

LEARNING DISORDERS

C. KEITH CONNERS
ANN C. SCHULTE

NOSOLOGY AND CLASSIFICATION

Current conceptualizations of *learning disorders* (LDs), formerly referred to as “academic skills disorders” (1), follow the traditional approach of classifying learning by specific academic skills. These skills include reading, mathematics, and written expression. In each case, the skills are measured by standardized tests whose scores must fall substantially below the level expected from chronologic age, intelligence, and age-appropriate education. The deficits must significantly interfere with academic or daily living activities requiring the skills. When LDs result from sensory, medical, or neurologic conditions, they are coded on Axis III (medical conditions) within the DSM-IV nomenclature.

Commonly associated features of LDs include low self-esteem and demoralization, social skills deficits, school dropout, and difficulties in employment or social adjustment. Patients with conduct disorder, oppositional disorder, attention-deficit/hyperactivity disorder (ADHD), major depression, dysthymic disorder, and Tourette syndrome all have substantially elevated rates of LD. Academic skills in pervasive developmental disorders are often not discrepant from the measured intelligence and language abilities associated with the pervasive development disorder. Communication disorders and motor skills disorders are also common in LDs, including expressive language disorders, phonologic disorder, and stuttering. Spelling disorders are usually not considered separate from other reading- and writing-related deficits.

Although this approach to classification of LDs is useful in a practical context and allows for an operational definition for detection and remediation, it has several drawbacks from a theoretic and scientific point of view. Reading, mathematics, and writing comprise many processing skills, giving rise to subtypes with different underlying mechanisms.

Thus, reading at the word level may involve visual, lexical, or semantic processes (2,3), with correspondingly different neuroanatomic circuitry and computational mechanisms within the brain. There are subtypes characterized both by the pattern of skills deficits (e.g., reading and spelling, but no mathematics disorder) and by different patterns of neuropsychological function, such as the relative strength of verbal and nonverbal factors on intelligence tests (4). There are also important developmental changes in LD, such that variables characterizing the disorder at earlier ages may be different from those seen in older patients (5). Advances in the genetics and neuroimaging of LDs will depend on more homogeneous clinical definitions at the symptomatic level (6).

PREVALENCE

The DSM-IV reports prevalence estimates of 2% to 10% for LDs, depending on the nature of ascertainment and the definitions applied (1). In most prevalence studies, a diagnosis of LD has been made on the basis of a significant discrepancy between IQ and achievement in one or more areas (7), with studies varying in terms of the manner in which a discrepancy has been determined and the cutoff score for considering a discrepancy “severe.” One study of the prevalence of regression-based ability/achievement discrepancies using the co-norming sample from the Wechsler Intelligence Scale for Children III and the Wechsler Individual Achievement Scales found that 17% of the norming group had ability/achievement discrepancies at the .05 significance level in one or more areas of achievement (8). This figure can probably be considered the upper limit for LD prevalence estimates based on ability/achievement discrepancies, given that a diagnosis of LD would also require determining both that the discrepancy was not the result of poor instruction and that it interfered with daily functioning.

Several researchers have questioned the conceptual and empiric basis for the use of ability/achievement discrepancies in the diagnosis of LDs, as well as current operationalizations of the exclusionary criteria. Reasons for concern on

C. Keith Connors: Behavioral Neurology Department, Durham, North Carolina.

Ann C. Schulte: Department of Psychology, North Carolina State University, Raleigh, North Carolina.

the use of ability/achievement discrepancies are (a) findings that the cognitive profiles of children with low achievement are similar regardless of whether they evidence an ability/achievement discrepancy (9), (b) findings that the same deficits that lead to poor achievement may also lower IQ (10), and (c) the finding that the use of such definitions prevents early identification and treatment because the underlying cognitive deficits that cause the disability must retard growth in academic skills before intervention can begin (11). Alternate proposals for identification include simply using a low achievement criterion (e.g., academic functioning 1 to 2 standard deviations [SD] below the mean), using a definition that combines the ability/achievement discrepancy and low achievement approaches, and use of domain-specific rather than general cognitive ability tests as predictors of academic achievement. In general, these alternate procedures are likely to raise prevalence rates.

There is some indication that more rigorous operationalization of the exclusionary criteria in the LD definition could substantially reduce LD prevalence rates. For example, when Vellutino and his colleagues used daily tutoring as a “first cut” diagnostic criterion to distinguish between children who had reading difficulties caused by cognitive deficits and those whose deficits were the result of poor instruction, they found that two thirds of their sample scored within the average range in reading (thirtieth percentile and higher) after one semester of one-to-one tutoring (12). This relatively stringent criterion for establishing an “adequate educational environment” resulted in a drop in the prevalence rate of reading disorders (RDs) from 9% to 3%. Geary used failure to respond to short-term intensive remedial instruction as a diagnostic criterion for mathematics disability (MD) and noted a marked drop in prevalence (13). Clearly, the definition of caseness in these studies has implications for how phenotypes are characterized in genetic and neurobiological investigations. The use of the more conservative methods of case definition are clearly more costly for selecting subjects, but they may prove more valid and useful in finding biological markers of LD.

COMORBIDITY

Many psychiatric and medical conditions include LD as an associated deficit. The most common childhood condition comorbid with LD is ADHD. Estimates of comorbidity range from 20% to 90%, with the lower figures appearing in epidemiologic samples and the higher figures appearing in clinically referred samples. The high degree of overlap in clinical samples suggests that common mechanisms may be at work in the neurologic basis for both disorders. LDs were once considered a necessary criterion for minimal brain dysfunction. Although some studies suggest that ADHD may simply be the result of an LD, most studies indicate that when both conditions are present, characteristics of

each are found, whereas in LDs alone, only symptoms of LD, not those of ADHD, are present, and vice versa (14). The high degree of overlap has the practical implication that when one disorder is identified, it is always prudent to expect the presence of the other and to make appropriate diagnostic probes.

PHONOLOGIC PROCESSING

As noted earlier, the present classification approach to LD subdivides the disorder on the basis of impairment in specific academic areas (reading, math, written expression). However, given that performance in each of these areas draws on numerous cognitive processes, it is likely that the present classification system will eventually be replaced by one that focuses on the specific cognitive deficits that underlie poor academic performance and their impact on the development and execution of specific subskills within and across academic areas.

The greatest progress in specifying the cognitive and neuropsychological dysfunctions underlying LDs has occurred in reading. Numerous investigations using longitudinal, intervention, genetic, and neuroimaging methods have produced strong and converging evidence that deficits in phonologic processing are the proximal cause of reading difficulties in a large proportion of children with RDs (see refs. 15 and 16 for reviews). Deficits in phonologic processing also appear to affect spelling, written expression, and mathematics.

Phonologic processing refers to the ability to use and manipulate the sound structure of one's oral language (17). Although conceptualizations of phonologic processing and its components vary, within the Wagner and Torgesen model of phonologic processing, it consists of three related abilities: phonologic awareness, phonologic memory, and rapid naming (18,19). *Phonologic awareness* refers to the understanding that words can be broken down into phonemes and the ability to identify phonemes and manipulate them in words (16). Phonemes are the smallest sound unit that changes the meaning of a word (e.g., tap and lap differ by one phoneme). Phonologic awareness is a critical ability in learning to read because it allows beginning readers to link letters and letter combinations in text to sound strings in oral language (20). Knowledge of these links allows readers to discover the regularities in written text so written words can be rapidly translated into their spoken equivalents. Such recoding allows the reader to access the semantic code (or meaning) for the letter string. The repeated pairing of the visual letter string and its spoken equivalent is thought eventually to allow the reader to develop direct visual word recognition strategies that bypass the phonologic code (10, 21).

Phonologic memory is an individual's ability to represent verbal information in working memory in terms of a se-

quence of sounds or a phonetic code. When children have difficulty with phonologic coding, reading acquisition is impaired because of difficulty in performing the rapid comparison and blending needed to identify unfamiliar written words. Difficulties in verbal short-term memory are also hypothesized to be a major factor underlying MDs (22), and they may affect the acquisition of foreign languages (20).

Rapid naming is the ability to access phonologic information that is stored in long-term memory rapidly. It is typically assessed by asking children to name well-known items as rapidly as possible (e.g., presentation of a series of colored squares with the child naming the color of each square as fast as possible). Such tasks are thought to tap many of the same cognitive processes required in skilled reading, such as rapid scanning, sequencing and processing of serially presented visual stimuli, and rapid access to strings of phonemes (e.g., color names) (16). There is debate about whether the difficulty with rapid naming tasks observed in many children with RDs is a reflection of a core deficit in phonologic processing or whether it represents a deficit in a second set of processes that impairs reading. If this is the case, there may be “double-deficit” readers who are impaired in both phonologic and rapid naming processes (23). Such disabled readers would be less responsive to interventions that address phonologic processing and would require

additional interventions targeted toward increasing language and reading fluency.

Efforts are also under way to understand more fully the core cognitive deficits underlying other types of LD. For example, Berninger et al. proposed a model of the cognitive processes underlying written language and writing disabilities (24). Geary proposed that there are three subtypes of MDs, with corresponding deficits in semantic memory, procedural knowledge of mathematics, and visuospatial processes (22).

GENETICS

It has been known for decades that LDs run in families. In the 1990s, family aggregation studies, twin studies, and genetic linkage analyses confirmed the strong hereditary influences on RD and MD (Table 44.1). The genetic studies also confirm the heterogeneity of the phenotype, with both orthographic and phonologic traits implicated but not having identical sources of genetic influence. A genetic link between RD and MD was confirmed in several studies. A strong link of Tourette syndrome, ADHD, and LD has been suggested by studies of patients who have Tourette syndrome with and without ADHD. Evidence has accumulated that locations on the short arm of chromosome 6

TABLE 44.1. GENETICS OF LEARNING DISORDERS

Study	Subjects	Method	Comment
Comings and Comings, 1987 (99)	47 normal controls, 246 TS	Comparison of TS and control	27% of TS had LD vs 4.2% of controls
Comings and Comings, 1990 (100)	130 TS probands with 1,851 relatives, 25 control probands with 541 relatives	Comparison of TS and control	Suggests LD/ADHD are integral part of the expression of the Gts gene(s)
Comings et al., 1999 (101)	274 TS and 62 normal controls	Tested associations and additive effects between polymorphisms at 3 nonadrenergic gene sites	Suggests additive effects of nonadrenergic genes related to presence of LD
DeFries et al., 1987 (102)	64 pairs identical, 55 pairs fraternal twins in which at least one member of pair is dyslexic	Multiple regression analysis	Significant genetic etiology for dyslexia
Fagerheim et al., 1999 (103)	80 Norwegian family members	Genome search for linkage and non-parametric multipoint GENEHUNTER analysis	Localization to 2p15–16 and to 6p21.3–23 give strong evidence of genetic heterogeneity in dyslexia
Field and Kaplan, 1998 (104)	79 families having at least 2 affected sibs with phonologic coding dyslexia (617 genotyped, 294 affected)	Tested for linkage	No evidence for linkage by LOD score analysis or affected-sib-pair methods; however, affected-pedigree-member (APM) method detects significant linkage; concludes APM may generate false-positive results

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TABLE 44.1. (continued)

Study	Subjects	Method	Comment
Fisher et al., 1999 (105)	181 sib pairs from 82 nuclear families with a dyslexic proband	Assessed linkage directly for several quantitative measures rather than a single composite measure or categoric definition	Pointwise analysis of sib-pair trait differences suggests presence in 6p21.3 of a QTL influencing multiple components of dyslexia: reading of irregular words and nonwords; shows that both orthographic and phonological skills are affected
Gayan and Olson, 1999 (106)	—	Review with focus on twin study design and sib-pair linkage techniques	DeFries-Fulker multiple regression analyses show significant estimates of heritability for group deficits on several reading and language measures, and presence of significant common and independent genetic effects on individual differences on reading skills; linkage techniques confirm a candidate locus for RD on chromosome 6
Gayan et al., 1999 (107)	126 sib pairs	Multipoint mapping method and 8 informative DNA markers on chromosome 6	Significant linkage across a distance of at least 5 cM for deficits in orthographic (LOD = 3.10) and phonological (LOD = 2.42) skills, confirming previous findings
Gillis et al., 1992 (108)	264 RD twin pairs and 182 matched control twin pairs	Multivariate behavior genetic analysis	Individual differences in both reading and math performance are highly heritable and appear to be caused by many of the same genetic influences
Knopik et al., 1997 (109)	102 identical and 77 same-sex fraternal twin pairs in which at least one member of each pair is reading disabled; and 42 identical and 23 same-sex fraternal twin pairs in which at least one member is math disabled	Multiple regression model for the analysis of selected twin data and its bivariate extension	The comorbidity between math and RD is due in part to genetic influences
Knopik and DeFries, 1999 (110)	526 twin pairs selected for RD (290 identical and 236 same-sex fraternal); and 355 control pairs (220 identical and 135 same sex fraternal)	Confirmatory factor analyses and heritability estimation	Heritability in proband and controls were 0.81 and 0.69; and those for math 0.88 and 0.67; genetic influences accounted for 83% of the covariation between reading and math factors in the proband group and 58% in the control group; shared environmental influences did not contribute to the relationship between reading and math factors, nor to their independent variation
Petryshen et al., 2000 (111)	79 families with at least 2 affected sibs	Two-point and multipoint quantitative-trait sib-pair linkage and variance-components analyses	No evidence for a locus in the 6p23-p21.3 region for several quantitative measures; speculates that perhaps families with subtypes of dyslexia linked to this region are underrepresented in the sample, either by chance or ascertainment criteria
Reynolds et al., 1996 (112)	Twins of the Virginia Twin Study	—	69% of variability in oral reading due to heredity vs 13% due to shared environmental effects; genetic and environmental influences were equivalent for males and females, but males showed greater phenotypic variability than females

ADHD, attention deficit hyperactivity disorder; LD, learning disorder; QTL, quantitative trait locus; RD, reading disorder; TS, Tourette syndrome.

(6p21.3) and the short arm of chromosome 15 are involved. Odds for linkage to chromosome 15 are reported as being 1,000 to 1, with evidence that 30% of an extended series of families showed linkage to chromosome 15 polymorphisms. Some variations in results may reflect sampling methods or trait markers. The excess of affected males with LDs identified in clinic and referred samples disappears in research-based samples (25).

NEUROIMAGING

The neuroanatomic and functional pathways in the brain involved in LDs were greatly clarified in the 1990s by a variety of neuroimaging techniques. Reviews of neuroimaging of LDs describe rapid progress in identifying the brain regions and functional pathways involved (20,26–29).

However, these reviews also call attention to discrepancies in findings, possibly the result of small cohorts, variations in sampling, and heterogeneity of the LDs. Table 44.2 provides selected studies from several hundred investigations, mainly of RDs. Many studies confirm earlier findings of abnormalities of the microstructure of the planum temporale from autopsy studies, but conflicting data emerge, possibly related to the method employed or the sampling techniques and definition of the RD (30). Although most studies implicate abnormalities in left temporal-parietal anatomic areas, additional findings have identified white matter, right hemisphere anomalies, motor cortex, cingulate gyrus, and the splenium of the corpus callosum.

One of the older controversies regarding the functional brain basis of dyslexia is whether dyslexia represents a visual (orthographic) disorder or a language-based (phonologic processing) disorder. Neuroimaging studies now appear to provide evidence that brain structures involving both the

TABLE 44.2. NEUROIMAGING IN LEARNING DISORDERS

Study	Method	Subjects	Results
Klingberg et al., 2000 (113)	Diffusion tensor magnetic resonance	Adults with poor or normal reading ability	Subjects with reading difficulty exhibited decreased diffusion anisotropy bilaterally in temporoparietal white matter. White matter diffusion anisotropy in the temporoparietal region of the left hemisphere was significantly correlated with reading scores within the reading-impaired adults and within the control group. The anisotropy reflects microstructure of white matter tracts, which may contribute to reading ability by determining the strength of communication between cortical areas involved in visual, auditory, and language processing.
Fersten et al., 1999 (114)	Blood flow velocity in MCA in left and right hemisphere measured with the transcranial Doppler method	10 dysgraphic or dysorthographic students and 10 normal subjects	The dysgraphic persons had significantly higher blood flow velocity in the right hemisphere compared to the reference group.
Duncan et al., 1994 (115)	Event-related brain potentials	13 severely dyslexic men, 15 matched controls	As task demands increased, visual P300 was reduced in the dyslexic men as compared with the normal readers. Dyslexics with a history of many symptoms of ADHD in childhood (high ADHD) accounted for the group differences in P300; the dyslexics with a history of few or no such symptoms (low ADHD) were indistinguishable from the controls at all electrode sites. The results are interpreted as suggesting that a distinct brain organization may characterize dyslexic men with a history of concomitant deficits in attention.

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TABLE 44.2. (continued)

Study	Method	Subjects	Results
Georgiewa et al., 1999 (116)	fMRI	17 phonologically impaired developmental dyslexics and 17 normal reading children	Significant differences in Broca area and the left inferior temporal region for both, nonword reading and the phonologic transformation task.
Rumsey et al., 1999 (117)	rCBF	17 right-handed dyslexic men, ages 18–40, and 14 matched controls	Correlations between reading skill and rCBF during a series of reading tasks; uniquely identified the left angular gyrus as the most probable site of a functional lesion in dyslexia: Here, higher rCBF was associated with better reading skill in controls ($p < .01$), but with worse reading skill in dyslexia ($p < .01$).
Helenius et al., 1999 (118)	Magnetoencephalography	10 dyslexic male adults and 10 normal controls	Early visual responses were similar in dyslexic and nonimpaired readers. In contrast, the letter-string-specific responses peaking around 150 ms predominantly in the left inferior occipitotemporal cortex in fluent readers were undetectable in dyslexic readers. Thus, while the early visual processing seems intact in dyslexic adults, the pattern of cortical activation starts to differ from that of fluent readers at the point where letter-string-specific signals first emerge during reading.
Best and Demb, 1999 (32)	Sagittal magnetic resonance images of PT and magnocellular visual pathway	Dyslexics with documented MC deficits and controls	Dyslexic subjects did not deviate from normal leftward PT asymmetry, but both groups became less left-lateralized with methods that excluded sulcal tissue. Results suggest that dyslexic subjects with a magnocellular deficit do not always have abnormal symmetry of the PT. PT symmetry may instead be related to a different subtype of dyslexia. In addition, PT asymmetry in any subject group depends on the measurement method.
Nicolson et al., 1999 (119)	PET	6 dyslexic adults and 6 matched controls	Brain activation was significantly lower ($P < .01$) for the dyslexic adults than for the controls in the right cerebellar cortex and the left cingulate gyrus when executing a prelearned motor sequence, and in the right cerebellar cortex when learning the new sequence.
Pennington et al., 1999 (120)	MRI	75 subjects with RD and 22 controls	Insula and anterior superior neocortex were smaller and the retrocallosal cortex was larger in the RD group. In contrast, no group main or interaction effects for the subcortical or callosal structures. Results were not due to ADHD.
Green et al., 1999 (121)	MRI-based surface reconstruction technique that models the curvature of the cerebral cortex in three dimensions to obtain whole-hemisphere and regional surface area estimates	8 male right-handed male dyslexics and matched controls	The caudal infrasyllvian surface that encompasses the supratemporal plane and the inferior bank of the posterior ascending ramus of the sylvian fissure was significantly larger than that of control subjects, and this result was not attributable to a difference in whole-hemisphere surface area.

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TABLE 44.2. (continued)

Study	Method	Subjects	Results
Richards et al., 1999 (122)	MR spectroscopic imaging technique called proton echo-planar spectroscopic imaging	6 dyslexic boys and 7 age- and IQ-matched right-handed good readers	Dyslexic boys showed a greater area of brain lactate elevation (2.33+/-SE 0.843 voxels) as compared with the control group during a phonological task in the left anterior quadrant. No significant differences were observed in the nonlanguage tasks.
Price et al., 1998 (31)	fMRI	2 boys with deep dyslexia	Activation patterns primarily reflect semantic and phonologic systems in spared regions of the left hemisphere. These results preclude an explanation of deep dyslexia in terms of purely right-hemisphere word processing.
Demb et al., 1998 (123)	fMRI	Group of dyslexic and normal readers	Dyslexics showed reduced brain activity compared with controls both in primary visual cortex (VI) and in several extrastriate areas, including area MT and adjacent motion-sensitive areas (MT+) that are believed to receive a predominant magnocellular pathway input.
McPherson et al., 1998 (124)	Event-related potentials	Adolescents who were good phonetic decoders or poor (dysphonetic)	Phonetics showed both orthographic and phonological priming but had a marked reduction in their CNV. These results support the separation of the reading disabled into a group that has difficulty translating orthography into phonology and a group that is slower functioning and has reduced capacity in preparing for a response.
Shaywitz et al., 1998 (125)	fMRI	Dyslexic and normal readers	Brain activation patterns differed significantly between the groups with dyslexic readers showing relative underactivation in posterior regions (Wernicke area, the angular gyrus, and striate cortex) and relative overactivation in an anterior region (inferior frontal gyrus). These results support a conclusion that the impairment in dyslexia is phonologic and that these brain activation patterns may provide a neural signature for this impairment.
Richardson et al., 1997 (126)	<i>In vivo</i> cerebral phosphorus-31 magnetic resonance spectroscopy	12 dyslexic and 10 nondyslexic adults	Membrane phospholipid metabolism is abnormal in dyslexia.
Halperin et al., 1997 (127)	Plasma levels of MHPG	ADHD children with and without RD	Plasma levels of MHPG were significantly lower in ADHD children without RD, compared with those with RD, replicating a published finding.

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TABLE 44.2. (continued)

Study	Method	Subjects	Results
Rumsey et al., 1997 (30)	MRI	16 RH dyslexic men 18–40 and 14 matched controls	Results challenge the notion that anomalous asymmetry of the PT is strongly associated with developmental dyslexia. Given the heterogeneity of the dyslexic population, some subgroup of dyslexic individuals (i.e., those with developmental language disorders) may show unusual symmetry or reversed asymmetry in this region. However, anomalous asymmetry of the planum did not contribute to functional abnormalities demonstrated in these patients by positron emission tomography.
Rumsey et al., 1996 (128)	MRI	21 dyslexic men and 19 matched controls	As predicted, the area of the posterior third of the corpus callosum, roughly equivalent to the isthmus and splenium, was larger in dyslexic men than in controls. No differences were seen in the anterior or middle corpus callosum. The increased area of the posterior corpus callosum may reflect anatomical variation associated with deficient lateralization of function in posterior language regions of the cortex and their right-sided homologues, hypothesized to differ in patients with dyslexia.
Paulesu et al., 1996 (129)	PET	5 adult dyslexics with phonological processing deficits	Proposes that the defective phonologic system of these dyslexics is due to weak connectivity between anterior and posterior language areas. This could be due to a dysfunctional left insula which may normally act as an anatomic bridge among Broca area, superior temporal, and inferior parietal cortex. The independent activation of the posterior and anterior speech areas in dyslexics supports the notion that representations of unsegmented and segmented phonology are functionally and anatomically separate.
Eden et al., 1996 (130)	Review	—	The pathophysiology of developmental dyslexia is more complex than originally thought, extending beyond the classically defined language areas of the brain.
Shapleske et al., 1999 (131)	Review	PT studies	Overall, there is a significant leftward asymmetry in normals, which is reduced in left handers and females. The leftward asymmetry is much reduced in patients with schizophrenia due to a relatively larger right PT than normal controls.
Deb et al., 1997 (26)	Review	—	Brain abnormalities can be detected in cases of idiopathic and nonidiopathic learning disability, but their significance is not clear due to discrepancies in study findings and the small cohorts involved.

ADHD, attention deficit hyperactivity disorder; fMRI, functional magnetic resonance imaging; MCA, middle cerebral artery; MHPG, XXX; MT, XXX; PET, positron emission tomography; PT, planum temporale; rCBF, regional cerebral blood flow; RD, reading disorder.

striate visual magnocellular pathways and specific phonologic processing pathways in the left hemisphere are involved in dyslexia, a finding possibly reflecting different subtypes at the behavioral level. As noted earlier, cognitive behavioral analysis suggests that distinctive mechanisms for visual, lexical, and semantic processing are required to explain normal human reading (2,3). Pathologic studies indicate that each of these mechanisms can be affected separately in acquired dyslexias. For example, in *deep dyslexia*, it is primarily the semantic aspects of reading that are disturbed, whereas orthography and lexicality are preserved. Thus, a patient may read “spirit” as “whiskey,” or “church” as “priest.” Evidence suggests that, unlike the more typical left-hemisphere–based phonologic and visual deficits in dyslexia, deep dyslexia may reflect a right-hemisphere–based processing mechanism (31).

Whereas some investigators interpret functional magnetic resonance imaging studies as giving strong support to the hypothesis that dyslexia represents a disorder of the language system, involving the segmentation and synthesis of phonemes (20), others find evidence that magnocellular pathways without involvement of phonologic regions occur in dyslexia (32,33). As noted by Filipek, cognitive neuroscience identifies specific computational tasks that should be used to provide more homogeneous samples at the behavioral level for further advances in the neurobiology of developmental disorders (28). For example, rather than using classic clinical criteria for dyslexia, which leads to samples with diverse subtypes, neuroimaging studies may do better to select samples by visual, lexical, and semantic criteria first.

EDUCATIONAL MANAGEMENT

Various educational treatments have been developed for LD. In general, the most effective treatment approach is one that involves careful delineation of the specific academic deficits evidenced by the child and intensive instruction in the skill areas in which deficiencies are documented (34). Response to treatment varies by individuals, so it is important that careful monitoring take place throughout treatment to ensure that an intervention is effective for a particular child (35). In this section, we briefly summarize the educational treatment literature by academic area and then summarize research related to treatment monitoring or formative evaluation of interventions.

Reading

Considerable progress has been made in the development of preventive and early intervention approaches for beginning readers. Several studies have demonstrated that explicit instruction in phonologic awareness (generally combined with letter identification and reading instruction) in preschool

and early elementary years can reduce the overall rate of RDs (36,37) and can improve outcomes for children who are at high risk of RD (38,39). One metaanalysis reported a combined effect size for phonologic awareness training of 1.16 for phonologic awareness skills and .40 for reading skills across studies that used samples of normal readers and .54 and .60 for studies that used samples of students who were either at risk of, or had shown evidence of, reading difficulty (40).

The difference in training effect on phonologic awareness between normal and impaired readers appears to reflect the difficulty many poor readers have in mastering phonologic processing, even when they are provided with intensive instruction to address these difficulties (40). Torgesen examined results from five large-scale early reading intervention studies and concluded that even with use of the best current methods of early reading remediation, 2% to 6% of children would still evidence inadequate reading skills in the early elementary grades (41). Such findings point to the need for the development of even more powerful intervention techniques to facilitate the acquisition of early reading skills.

Current models of reading skill acquisition characterize phonologic awareness as a necessary, but not sufficient condition for the development of skilled reading (15). Fluent reading requires the development of orthographic reading skills or the ability to recognize words by sight (41). Impaired readers generally show deficits in this area that persist into adulthood (41,42). Interventions to improve fluency are less well developed than interventions for the development of decoding skills (i.e., phonologic awareness interventions). The *repeated readings technique*, which involves multiple readings of the same passages, is the most researched approach to improving fluency (43), and it has shown limited but positive effects on fluency (44). The increased attention to issues of fluency in reading research has resulted in the development of new, comprehensive intervention approaches that ultimately may be more effective than existing techniques in addressing fluency deficits (23). At present, however, fluency deficits remain one of the most persistent and intransigent symptoms of RD (20).

Although most children with RDs show deficits in word recognition skills, comprehension deficits are also common. These may occur alone or in the presence of impaired word recognition skills (45). When impaired word recognition is the primary source of the comprehension deficit, decoding and fluency interventions such as those discussed earlier can improve reading comprehension (46). However, interventions have also been developed to address comprehension deficits directly. Two metaanalyses found substantial improvements for disabled readers who receive intensive instruction in reading comprehension (47,48). In both studies, metacognitive approaches (e.g., self-questioning, comprehension monitoring) produced the largest effect sizes.

Math

Geary characterized research in the area of MDs as “primitive” in comparison with studies of RDs (22). Nevertheless, effective remediation techniques for MDs have been developed. Mastropieri et al. presented a comprehensive review of mathematics instructional techniques that have been effective for students with LDs (49). However, Cawley et al. questioned the efficacy of available math computation instructional techniques (50). In a metaanalysis of math word problem interventions, Xin and Jitendra found that instruction in problem representation was an effective remedial strategy for addressing this type of difficulty in children with a range of mild disabilities (51). These investigators also found that problem representation instruction was most effective when it was presented in a computer-assisted format. Long-term interventions (i.e., more than 1 month) resulted in better maintenance and generalization of training.

Written Expression

Difficulties with composition and writing fluency are common in children with LDs. Several researchers have shown that cognitive strategy instruction is effective in improving the composition skills of children with written language deficits (52–54). Generally, such interventions provide students with explicit instruction in thinking and problem-solving strategies that allow them to break down the complex task of composing written text into manageable sub-steps.

Difficulties with handwriting fluency appear not only to impair the speed with which children can take notes or copy but also to affect compositional fluency and quality (55). For example, Berninger et al. found that instruction in handwriting increased students’ scores on a writing composition test (56).

With more widespread use of computers in classrooms, word processing tools are increasingly being used to address the writing problems of children with LDs (57). When writing fluency is a problem, word processing may be used as a text entry strategy on its own, or it can be combined with word prediction programs (58). Voice recognition software has improved to the point that it may be a practical text entry strategy for many students with writing disabilities (59). However, research on the efficacy of these tools remains sparse. In one of the few studies to compare the efficacy of different word processing strategies for improving writing fluency, accuracy, and composition in students with LDs, Lewis et al. compared groups of students after a year of writing instruction using either keyboarding, keyboarding with word prediction software, or keyboarding with word prediction and synthesized speech software (60). All groups using word processing tools showed *decreases* in speed of text entry over handwriting, although the key-

boarding with text prediction group showed the smallest decrease. There were no improvements in composition skills in any of the treatment groups.

Treatment Monitoring

The unexpected results of the foregoing study by Lewis et al. reinforce the need to monitor response to treatment and to verify that interventions for children with LDs achieve their intended results. *Curriculum-based measurement* (CBM) is a relatively new development in special education and provides a useful tool for continuous monitoring of children’s response to treatment in a number of academic areas (61–64). CBM involves the collection of brief samples of students’ performance on basic skills on a weekly or monthly basis. For example, CBM procedures in reading involve the administration of short reading probes (e.g., passages of 200 words) to children once or twice per week. The number of correct responses per passage is charted, and slope is then used as an indicator of a child’s response to treatment. Slopes that do not differ from zero are an obvious indicator of the need for a new treatment approach. However, estimates of typical response to treatment for students with LDs are also available and can be used as a basis for deciding whether a given treatment is producing sufficient progress (65). When formative evaluation strategies such as CBM are incorporated into treatment strategies, outcomes for students with disabilities improve markedly (66).

PSYCHOPHARMACOLOGY

Psychostimulants

Early studies of psychostimulants in children with LDs suggested strong immediate effects in enhancing reading, spelling, and arithmetic as well as in laboratory measures of learning (67–71). However, reviews concluded that lasting educational gains resulting from psychotropic drugs have not been demonstrated (72,73). Stimulant drug effects have generally been dose related, with linear increases in performance with higher doses (74–77). Drug-induced changes reflect increased output, accuracy, efficiency, and improved learning acquisition. There is also evidence of increased effort and self-correcting behaviors (78). Some studies suggest a positive effect of stimulants on memory consolidation that is not accounted for by concomitant effects on acquisition (79). Because most studies involve students with comorbid ADHD, measures of specific effects of stimulants on LDs are rare. However, because improvement in learning acquisition occurs in both clinical cases and neurologically normal persons treated with amphetamine (80), it seems likely that stimulant effects on learning are nonspecific with respect to diagnosis.

Stimulants have been widely used in rehabilitation of memory and LDs in brain injuries and encephalopathies

secondary to medical X-irradiation of the brain. Animal models of selective exposure to X-irradiation during infancy show enhanced learning from amphetamine treatment (81).

Nootropics

Piracetam (Nootropil, Nootropyl, 2-oxo-1-pyrrolidone acetamide) was originally developed as a molecular analogue of γ -aminobutyric acid (GABA) for the purpose of altering vestibular function in motion sickness, but it is probably neither a GABA receptor agonist nor antagonist. Numerous analogues of the piracetam molecule are currently under study, including oxiracetam (Neuromet), pramiracetam, etiracetam, nefiracetam, aniracetam, and rolziracetam. This group of nootropics is commonly referred to as the “racetams.” Piracetam has virtually no detectable peripheral effects at any dose in animals or humans and does not affect cerebral blood flow, unlike other putative cerebral enhancers. It appears to alter cellular brain metabolism, however, because it increases the concentration ratio of brain adenosine triphosphate. In neurologically normal volunteers, a single dose of piracetam was found to change brain global functional state as measured by multichannel electroencephalographic recordings (82). Investigators have suggested that the defining characteristics of nootropics should include lack of peripheral effect, absence of action on blood flow, and an increase in brain metabolism (83).

Animal research indicates that memory deficits induced by epileptogenic kindling procedures are prevented by pretreatment with piracetam (84). Piracetam (100 mg/kg, IP) and oxiracetam (10 mg/kg, IP) prevented the negative effects of microwaves on memory processes in exposed rats (85). Hypobaric hypoxia of pregnant rats is followed by the reduction of weight gain of the newborn pups, delayed impairment of memory (passive and active tasks), and changes of extrapolative water escape. Piracetam (200 mg/kg/d) administered at early postnatal period (from the eighth to the twentieth day of life) corrected behavioral disturbances and physical development in rats (86). Piracetam (800 mg/kg) administered orally once daily for 5 days before training completely antagonized the scopolamine-provoked amnesia in step-through-trained mice, and piracetam (600 mg/kg) administered orally once daily for 5 days before training abolished the memory-impairing effect of clonidine in shuttle-box-trained rats and the amnesic effect of methergoline in step-down-trained rats.

Early studies by Dimond and Brouwers suggested that piracetam could facilitate transfer of information across the callosal pathways and hence is a “superconnector” drug (87). Numerous studies with neurologically normal and dyslexic adults indicated that the drug could enhance verbal learning. These studies were reviewed by Wilshire (88). An early report on reading involved 16 dyslexic men matched with 14 student volunteers for a 21-day trial of piracetam. It was found, using a double-blind crossover technique, that

the dyslexic men significantly increased their verbal learning by approximately double that of control students (89). Early uncontrolled trials with a broader group of LDs were followed by a series of systematic studies of learning, memory, and reading (90).

Studies of 60 dyslexic boys 8 to 14 years old, who were carefully selected for exclusion of intellectual, sensory, psychiatric, and neurologic impairment and educational deprivation, were conducted to determine the efficacy of piracetam, over a 12-week period, in improving reading and other related skills (91). There were no changes at the end of 12 weeks to distinguish the groups in accuracy or comprehension of prose reading. Short-term memory gains, however, were recorded for the treated group on two different tests, digit span, and a test (Neimark) of immediate and delayed recall. The mean digit span scaled score for the entire group was 1 SD below their mean IQ. Considering only the performance of children whose digit span scaled scores were 1 SD or below the mean (7 or less), the treated group made a significant gain at the end of 12 weeks. On the Neimark test, the treated group was significantly superior to the untreated group on first trial learning, and they also lost significantly fewer object names after a delay. Improved retrieval from long-term storage could be demonstrated for the treated group on the rapid automatized naming test. Although there was no significant difference between the groups at screening, the treated group was significantly faster on letter naming at the end of the drug trial. The treated group also improved their single word reading on the Wide Range Achievement Test (WRAT).

After previous research suggested that piracetam improves performance on tasks associated with the left hemisphere, a 12-week, double-blind, placebo-controlled study of developmental dyslexics was conducted. Six study sites treated 257 dyslexic boys between the ages of 8 and 13 years who were significantly below their potential in reading performance. The children were of at least normal intelligence, had normal findings on audiologic, ophthalmologic, neurologic, and physical examination, and were neither educationally deprived nor emotionally disturbed. Piracetam was found to be well tolerated in this study population. Children treated with piracetam showed improvements in reading speed. No other effects on reading were observed. In addition, improvement in auditory sequential short-term memory was observed in those piracetam-treated patients who showed relatively poor memory at baseline (92).

Piracetam was given in a 3,300-mg daily dose to half of a group of 55 dyslexic boys aged 8 to 13 years, in a 12-week, double-blind, placebo-controlled study. The other half of the subjects received placebo. Compared with the placebo control group, the boys treated with piracetam did not show statistically significant improvements above their baseline scores on measures of perception, memory, language, reading accuracy or comprehension, or writing accuracy. However, reading speed and numbers of words written in a timed

period were significantly enhanced in subjects treated with piracetam as compared with placebo. Effective reading and writing ability, taking both rate and accuracy into consideration, were also significantly improved in the piracetam group as compared with the placebo treatment group (93).

Two hundred twenty-five dyslexic children between the ages of 7 years 6 months and 12 years 11 months whose reading skills were significantly below their intellectual capacity were enrolled in a multicenter, 36-week, double-blind, placebo-controlled study. Piracetam-treated children showed significant improvements in reading ability (Gray Oral Reading Test) and reading comprehension (Gilmore Oral Reading Test). Treatment effects were evident after 12 weeks and were sustained for the total period (36 weeks) (94).

The neurophysiologic mechanisms involved in the effects of piracetam were examined in studies using event-related potentials. Eight- to 12-year-old dyslexic boys were randomly assigned to 3.3 g of piracetam or matching placebo per day in two divided doses over a 12-week period. Children performed a vigilance task in which they pressed a key when two alphabetic letters or shapes occurred in sequence. Event-related potentials to letters and shapes, for active and passive responses, were recorded at the vertex and left and right parietal areas of the scalp. Performance measures included letter and form hits, misses, commission errors, and reaction times. Piracetam increased the amplitude of a late positive component (believed to correspond to P300) at the vertex for letter hits. Piracetam also increased the latency of this component in both hemispheres, but only for active responses (letter hits) in the left hemisphere and passive responses (correct rejections and misses) in the right hemisphere. Reaction time to letter hits was significantly correlated with the latency of the P300 component, a finding suggesting that letters created increased effort or attentional demand on the subjects compared with forms. An early event-related potential component (P225) also showed increased amplitude to piracetam in both hemispheres, and effects were limited to form hits. These effects were thought possibly to reflect slow negative potentials arising from stimulus anticipation in the CNV-like paradigm. The results were cautiously interpreted as indicating a facilitation of verbal processing mechanisms responsible for analyzing the verbal significance of visual stimuli (95).

In a subsequent study, 29 dyslexic children (aged 7 to 12 years) were assigned to piracetam or matching placebo for 36 weeks. Event-related potentials were obtained at the end of treatment from a vigilance paradigm that required a response to letter or form matches. The drug group showed a significant advantage in letter hits compared with placebo and a reduced variance in reaction time. The drug increased the amplitude of three factors from a principal components analysis of event-related potentials and was interpreted as increasing a processing negativity when stimuli were letters. Piracetam was interpreted as enhancing feature

analysis and increasing attentional resources among dyslexic children when the stimuli are recognized as having linguistic significance (96). These effects were shown to be dose related in a subsequent study (97).

One negative study examined the interaction of piracetam and tutoring (98). Sixty children with dyslexia (41 boys, 19 girls; ages 9 to 13 years) were enrolled in a 10-week summer tutoring program that emphasized word-building skills. They were randomly and blindly assigned to receive either placebo or piracetam. The children were subtyped as "dysphonetic" or "phonetic" on the basis of scores from tests of phonologic sensitivity and phoneme-grapheme correspondence skills. Of the 53 children who completed the program, 37 were classified as dysphonetic and 16 as phonetic. The phonetic group improved significantly more in word-recognition ability than the dysphonetic group. Overall, the children taking medication did not improve more than the nonmedicated children in any aspect of reading. However, within the medication-treated group, the phonetic subgroup gained most in word recognition.

SUMMARY AND CONCLUSIONS

Significant difficulties continue to bedevil the definition of LD, including problems surrounding various criteria such as an IQ/learning discrepancy or low absolute achievement level. Approaches that define the disorder by resistance to high-quality instruction may be the most valid for purposes of identifying persons with LDs in genetic, neuroimaging, and pharmacologic studies. The high degree of comorbidity with many psychiatric disorders raises further issues for studies requiring a homogeneous symptom pattern, and it seems likely that further advances will require replacing broad clinical patterns with more specific processing deficits based on cognitive neuroscience. Despite these limitations, existing research is encouraging regarding the possibility of precise genetic and neuroanatomic localization of LDs, particularly for RDs. Again, however, subtyping issues at the phenotypic level require elucidation before further progress is likely.

Much of the pharmacologic work has been confounded by the comorbidity of LD with ADHD and other childhood disorders. Evidence generally supports the finding that psychostimulants (e.g., dextroamphetamine and methylphenidate) have positive effects on immediate learning *performance* but less impact on long-term academic gains. Work with nootropic drugs shows intriguing effects on verbal learning, single-word reading, and left-hemisphere processing of alphabetic stimuli. Good controlled trials indicate that piracetam may be a safe and effective enhancer of reading in school-aged children, with gains double the rate expected in seriously impaired readers. LD remains a large public health problem, is significantly undertreated, has devastating lifetime outcomes, and therefore merits greater

research efforts to understand its neurobiology and treatment needs.

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