation), and that it remains quite nearly impossible to achieve expertise in fields as diverse as molecular genetics to clinical behavioral evaluation (thus constraining efforts to integrate data on LD populations fully). Nonetheless, researchers continue to move forward in refining and reshaping our conceptions of language-related developmental disorders from a behavioral perspective and in adding new information to the database of neural and genetic features that characterize these populations. Finally, animal studies provide a unique opportunity to test and assess some of the putative genetic–neural–behavioral links in an experimental manner that is virtually impossible to employ with human subjects.

With regard to future directions, two of the most promising goals toward which research efforts continue to strive are (1) the development and implementation of effective early diagnostic criteria that might detect infants at risk for later language problems, and provide an opportunity for very early intervention (while brain systems are still highly plastic), and (2) the development of effective remediation strategies tailored to unique patterns of deficits in subpopulations of LD (Hoeft et al., 2006). Promising efforts currently continue in both respects. For example, studies have shown that measures of acoustic processing obtained from infants as young

as 6 months of age may predict their later risk for language difficulties (Benasich et al., 2006; Choudhury et al., 2007). In addition, intriguing neuroimaging studies have shown that effective intervention strategies can actually shift the abnormal patterns of brain activity in affected subjects observed during language tasks toward more normative patterns following training (e.g., Gaab et al., 2007). All of these promising routes of investigation will continue in the next decade, as we continue to make inroads in our diagnosis, understanding, and treatment of developmental LD.

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