In H.D. Tobias (Ed.) Focus on Dyslexia Research. Hauppauge, NY: Nova Scientific Publishers, 2004.

FUNCTIONAL BRAIN ORGANIZATION IN DEVELOPMENTAL DYSLEXIA

Gerry Leisman[†]
Robert Melillo[‡]

[†]Department of Psychology
The College of Staten Island of the
City University of New York 10314 USA

[‡]Long Island Integrated Medical
Ronkonkoma, New York USA

Address for Correspondence:
Dr. Gerry Leisman
16 Cortelyou Road Merrick, NY 11566
516-223-2479
516-902-9699 [24-hrs world-wide]
drgersh@yahoo.com

This work was supported in part by a grant-in-aid from the Foundation for Conservative Therapies Research and the Ministry of Science of the State of Israel, and the New York State Department of Health.

ABSTRACT

Left parieto-occipital EEG leads record a frequency spectrum in dyslexics that is consistently different from the spectrum obtained from normals. It is suggested that these effects represent significant differences in the functional organization of these areas. EEG coherence values indicate that normals have significantly greater sharing between hemispheres at symmetrical locations. Dyslexics demonstrate significantly greater sharing within hemisphere than do normals. The data supports developmental dyslexia being a functional hemispheric disconnection syndrome.

FUNCTIONAL BRAIN ORGANIZATION IN DEVELOPMENTAL DYSLEXIA

INTRODUCTION

A definition of developmental dyslexia of the World Federation of Neurology (Crichley, 1973) indicates that it is a difficulty in learning to read despite adequate intelligence and appropriate educational opportunities. Children, most commonly boys, may be bright and articulate and even excel in other areas of achievement, but they show severe delays in learning how to read.

The nature of reading disability has been one of the most difficult and puzzling problems facing psychologists. Reading is a process requiring both linguistic and visual perceptual processing which are abilities normally attributed to control by different cerebral hemispheres (Leisman, 1976; 1978; Leisman & Schwartz, 1976; 1977; Leisman & Ashkenazi, 1980). The development of non-invasive techniques with which to study hemispheric specialization, while yielding considerable knowledge about hemispheric function and organization has, unfortunately provided conflicting knowledge of hemispheric processing in dyslexia.

The literature on cerebral asymmetry and reading disability has almost exclusively concentrated on the poor performance in the left hemispheres of poor readers although there is an understated implication of superior right hemisphere performance by the reading disabled. Marcel and Rajan (1975) among others report that poor readers are less lateralized for verbal material than good readers and showed poor performance in the left hemisphere on word recognition tasks. Neurophysiological studies have made an

association between developmental reading problems and reduced or delayed left hemisphere specialization for language processing (Galaburda, Menard & Rosen, 1994). For example, dyslexics are more likely than normal readers to display symmetry of the planum temporale (Kusch, *et al.*, 1993) and in the posterior regions of the brain across the posterior tip of the *splenium* (Leisman & Ashkenazi, 1980; Tallal & Katz, 1989; Hynd & Symrund-Clikeman, 1989). They are also more likely to display reversed asymmetry in the parietooccipital region (Rosenberger & Hier, 1980; Leisman & Ashkenazi, 1980; Leisman, 2002). It is possible that these findings may indicate a reduction in the normal left hemisphere superiority for the processing of verbal information in dyslexics (Hynd *et al.*, 1990). There is evidence from MRI studies that the reduction in the normal asymmetry of the *planum temporale* is found in adult dyslexics whose chief characteristic was poor phonological processing (Larsen *et al.*, 1990).

Post-mortem examinations have also indicated structural differences between the brains of good and impaired readers. High concentrations of microdysgenesis have been noted in the left temporoparietal regions of dyslexic brains. The concentration is most evidenced in the planum temporale region (Galaburda *et al.*, 1985; Kaufman & Galaburda, 1989; Duane 1989) and is discussed in further detail below. These microdysgeneses seriously impair the normal pattern of architecture of dyslexics and remove the asymmetry normally observed between the enlarged language areas of the left temporoparietal region and the smaller homologous areas of the right hemisphere (Galaburda *et al.*, 1985).

The capacity for language is generally correlated with a significant development in the magnitude of the left temporoparietal region and an attrition of neurons in the right

hemisphere. These neuronal casualties may produce the observed asymmetry between corresponding areas in the left and right hemispheres (Geshwind & Levitsky, 1968). The relative symmetry in the dyslexics' brains might reflect their impaired linguistic development.

On the other hand, Pirozzolo and Rayner (1979) found that good readers make significantly more errors on tachistoscopic word recognition tasks in the right hemisphere when compared to the left hemisphere, but the poor readers do not show such deficit. It is also interesting that there is no significant difference between the overall performances of the two groups. Physiological symmetries observed in dyslexics brain may not be the result of smaller than expected left hemisphere regions but of abnormally large cortical regions in the right hemisphere (Galaburda *et al.,* 1985; Kaufman & Galaburda, 1989). It has been suggested that that this symmetry may be due to the unexpected survival of neurons in the right hemisphere.

Kershner (1977) reported that poor readers demonstrate significantly better right hemisphere performance than gifted children. Others (Marcel & Rajan, 1975) have demonstrated that poor readers are inferior to good readers in left hemisphere performance for linguistic material. In both studies, however, the poor readers are superior to good readers in letter recognition when the stimuli are presented to the right hemisphere. In fact, the right hemisphere superiority of the poor readers is significantly better than the left hemisphere superiority of the good readers.

The process of reading involves the left hemisphere functions of sound analysis and linguistic processing. However, reading also involves the right hemisphere functions of non-linguistic form perception as in the visual discrimination of letters and in the

perception and memory of the total word as a picture (Leisman & Zenhausern, 1982, Leisman & Ashkenazi, 1980) An alternative theoretical view is that dyslexia is a right hemisphere deficit. Yeni-Komshian and her colleagues presented normals and dyslexics with hemi-retinal numbers with dyslexics demonstrating a left visual half-field deficit when compared with normals (Yeni-Komshian *et al.*, 1975). To the extent that learning to read involves gestalt perception and right-hemisphere processing, abnormal right hemisphere processing may also be an instrumental factor in developmental dyslexia. However, the results reported here are based on the responses to digit stimuli. When the verbal form of these digits serve as stimuli, no between-group differences are noted. In fact, poor readers are slightly superior to good readers in the right hemisphere.

An alternative position presented by Sandra Witelson (1976; 1977) is that spatial form perception is bilaterally represented. This she concluded based on a lack of performance asymmetry among dyslexic boys on a dihaptic shapes perception test. This hypothesis was supported by similar differences between dyslexic and normal boys on a spatial task in the visual modality (tachistoscopic presentation of human figures). Again, the lack of left visual field superiority in dyslexic boys suggested to Witelson the bilateral representation of spatial perception and processing in dyslexia.

These studies suggest that not only is there evidence supporting a right hemisphere superiority in poor readers, but this superiority seems to be strongly associated with verbal material. Witelson did not find it with either nonsense shapes or tachistoscopic presentations of human figures. Yeni-Komshian did not find it with digits. Thus the literature seems to show that poor readers can process linguistic material better in the right hemisphere than good readers and this compensates for the superiority of the

good readers in the left hemisphere resulting in no difference in overall performance. Since good and poor readers do differ in reading performance, hemispheric specialization can provide only part of the answers to the nature of reading disability. Reported impairments then, in both right and left hemisphere processing in dyslexics may also be the result of reduced intrahemispheric specialization. Dyslexics may display less differentiation between the hemispheres in terms of the type of processing that they mediate. Neither hemisphere would be in this scenario, dominant for the processing of language (Porac & Coren, 1981; Galaburda *et al.*, 1985).

ERP studies examining interhemispheric differences between good and poor readers in response to auditory linguistic stimuli have reported evidence of greater symmetry in ERP amplitude (Cohen & Breslin, 1984; Brunswick & Rippon, 1994) and latency (Sutton *et al.*, 1986) in poor readers than in controls. These findings may indicate a lesser degree of hemispheric specialization in dyslexics.

HISTORICAL PERSPECTIVES OF CORTICAL ASYMMETRIES OF THE HUMAN BRAIN

One of the first clinicians to notice the existence of human brain morphological asymmetries was Paul Broca, having discovered the left hemisphere's lateralization of language function. This discovery reported by Broca (1865) laid the foundation of the concept of cerebral dominance. Broca noted that, " The hemispheres of the brain are perfectly similar. If cerebral convolutions display some slight and accessory variations from individual to individual, there is none…to be noticeable from one side to another of the encephalon" (Broca, 1865).

Stimulated by Broca's discovery, several works of the late 19th and early 20th Centuries sought to compare the left and right parts of the brain focusing on the respective size or weight of the hemispheres, supporting the so-called "dominance" of the left hemisphere; others found exactly the opposite. The most consistent results were those showing a larger volume the left occipital lobe in normals (Cunningham, 1892; Smith, 1907).

During the early part of the 20th Century, the anatomical approach to brain asymmetry largely fell into oblivion and in 1962, the anatomist Gerhard von Bonin re-opened the subject noting that the morphological differences between the hemispheres were, quite small compared to the astonishing differences in function" (von Bonin, 1962). In 1968, Geschwind and Levitsky published a paper that stimulated the impressive renewal of interest in the domain of cerebral dominance. Geschwind and Levitsky started from an earlier report of Pfeiffer (1936) who studied the anatomical asymmetries of the temporal speech region, the *planum temporale*. The *planum* is a triangular-shaped cortical region located at the upper aspect of the temporal lobe buried in the posterior end of the Sylvian fissure just posterior to the primary auditory cortex or *Heschel's gyrus*. The region is roughly the same as Brodmann's area 22 and includes a unique cytoarchitectonic area named *Tpt* (Galaburda & Sanides, 1980), which bears characteristics of both specific auditory association and parietal higher order association cortices (Melillo & Leisman, 2003).

In autopsy research, Galaburda and his colleagues have been the main contributors to this area of investigation (Galaburda, 1988; 1989; 1993; 1994; 1997; Galaburda & Livingstone, 1993; Galaburda, Menard, & Rosen, 1994; Humphreys,

Kaufmann, & Galaburda, 1990; Livingstone, Rosen, Drislane, & Galaburda, 1991; Rosen, Sherman, & Galaburda, 1993). These researchers have found areas of symmetry and asymmetry in normal brains that differ in individuals with reading disabilities. The autopsied brains of individuals with dyslexia show alterations in the pattern of cerebral asymmetry of the language area with size differences, and minor developmental malformations, which affect the cerebral cortex.

The *planum temporale* as represented in Fig. 1, is an area of the temporal lobe known to be language-relevant in normal controls (Steinmetz & Galaburda, 1991). The *planum temporale* lies on the supratemporal plane deep in the Sylvian fissure and extends from the posterior border of *Heschel's gyrus* to the bifurcation of the Sylvian fissure. It is believed to consist cytoarchitectonically of secondary auditory cortex (Shapleske, Rossell, Woodruff, & David, 1999). The work of Galaburda and colleagues has shown that about two-thirds of normal control brains show an asymmetry; the planum temporale of the left hemisphere is larger that that of the right hemisphere. Between 20 percent and 25 percent of normal control brains show no asymmetry, with the remaining having asymmetry in favor of the right side (Best & Demb, 1999). This asymmetry is thought to be established by 31 weeks of gestation (Chi, Dooling, & Gilles, as cited in Best & Demb, 1999), and Witelson and Pallie (1973) have shown hemispheric asymmetry of the *planum temporale* to be present in fetal brains.

INSERT FIGURE 1 ABOUT HERE

In contrast, the brains of reliably diagnosed cases of developmental dyslexia have shown the absence of ordinary asymmetry; symmetry is the rule in the *planum temporale* of brains of dyslexic subjects studied at autopsy, and increased symmetry is also found in

imaging studies (Best & Demb, 1999; Galaburda, 1993; Leisman & Ashkenazi, 1980). These findings are relevant since individuals with dyslexia have language-processing difficulties, and reading is a language-related task. Therefore, anatomical differences in one of the language centers of the brain are consistent with the functional deficits of dyslexia.

Because abnormal auditory processing has been demonstrated in individuals with dyslexia, accompanying anatomical abnormalities in the auditory system have also been the focus of autopsy studies, specifically in the *medial geniculate nuclei* (*MGN*), which are part of the metathalamus and lie underneath the *pulvinar*. From the *MGN*, fibers of the acoustic radiation pass to the auditory areas in the temporal lobes. Normal controls show no asymmetry of this area, but the brains of individuals with dyslexia show that the left side MGN neurons are significantly smaller than those on the right side. In addition, there are more small neurons and fewer large neurons in the left *MGN* in individuals with dyslexia compared to controls (Galaburda & Livingstone, 1993; Galaburda *et al.*, 1994). These findings are of particular relevance in view of the left hemisphere-based phonological defect in individuals with dyslexia (Tallal, Miller, & Fitch, 1993).

Neuroanantomical abnormalities in the magnocellular visual pathway have been reported (Galaburda & Livingstone, 1993), and these have been postulated to underlie functioning of the transient visual system in individuals with reading disabilities (Iovino, Fletcher, Breitmeyer, & Foorman, 1998). Jenner, Rosen, and Galaburda (1999) concluded that there is a neuronal size difference in the primary visual cortex in dyslexic brains, which is another anomalous expression of cerebral asymmetry (similar to that of the *planum temporale*) which, in their view, represents abnormal circuits involved in reading.

In addition to the asymmetries anomaly, autopsy studies have also revealed multiple focal areas of malformation of the cerebral cortex located in the language-relevant perisylvian regions (Galaburda, 1989).

The perisylvian cortices found to be affected by the minor malformations include the following: the frontal cortex (both in the region of and anterior to Broca's area), the parietal *operculum*, the inferior parietal lobule, and the temporal gyrus. Studies have shown that when scarring was dated according to the stages of brain development, it was determined that the abnormality in development had occurred sometime between the end of pregnancy and the end of the second year of life (Galaburda, 1989; Humphreys *et al.*, 1990). These findings have been related to experimental animal research. According to Galaburda, symmetry may represent the absence of necessary developmental "pruning" of neural networks, which is required for specific functions such as language. In other words, the pruning, which takes place in normal controls, does not take place in individuals with dyslexia (Galaburda, 1989, 1994, 1997), thereby resulting in atypical brain structures, which are associated with language-related functions.

NEUROPSYCHOLOGICAL STUDIES

Neuropsychological investigations of learning disabilities have been based on psychometric testing of a variety of cognitive, sensory, motor and behavioral/emotional functions. These functions have been correlated with other types of measures of brain structure and function. This research, therefore, has provided a greater understanding of the neuropsychological profile of individuals with learning disabilities and indirect evidence of underlying cerebral dysfunction. Within the neuropsychological literature, considerable attention has been focused on problems with either the acquisition of

reading (developmental dyslexia) or math (dyscalculia) skills. The vast majority have focused on reading disabilities.

Deficient phonological awareness is now viewed as a primary problem in developmental dyslexia (Eden, Stein, Wood, & Wood, 1993; Heilman, Voeller, & Alexander, 1996; Ogden, 1996; Slaghuis, Lovegrove, & Davidson, 1993; Slaghuis, Twell, & Kingston, 1996). Evidence from neuroimaging (fMRI, PET, and SPECT scans) and electrophysiological studies have shown that the brains of those with reading disabilities respond differently from those of control subjects, particularly on tasks involving phonological awareness. Weaknesses in the activation of motor articulatory gestures may account for the difficulty in grapheme-to-phoneme conversion, which in turn impairs the development of phonological awareness (Heilman *et al.,* 1996). Dysfunctions of the central auditory system (Katz & Smith, 1991) and temporal information processing deficits in both the auditory and visual modalities (Bakker, 1992; Eden, Stein, Wood, & Wood, 1995a) have also been identified. Independent deficits in speech and non-speech discriminative capacity have been reported as a significant factor in reading disabilities (Studdert-Kennedy & Mody, 1995). The critical work of Tallal, Miller, and Fitch (1993) has provided evidence of a basic temporal processing impairment in language-impaired children that affects speech perception and production and is thought to result in these phonological processing deficits. Visiospatial deficits have also been reported in a number of studies (Curley & Ginard, 1990; Eden *et al.*, 1993; 1995a; Eden, Stein, Wood, & Wood, 1995b; Lovegrove, 1993; Slaghuis *et al.*, 1993,1996).

Irregular neurophysiological dynamics of the visual system may account for the random omissions and insertions of individuals with dyslexia during the reading process (Been, 1994). Differences in the control of saccadic eye movements have been found between individuals with dyslexia and controls (Lennerstrand, Ygge, & Jacobsson, 1993). A slow rate of processing of low spatial frequency information in the magnocellular channel of the lateral geniculate nucleus has been proposed as one deficiency accounting for some reading disabilities (Chase, 1996; Chase & Jenner, 1993). These results are consistent with the neuroanatomical findings. In the normal reader, the magnocellular pathway processes information more rapidly than the parvocellular route, providing the cortical maps with the global pattern information before information about the finer visual details arrives via the parvo pathway. When low spatial frequencies are processed too slowly, the ability to make rapid visual discriminations and to establish internal representations of letters and grapheme clusters in lexical memory is critically affected. This low spatial frequency deficit hypothesis has been supported by various studies (Chase, 1996; Chase & Jenner, 1993; Livingstone, 1993; Stein, 1994, 1996). It has been speculated that abnormality of the magnocellular system is not limited to the visual modality, but is generalized, affecting the auditory, somesthetic, and motor systems (Stein, 1996).

Numerous studies have attempted to identify the neurological basis of learning disabilities in terms of left–versus right–hemisphere dysfunction. Adult strokes were found to affect cognitive abilities such as reasoning, perceptual speed and memory clusters, scholastic aptitude, written language (Aram & Ekelman, 1988), reading, language or verbal learning (Aram, Gillespie, & Yamashita, 1990; Eden *et al.*, 1993;

Leavell & Lewandowski, 1990), and arithmetic processing (Ashcraft, Yamashita, & Aram, 1992). It is hypothesized that, as a result of genetic or epigenetic hormonal and/or immunological factors, the cortical language areas are disturbed in their development through migration disorders and abnormal asymmetry, such that normal left hemisphere dominance does not develop, resulting in dyslexia in some children (Njiokiktjien, 1994).

Several subtypes of reading disabilities have been reported (Boder, 1971; Doehring, 1978; Doehring & Hoshko, 1977; Doehring, Trites, Patel, & Fiedorowicz, 1981; Fiedorowicz, 1986; Fiedorowicz & Trites, 1991; Trites & Fiedorowicz, 1976). Research has shown that the locus of an abnormality in the brain is significant, in that, abnormalities in different areas of the brain relate to different reading problems. Therefore, the reason that one individual has difficulty reading may not be the same reason as another individual.

Not only have different subtypes of reading disabilities been identified, but also different learning disabilities, including the nonverbal learning disability (NLD) subtype (Gross-Tsur, Shalev, Manor, & Amir, 1995; Harnadek & Rourke, 1994; Rourke & Fuerst, 1992, 1995, 1996; Spafford & Grosser, 1993). Individuals with nonverbal learning disabilities typically have well-developed auditory perception (including phonological awareness) and simple motor skills, but have primary neuropsychological deficits involving visual perception, tactile perception, and complex psychomotor skills and psycho-social functioning, as well as difficulties in processing novel information (Rourke & Fuerst, 1992, 1995, 1996; Tranel *et al.*, 1987). This pattern of strengths and deficits has now been identified in individuals with a wide variety of congenital and developmental

disorders and is associated with diffuse brain dysfunction, leading some researchers to speculate that it is characteristic of white matter disease or dysfunction (Rourke, 1995). Some specific areas of dysfunction have been identified in association with developmental dyslexia, namely, frontal lobe dysfunction (Heilman *et al.*, 1996), underlying immaturity in the myelination within the central nervous system (Condor, Anderson, & Sailing, 1995), left temporal lobe dysfunction (Cohen, Town, & Buff, 1988), and cerebellar impairment (Fawcett, Nicholson, & Dean, 1996). The attentional problems associated with some cases of learning disabilities appear to have a widely distributed neurobiological basis ranging from the brainstem reticular activating system to the basal ganglia and on into the frontal cortex (Bakker, 1992).

FINDINGS FROM STRUCTURAL NEUROIMAGING TECHNIQUES

MRI (magnetic resonance imaging) studies have substantiated the findings of autopsy studies; namely, individuals with dyslexia do not have the asymmetry or the same patterns of asymmetry of brain structures that is evident in individuals without dyslexia. A number of investigators have demonstrated a high incidence of symmetry in the temporal lobe in individuals with dyslexia. (Best & Demb, 1999; Hugdahl *et al.*, 1998; Kushch *et al.*, 1993; Leonard *et al.*, 1993; Logan, 1996; Rumsey *et al.*, 1996; Schultz *et al.*, 1994). Duara *et al*. (1991) and Larsen, Høien, Lundberg, and Ødegaard (1990) showed a reversal of the normal leftward asymmetry in the region of the brain involving the angular gyrus in the parietal lobe. Dalby, Elbro, and Stodkilde-Jorgensen (1998) demonstrated symmetry or rightward asymmetry in the temporal lobes (lateral to insula) of the dyslexics in their study. Further, the absence of normal left asymmetry was found to correlate with degraded reading skills and phonemic analysis skills.

Logan (1996) reported that individuals with dyslexia had significantly shorter *insula* regions bilaterally than controls. Hynd and colleagues (1995) identified asymmetries in the *genu* of the corpus callosum of individuals with dyslexia and positively correlated both the *genu* and *splenium* with reading performance. This supports the hypothesis that, for some individuals with dyslexia, difficulty in reading may be associated with deficient interhemispheric transfer. Hynd and his colleagues (Hynd, Marshall, & Semrud-Clikeman, 1991) also reported shorter *insula* length bilaterally and asymmetrical frontal regions in individuals with dyslexia. The latter was related to poorer passage comprehension. Best and Demb (1999) examined the relationship between a deficit in the magnocellular visual pathway and *planum temporale* symmetry. They concluded that these two neurological markers for dyslexia were independent.

There has been substantial replication of findings, particularly with respect to the *planum temporale*. On the other hand, there have been conflicting reports regarding other areas, especially the corpus callosum (Hynd *et al.,* 1995 versus Larsen, Höien, & Ødegaard, 1992). Methodological and sampling differences, such as slice thickness, orientation and position, and partial volume effects may account for this variability. In a review of the literature on the planum temporale, Shapleske *et al*. (1999) summarized the methodological concerns in operationalizing consistent criteria for anatomical boundaries when measuring the planum temporale and the need to use standardized measures of assessment and operationalized diagnostic criteria. They concluded that dyslexics may show reduced asymmetry of the planum temporale, but studies have been confounded by comorbidity. Njiokiktjien, de Sonneville, and Vaal (1994) concluded that, despite a multitude of developmental factors influencing the final size, total corpus callosal size is

implicated in reading disabilities. In a study by Robichon and Habib (1998), in which methods that are more rigid were applied, MRI and neuropsychological findings of dyslexic adults were correlated and compared with normal controls. Different morphometric characteristics were positively correlated with the degree of impairment of phonological abilities. The corpus callosum of the dyslexic group was more circular in shape and thicker, and the midsaggital surface was larger, particularly in the isthmus.

Pennington (1999) summarized the findings of a structural MRI study of brain size differences in dyslexia, reportedly the largest dyslexic sample yet studied, in which he and his colleagues investigated 75 individuals with dyslexia and 22 controls involving twin pairs. The *insula* was significantly smaller, the posterior portion of the corpus callosum (isthmus and *splenium*) was marginally smaller, and the callosal thickness was smaller. Based on a preliminary test within twin pairs discordant for dyslexia, it was suggested that these size differences in the insular and posterior corpus callosum were not specific to dyslexia, but rather represented a neuroanatomical difference in dyslexic families. Further, it was concluded that genetic influences play a dominant role in individual differences in brain size. The importance of controlling variance due to gender, age, IQ, and Attention Deficit/Hyperactivity Disorder was emphasized by Pennington. He did not find clear evidence of differences in the corpus callosum in a reading-disabled group. In view of the inconsistencies, more research to clarify the findings was recommended.

Functional neuroimaging techniques, including PET (positron emission tomography), rCBF (regional cerebral blood flow), fMRI (functional magnetic resonance imaging), and SPECT (single photon emission computed tomography) have added a

unique dimension to the study of the neurobiological basis of learning disabilities, by measuring the activity in the brain of individuals with dyslexia while they are engaged in reading tasks. These are therefore *in vivo* studies of the brain. Using this method, atypical brain activity in specific areas has been identified and directly correlated with developmental language disorders and reading subskill functions.

Potentially confounding variables are associated with functional neuroimaging investigations, especially when studying young children. These include such factors as the effects of task difficulty in relation to developmental level of the subjects, necessity to account for changes in brain size and shape with development, as well as technical difficulties in providing a suitable testing environment for children. Regardless, impressive data have been collected. A significant difference in cerebral blood flow in children diagnosed with dyslexia has been reported (Flowers, Wood, & Naylor, 1991; Flowers, 1993). In these studies, controls showed activation to the left superotemporal region corresponding to Wernicke's area, whereas the reading-disabled group showed activation of the immediately posterior temporoparietal region. Interestingly, the cerebral blood flow patterns of remediated subjects with dyslexia did not differ from those of subjects with persistent impairment. Further, an association between dyslexia and phonological awareness deficits has been demonstrated (Flowers, 1993; Paulesu *et al.*, 1996).

Functional imaging studies have shown gender differences in patterns of brain activation during phonological processing and that separation of males and females is required in future studies (Lambe, 1999). There have been a number of findings of differences in individuals with reading disabilities. Hagman and colleagues (1992)

reported significant differences in the medial temporal lobe with PET studies, and Logan (1996) indicated that individuals with dyslexia had significantly higher glucose metabolism in the medial left temporal lobe and a failure of activation of the left temporoparietal cortex.

In a PET scan study, Horwitz, Rumsey, and Donohue (1998) demonstrated that in normal adult readers there was a correlation of regional cerebral blood flow in the left angular gyrus and flow in the extrastriatal, occipital, and temporal lobe regions during single word reading. In men with dyslexia, the left angular gyrus was functionally disconnected from these areas. Gross-Glenn and associates (1991) found regional metabolic activity measured with PET scan to be similar in individuals with dyslexia and those without dyslexia, reflecting that reading depends on neural activity in a widely distributed set of specific brain regions. There were also some differences concentrated in the occipital and frontal lobe regions. In contrast to controls, individuals with dyslexia showed little asymmetry. These findings correspond well with the reduced structural posterior asymmetry observed in the CT scan and postmortem studies. Prefrontal cortex activity was also symmetrical in individuals with dyslexia versus asymmetrical in normal controls. Higher metabolic activity (local utilization rate for glucose) in the lingual area (inferior occipital regions bilaterally) was reported by Lou (1992) with PET studies, and a SPECT (single photon emission computed tomography) scan showed striatal regions as hypoperfused and, by inference, under-functioning.

Nicolson and colleagues (1999) demonstrated a significant difference in rCBF activation in the cerebellum during motor tasks in a group of dyslexic adults. It was concluded that cerebellar deficits alone could not account for the reading disability but

adversely affected acquisition of automatic, overlearned skills. An fMRI investigation supported the autopsy findings of abnormalities in the magnocellular pathway and implied a strong relationship between visual motion perception and reading (Demb, Boynton, & Heeger, 1998).

Rumsey (1996) reviewed functional neuroimaging studies of individuals with dyslexia compared to controls. All of the studies reported some differences in brain activity, and the differences were found in multiple brain sites, including: Wernicke's area, the temporoparietal junction, the lingual gyrus, the left *insula* (Paulesu *et al.,* 1996), posterior perisylvian area (Rumsey *et al.*, 1997), and ventral visual pathway (Eden *et al.*, 1996).

Pennington (1999) has cautioned that the interpretation of these functional neuroimaging studies remains ambiguous, since the identified differences in brain activity could be secondary to dyslexia, or dyslexia could be secondary to the brain activity differences, or both dyslexia and the activity difference could be caused by a third factor. Pennington considered that differences in brain activation may be an indication of greater effort by the dyslexic group, may represent a compensatory strategy, or may reflect impaired processing capacity. Therefore, establishing causal links with this methodology is difficult. Nevertheless, it is apparent that there are significant differences in brain activity in individuals with dyslexia in comparison to normal readers.

Studies using functional imaging techniques including PET and functional MR imaging (fMRI) have examined differences in cortical activation between dyslexic and normal readers (for a complete review, *cf.* Demb *et al.,* 1999). Because phonological processing difficulties are prominent in dyslexia, a number of studies have examined

activation on tasks requiring phonological processing (such as rhyme judgments). A consistent finding of these studies has been decreased activation of the left temporo-parietal region in dyslexic individuals compared to normal readers. Decreased activation in the left temporo-parietal cortex of adult dyslexics during phonological processing was first found by Rumsey *et al*. (1992) using PET, and has subsequently been replicated by other groups using both PET (Paulesu *et al.,* 1996) and fMRI (Shaywitz *et al.,* 1998). Temple and associates (Temple *et al.,* 2001) recently found a similar decrease in dyslexic children performing a rhyme judgment task. Another PET study found decreased activation in this region during reading of both exception words and pseudowords, as well as during phonological and lexical decision tasks (Rumsey *et al*., 1997). Further analysis of this dataset found that the level of blood flow in the angular gyrus region was significantly correlated with reading skill in normal subjects but inversely correlated with reading skill in dyslexic readers (Rumsey *et al.,* 1999). Together, these results provide strong support for functional differences in the angular gyrus in developmental dyslexia.

FUNCTIONAL CONNECTIVITY IN DYSLEXIA

The abnormal activation of temporoparietal cortex in developmental dyslexia observed using functional imaging could reflect localized malfunction of the cortical structures in this region. Alternatively, this abnormal activation could reflect a derangement of the inputs from other cortical regions into the angular gyrus, that is, a functional disconnection of the angular gyrus. This question has been examined using techniques that measure the correlation of imaging signals between different brain regions, known as functional connectivity (Friston, 1994). Functional connectivity of the angular gyrus was first examined in dyslexic adults by Horwitz, Rumsey, and Donohue

(1998), who re-analyzed the PET data from Rumsey *et al*. (1997) using correlational techniques. During reading of both pseudowords and exception words, normal readers exhibited significant correlations between cerebral blood flow in the angular gyrus and a number of other brain areas including occipital, inferior temporal, and cerebellar regions. In addition, significant correlation between blood flow in the angular gyrus and inferior frontal cortex was observed during pseudoword reading. In dyslexic readers, there were no significant correlations between blood flow in angular gyrus and any of the other regions observed in normal readers; in a direct comparison, the correlation between angular gyrus and a number of frontal, temporal, occipital, and cerebellar regions was significantly greater in normal than dyslexic readers. These findings are consistent with the notion that the angular gyrus is functionally disconnected in dyslexia.

One question about the Horwitz *et al*. (1998) finding concerns the degree to which it is task-specific. The finding could reflect a general lack of functional connectivity between the angular gyrus and other cortices, perhaps reflecting some general dysfunction of the angular gyrus. Alternatively, it could reflect a deficit specific to reading or language processing. This question was examined by Pugh *et al*. (2000), who re-examined an fMRI dataset from Shaywitz *et al*. (1998) using functional connectivity analysis. In that study, dyslexic and normal-reading adults performed a set of tasks with varied phonological demands: line orientation, letter case, single letter rhyme, nonword rhyme, and semantic category judgments.

Correlations in fMRI activity during each of these tasks were examined between the angular gyrus and several other regions (primary visual cortex, lateral extrastriate cortex, and Wernicke's area/superior temporal gyrus). This analysis demonstrated that the

deficit in functional connectivity was specific to tasks requiring processing of written words. Whereas activity the left angular gyrus was significantly correlated with all other regions for all tasks in normal readers, this correlation was only significant for dyslexic readers on the letter-case and single-letter rhyme tasks. For both the nonword rhyme and semantic categorization tasks, the correlation was nonsignificant for the dyslexic group. This difference only occurred in the left hemisphere, consistent with previous functional imaging findings. The Pugh *et al*. (2000) results suggest that the breakdown in functional connectivity of the angular gyrus in developmental dyslexia is not a blanket disorder, but rather reflects cognitive demands specific to the processing of written language.

The imaging studies described heretofore have provided strong evidence in favor of functional disconnection of the inferior parietal cortex during reading in dyslexic adults, but they cannot determine the underlying neurobiological mechanisms for this disconnection. Differences in functional connectivity could reflect deficits in the fine timing of neural responses, which is thought to be important for synchronization of neural responses across brain regions (e.g., Roelfsema, Engel, Konig, & Singer, 1997). Given the extensive literature suggesting deficits in the processing of rapidly transient information in dyslexia (reviewed by Farmer & Klein, 1995; Wright, Bowen, & Zecker, 2000), it is plausible (but speculative) that deficits may occur in the fine timing of neural responses in dyslexia. The specificity of the disconnection to tasks involving reading suggests that it does not reflect a basic physiological deficit within the angular gyrus; rather, it is more plausible that task-driven decreases in functional connectivity may reflect deficits in the synchronization of neural processing between the angular gyrus and other cortical regions via white matter tracts.

Given the findings of functional disconnection in dyslexia, the status of white matter in dyslexia is of great interest. However, until very recently it was not possible to non-invasively image the structural integrity of white matter tracts. Although standard T1-weighted and T2-weighted magnetic resonance imaging (MRI) techniques can provide some information about the myelination of white matter (e.g., Paus *et al.,* 1999), they do not provide sufficiently specific information to make inferences about the structural integrity and directional orientation of white matter tracts. However, an MRI technique developed in the last decade now provides the ability to image the microstructure of white matter tracts. Known as diffusion tensor MR imaging (DTI), this technique allows noninvasive mapping of white matter tracts and determination of their structural integrity and coherence.

Diffusion-weighted MR imaging techniques measure the diffusion (on the order of microns) of water molecules in a particular direction (Basser, 1995; Basser, Mattiello, & LeBihan, 1994). DTI takes diffusion-weighted imaging a step further by imaging diffusion in a number of different directions (usually six directions). From these images, one can calculate the diffusion tensor at each voxel, which is a matrix describing the spatial orientation and degree of diffusion; this tensor can be visualized as an ellipsoid, which represents diffusion in a three-dimensional space. From the tensor are then derived the principal eigenvectors (corresponding to the principal axes of the diffusion ellipsoid) and their associated eigenvalues (corresponding to the relative strength of diffusion along each of the principal axes). These values provide a summary description of diffusion in each direction.

An essential concept in understanding the use of DTI in mapping white matter is that of *diffusion anisotropy*. In an unstructured medium (such as a large glass of water), most water molecules (except those very near the walls of the glass) will diffuse isotropically that is, they are equally likely to move in any direction. This corresponds to a diffusion ellipsoid that is a perfect sphere. In a medium with directionally oriented structure, diffusion becomes anisotropic, meaning that diffusion is not equal in all directions. In particular, Moseley and associates (1990) showed that diffusion is anisotropic in the white matter of the brain. The white matter tracts of the brain have highly regular directional structure, with large bundles of axons running in the same direction. In addition, these axons are sheathed in myelin, which repels water and thus prevents diffusion through the walls of the axon. The regular orientation of axons and their myelination leads to diffusion that is much greater along the length of the axon than against the axon walls. DTI can be used to image the major direction of diffusion (corresponding to the principal eigenvector of the diffusion tensor), which provides information about the orientation of axons in each voxel. In addition, one can measure the degree of anisotropy using a measure known as fractional anisotropy (Pierpaoli & Basser, 1996). This measure reflects the strength of the directional orientation of diffusion in each voxel (i.e., the degree to which diffusion occurs in one particular direction).

The use of DTI as a means to measure the orientation of white matter tracts has been validated by comparison to the classic postmortem studies of Dejerine (Makris *et al*., 1997). The location and extent of several major fiber tracts were predicted based upon the Dejerine map, and the DTI data were compared to these predictions based upon the orientation of the primary eigenvector in each voxel. The DTI results closely matched

the predicted locations of each fiber bundle (across regions of interest, 96 percent of the hypothesized fiber tract orientations were consistent with the DTI findings), demonstrating the validity of DTI in determining the orientation of white matter tracts.

It is tempting to attribute differences in anisotropy to myelination, and in fact, there is a strong positive relationship between myelination and diffusion anisotropy. Anisotropy is correlated with myelination as measured using histological markers (Wimberger *et al.*, 1995). In addition, diffusion anisotropy increases with myelination in newborns (Huppi *et al.*, 1998) and young children (Klingberg, Vaidya, Gabrieli, Moseley, & Hedehus, 1999), and anisotropy decreases in regions of demyelination in multiple sclerosis (Werring, Clark, Barker, Thompson, & Miller, 1999). However, there are a number of other biophysical properties that can also influence the degree of anisotropy. This is evident from the fact that diffusion is anisotropic even in unmyelinated white matter (Wimberger *et al.*, 1995), although to a lesser degree than in myelinated white matter. Other factors that may influence anisotropy include axonal packing density, axon size, axon number, and integrity of the cell membrane, and the coherence of axonal orientation. These factors are poorly understood at present, and more basic research is necessary before the biophysical bases of diffusion anisotropy are fully understood.

Each voxel in a DTI study may be as large as 3 cm^3, which corresponds to many thousands of axons per voxel of white matter. Diffusion within that voxel will be determined both by microstructural features of these axons (such as myelination) as well as the coherence of axonal orientation within the voxel. Although it is not possible to directly decompose these aspects of the DTI signal, it is possible to determine the degree

to which orientation is coherent between neighboring voxels, which provides an approximation to the degree of coherence within the voxel. Coherence is determined by measuring the dot product of the diffusional direction of neighboring voxels; to the degree that axons are regularly oriented across voxels, this coherence measure will be larger. Using such a measure, Klingberg and colleagues (1999) found that the frontal white matter in the right hemisphere exhibited more coherent axonal orientation than the left hemisphere, whereas anisotropy differed between children and adults. Although the crossing of multiple fiber tracts cannot be visualized using standard DTI techniques, recently developed methods (known as "supertensor" techniques) allow imaging of multiple fiber tracts within a single voxel, and may provide further knowledge about the relationship between coherence and diffusion anisotropy.

If the disrupted functional connectivity of the angular gyrus in dyslexia reflects white matter disruption, then this disruption should be evident using DTI. In order to investigate this question, Klingberg *et al*. (2000) administered DTI to eleven adults with no history of reading or language problems and six adults with a history of developmental dyslexia. The dyslexic group was significantly impaired on the Woodcock-Johnson Word ID task (mean 87.3 ± 4.4) compared to the normal readers (mean 111 ± 2.6), as well as on the Word Attack test (dyslexic mean 93.7 ± 5.9; normal reader mean 111 ± 4.3). The scores of the dyslexic subjects suggest that they exhibited some degree of compensation for their reading disorders, though all reported continued difficulties in reading.

Diffusion images for each subject were normalized into a standard stereotactic space (after motion correction), and anisotropy maps created from these images were compared statistically between the dyslexic and normal reading groups using SPM. This

analysis found regions in the temporo-parietal white matter bilaterally that exhibited greater anisotropy for the normal readers compared to the dyslexics (*cf*. Fig. 2). There are no corresponding differences found for T1-weighted anatomical images, suggesting that the difference was specific to the diffusion measure. In order to investigate the relationship between white matter structure and reading more directly, all subjects were entered into a whole-brain correlational analysis (without regard to group membership) that identified regions showing significant correlation between anisotropy and scores on the Woodcock-Johnson Word ID test. This analysis identified a region in the left temporo-parietal white matter that overlapped with the left-hemisphere region identified by the group analysis (as shown in Fig. 2). The correlation between reading ability and anisotropy remained significant when effects of age and gender were removed in an analysis of covariance (ANCOVA).

INSERT FIGURE 2 ABOUT HERE

One possible explanation for these findings was that they reflected general intelligence. Anisotropy in the left-hemisphere was correlated with scores on the Matrix Analogies Test (MAT: a test of nonverbal intelligence), providing some evidence for this explanation. In order to examine this issue, Klingberg *et al*. (2000) performed a stepwise regression on anisotropy values using both Word ID and MAT scores as regressors. This analysis found that the correlation between MAT scores and anisotropy was secondary to reading ability: When variance related to Word ID scores was removed there was no remaining correlation between MAT and anisotropy, whereas when variance related to MAT scores was removed there was still significant variance explained by Word ID

scores. These findings clearly showed that the observed relationship between reading ability and white matter structure was not mediated by general intelligence.

The orientation of the white matter tracts involved in reading was investigated by classifying the direction of diffusion in each voxel in terms of one of the three main axes of the brain (anterior-posterior, inferior-superior, or left-right). The group difference in white matter structure appeared in voxels that were primarily oriented in the anteriorposterior direction. This is most consistent with a disruption of long fiber tracts connecting frontal, parietal, and occipital cortices (Makris *et al.,* 1999). Because of the variability of the location of particular fiber tracts across individuals (e.g., Burgel, Schormann, Schleicher, & Zilles, 1999), it is difficult to precisely determine the tract in which this disruption occurred. On the basis of previous maps (Makris *et al.*, 1999; Makris *et al.*, 1997), the disruption is likely to fall within the arcuate fasciculus, superior longitudinal fasciculus, and/or external capsule.

Because the findings of the Klingberg *et al*. (2000) study were purely correlational, it is not possible to establish whether the differences in white matter structure are directly causal in reading ability. The results could reflect epigenetically-determined individual differences in white matter structure that lead to differences in reading ability. Such individual differences could affect any of a number of white-matter factors including the degree of myelination. One particular possibility is that immune system factors could affect the myelination of white-matter tracts. There are a number of immune factors that are known to result in myelin damage and death of *oligodendrocytes* (the glial cells that form myelin in the central nervous system) (Merrill & Scolding, 1999). It must be noted, however, that most developmental demyelinating diseases are

not focal and are associated with long tract signs (such as Babinski signs and increased spasticity).

An association between immune system dysfunction (including autoimmune disorders) and dyslexia was first proposed by Geschwind and Behan (Geschwind & Behan, 1982), but subsequent studies have found mostly negative results (e.g., Gilger, Pennington, Green, Smith, & Smith, 1992; Gilger *et al.,* 1998; Pennington, Smith, Kimberling, Green, & Haith, 1987). At the same time, it bears noting that the most prominent genetic linkage for developmental dyslexia has been localized to the human leukocyte antigen (HLA) region on chromosome 6 (Cardon *et al.,* 1994; Gayan *et al.*, 1999). Genes in this region code for a number of histocompatibility factors, which mediate the immune system's recognition of cells as self or other, and a number of autoimmune disorders (including lupus, rheumatoid arthritis, and Type 1 diabetes) have been linked to HLA in humans. The possibility of immune system mediation of white matter dysfunction is further suggested by the fact that a protein found on the surface of *oligodendrocytes* and myelin sheaths (myelin/oligodendroctye glycoprotein) is coded within the same HLA region that has been linked to dyslexia (Pham-Dinh *et al.,* 1993); however, this is a very large region of the genome and this link remains high speculative. Thus, it is possible that differences in white matter structure between individuals are related to genetic polymorphisms in HLA that have been found by linkage studies, but confirmation of this finding will require a combination of diffusion tensor imaging with genetic linkage studies.

Another possibility is that the disruption of white matter structure is a consequence of cortical malformations. Rosen, Burstein and Galaburda (2000) have

examined the effects of induced cortical malformations in rats, which have similar neuropathological features to the cortical malformations observed in postmortem studies of dyslexic individuals. These malformations result in impairments of the processing of rapidly changing acoustic information (Fitch, Tallal, Brown, & Galaburda, 1994; Herman, Galaburda, Fitch, Carter, & Rosen, 1997), similar to those observed in humans with specific language impairment (Tallal & Piercy, 1973) and dyslexia (Tallal, 1980). Recent work has demonstrated that these cortical malformations result in abnormal connectivity with the thalamus and contralateral hemisphere (Rosen, Burstein, & Galaburda, 2000), suggesting that localized cortical abnormalities could have widespread effects on connectivity. Of particular interest is the fact that similar cortical malformations and perceptual impairments occur spontaneously in autoimmune mice (Sherman, Galaburda, & Geschwind, 1985), which lends plausibility to an immunological basis for the neural deficits in dyslexia.

Although there are several possible avenues to disturbance of white matter structure in dyslexia, it is equally possible that differences in white matter structure could represent the effect rather than the cause of reading ability. For example, they could reflect differential reading experience in adults, since individuals with poor reading skills spend less time reading. Functional imaging studies have demonstrated differences in neural processing of spoken language between literate and illiterate adults (Castro-Caldas, Petersson, Reis, Stone-Elander, & Ingvar, 1998), consistent with changes in function related to acquisition of reading skill, but no similar results have been reported for brain structure. Although there is no evidence for experience-related plasticity in white matter structure, plausible pathways exist for activity-related mediation of

myelination. In particular, the phosphorylation of myelin basic protein (MBP) in *oligodendrocytes* (an important step in CNS myelination) is mediated by nonsynaptic extracellular signals (including nitric oxide and superoxide) that are released during neuronal activity (Atkins & Sweatt, 1999).

In the peripheral nervous system, *Schwann* cells (which are responsible for myelination of peripheral axons) are also sensitive to action potentials in premyelinated axons (Stevens & Fields, 2000). These findings provide indirect support for the possibility that activity-dependent mechanisms could lead to learning-related changes in myelination, but much more knowledge about the molecular neurobiology of myelination is necessary before such a relation can be established.

A large body of research suggests that dyslexic individuals exhibit difficulties with the processing of dynamic sensory information in addition to their problems with phonological processing. Recent work has shown that these impairments of dynamic sensory processing (both auditory and visual) are correlated with reading ability and correlated across modalities (Witton *et al.,* 1998), and it appears that dynamic sensory processing in auditory and visual modalities are correlated with different aspects of reading ability (Booth, Perfetti, MacWhinney, & Hunt, 2000; Talcott *et al.,* 2000). A number of imaging studies have examined neural processing of such signals in dyslexia.

Eden *et al*. (1996) first examined visual motion processing in dyslexia using fMRI. They found that whereas moving visual stimuli resulted in activation of area MT in normal readers, dyslexic readers did not exhibit such activation. This result was extended by Demb, Boynton, and Heeger (Demb, Boynton, & Heeger, 1998), who examined performance on a speed discrimination task in dyslexic and normal readers

using fMRI. Activation in and around area MT differed between dyslexic and normal readers, and was significantly correlated with reading speed. These results are consistent with anatomical evidence for deficits in the magnocellular visual pathway (Livingstone *et al.,* 1991). In the context of white matter disorders, it is of particular interest that area MT is highly myelinated (Tootell & Taylor, 1995), consistent with the need for rapid transmission of neural signals.

Processing of dynamic acoustic stimuli has been examined using fMRI by Temple *et al*. (2000). Normal and dyslexic adults were presented with nonspeech sounds containing either fast or slow frequency transitions (modeled after the formant transitions that distinguish some speech sounds). Normal readers exhibited activation of the left dorsolateral prefrontal cortex for fast versus slow transitions, whereas dyslexics failed to exhibit such activation. In addition, training that resulted in improved dynamic acoustic processing resulted in increased activation in the left prefrontal cortex. Another study using magnetoencephalography (MEG) found that the response of auditory cortex to brief successive acoustic events was impaired in dyslexic individuals (Nagarajan *et al.,* 1999). Together with the findings of the visual motion studies, these results confirm the existence of deficits in transient sensory signal processing across multiple sensory modalities.

It is possible that the disruption of white matter found by Klingberg *et al*. (2000) could relate directly to the disruption of dynamic sensory processing that has been observed in dyslexia. In particular, dysmyelination or reduction of axon size of white matter tracts connecting sensory cortices to higher-level cortex would result in selective disruption of rapid signal transmission. Because Klingberg *et al*. (2000) did not collect

measures of dynamic sensory processing, it is not possible to determine whether white matter structure was directly related to diffusion anisotropy. However, it is unlikely that the white matter disruption found by Klingberg *et al*. (2000) can provide a complete explanation for deficits in dynamic sensory signal processing in dyslexia, since such difficulties have been found on tasks that are likely to rely upon brainstem mechanisms (Dougherty, Cynader, Bjornson, Edgell, & Giaschi, 1998; McAnally & Stein, 1996).

Differences in neural structure have also been found in both the magnocellular components of both medial geniculate (Galaburda *et al.,* 1994) and lateral geniculate (Galaburda *et al.,* 1994) nuclei in the thalamus, consistent with disruption at a subcortical level. These findings suggest that deficits in dynamic sensory processing may reflect more systematic pathology of neural pathways for rapid processing that extends beyond the cerebral cortex and white matter. Further work is necessary to determine how white matter structure is related to dynamic sensory processing.

In a longitudinal study of a group of 414 children, Shaywitz *et al*. (1992) found that the reading skills of dyslexic children fell within a single normal distribution of reading performance, rather than making up a separate distribution at the tail of the normal reading distribution. In particular, Shaywitz and associates found that discrepancy scores (measuring the difference between reading ability and general intelligence) followed a normal distribution, and that the variability of these discrepancy scores over time equaled that predicted by a normal distribution model. On the basis of these data, Shaywitz and colleagues argued that dyslexia represents the far end on a continuum of reading skill, just as hypertension reflects one tail of a continuous distribution of blood pressure. The DTI results of Klingberg *et al*. (2000) are consistent with this notion, and

may provide a structural explanation for some of the variability in reading skill across individuals. In particular, the finding of a significant correlation between reading skill and white matter structure in both normal readers and dyslexics suggests that some continuously variable factor affects both white matter structure and reading ability.

The continuous nature of the white-matter/reading relationship seems on its face to be at odds with the findings of discrete neuropathology in postmortem studies of dyslexics (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Humphreys, Kaufmann, & Galaburda, 1990). However, there are a number of ways to resolve this apparent discrepancy. First, it is possible that both cortical malformations and white matter disturbance are driven by a common continuously-varying factor, but that white matter and gray matter respond differently to this factor. For example, an autoimmune process could result in discrete pathology in the cerebral cortex (Sherman *et al.*, 1985) while resulting in more graded effects on white matter myelination. It is also possible that the patients examined at postmortem by Galaburda and colleagues suffered from language-learning impairments in addition to dyslexia, and that the observed cortical malformations reflect the compound neuropathology related to these disorders in combination. Because there is limited neuropsychological information available about these patients, it is not possible to address this issue on the basis of existing data. Further work is necessary to understand the relationship between cortical and white matter pathologies in dyslexia.

In summary, neuroanatomical investigations have substantiated what had been surmised from the early traditional studies of acquired brain lesions and associated changes in functions and have brought forward new evidence to support the

neurobiological basis of learning disabilities. Advances in neuroimaging have permitted brain dissection "in vivo," a transparent window of brain functions, concurrent with neurological and neuropsychological evaluations. This methodology has supported previous findings and hypotheses while providing new evidence of brain structure/function relationships. Although the neuroanatomical correlates of dyslexia do not answer the question about whether dyslexia is a condition at one extreme in the normal distribution of reading skill (Dalby *et al.,* 1998), the neuroanatomical and neuroimaging studies have provided evidence linking learning disabilities to neurobiological etiology. Electrophysiological investigations, although less isomorphic, have also substantiated this association. Results using diffusion tensor MR imaging have demonstrated a relationship between white matter structure and reading ability in both normal and dyslexic readers. This finding provides a structural substrate for the findings of functional disconnection that have been found by a number of functional imaging and electrophysiological studies.

ELECTROPHYSIOLOGICAL STUDIES

Numerous variations in cortical and subcortical electrophysiological measurement techniques have been employed in the study of brain-behavior relationships of individuals with learning disabilities. Measurement strategies have included auditory, brain stem evoked responses (ABR), EEG/Power spectral analysis, cortical evoked responses (ERPs) and, more recently, magnetoencephalography (MEG). Although the latter is not purely an electrophysiological recording technique it does involve the detection and localization of small magnetic fields associated with intra-cranial electromagnetic activity.

ABR studies have generally not yielded significant data, and there have been methodological weaknesses associated with these studies. With the advent of more powerful computing and statistical procedures, however, quantitative analysis of electroencephalographic recordings has shown promise as an investigative research tool. For example dyslexic children exhibited more energy in the 3-7 Hz band in the parieto-occipital region during rest conditions (Sklar, Hanley, & Simmons, 1972, 1973; Hanley & Sklar, 1976; Leisman & Ashkenazi, 1980; Leisman, 2002)). This finding was replicated in a number of independent studies, but these studies were criticized for methodological reasons, and subsequently, there have been conflicting reports (Fein *et al.,* 1986).

In contrast, significant results have been found in studies using quantitative EEG methods which examined carefully screened subtypes of individuals with learning disabilities while they carried out specific tasks. Dyslexic children with dysphonemic-sequencing problems showed an increase in alpha during a phonemic discrimination task, suggesting relatively poor orientation to the external stimuli. These children also showed a decrease in beta, suggesting differences in information processing in contrast to normal controls. The increased alpha-decreased beta was more evident over the left posterior quadrant, implicating the posterior speech region around Wernicke's area (Ackerman, Dykman, Oglesby, & Newton, 1995; Ortiz, Exp¢sito, Miguel, Martin-Loeches, & Rubia, 1992). Proportionately less left hemisphere 40 Hz activity for a reading-disabled group, in contrast to normal controls or an arithmetic-disabled subgroup, was found, and conversely, the arithmetic-disabled subgroup exhibited proportionately less 40 Hz right-

hemispheric activity than the reading-disabled subgroup during a nonverbal task (Mattson, Sheer, & Fletcher, 1992).

Several recent, well-controlled, cortical evoked potential studies have shown significant differences on the P_3 waveform, with reading-disabled subjects having a longer P_3 and smaller amplitude to the target stimuli when compared with controls (Fawcett *et al.,* 1993; Harter, Anllo-Vento, & Wood, 1989; Harter, Diering, & Wood, 1988; Taylor & Keenan, 1990). A larger amplitude for normal controls versus children with learning disabilities was demonstrated for a negative wave at 450 ms. in response to single words during initial learning and the same words in a subsequent recognition memory test series (Stelmack, Saxe, Noldy-Cullum, Campbell, & Armitage, 1988). Similar results on a lexical task, involving distinguishing word pairs that rhymed or did not rhyme, have been reported (Ackerman, Dykman, & Oglesby, 1994). Using a probe technique, Johnstone *et al*. (1984) concluded that the language-dominant hemisphere was more involved in a reading task. With difficult reading material, reading-disabled groups generated a large bilateral central and parietal decrease in P_{300} as they changed from easy to difficult material.

Although there is some emerging consensus from the ERP literature that phonological awareness is critical in the acquisition of reading and spelling, there remain some fundamental differences as to whether phonological processing problems are problems in their own right or whether they are problems because of a more fundamental sensory information processing difficulty (e.g. a temporal order information processing deficit). For example Schulte-Körne, Deimel, Bartling, & Remschmidt (1998) concluded that dyslexics have a specific phoneme processing deficit. This finding could help to

identify children, at risk, as early as the preschool years. In contrast, Kujala, *et al*. (2000) presented evidence, observed in their sample of adults with dyslexia, which they suggest provides support for a more fundamental temporal information processing deficit.

ERP research has also been used in innovative ways to serve the needs of highly diverse patient populations. For example Byrne, Dywin, and Connolly (1995a) have made a case for its use with highly involved, difficult to assess individuals with cerebral palsy. Connolly, D'Arcy, Newman, and Kemps (in press) present a review of how ERPs have been used in the assessment of individuals with language impairment.

Research using auditory cortical evoked response technology has also yielded significant findings, particularly in identifying phonemic deficits as a significant variable in differentiating reading-disabled students from controls. Molfese and Molfese (1997) recorded neonatal auditory evoked potentials within 36 hours after birth to different sound contrasts. These same children, at follow up, were successfully classified into three language skill levels at 3 and 5 years of age, with 81 percent accuracy. This is a very impressive finding, since other perinatal predictors of later performance, e.g., Apgar score, the Brazelton Neonatal Assessment Scale, and low birth weight, were less effective as predictors of long-term developmental outcome.

Recently, research using MEG has uncovered interesting findings. MEG works on the principle that very weak magnetic fields are detected by means of an array of superconducting sensors. The superconductivity is preserved only at very low temperatures. These sensors are immersed into a helmet-shaped container of liquid helium that is brought close to the head for data collection. Salmelin *et al*. (1996) used whole-head MEG to track the cortical activation sequence during visual word recognition

in individuals with dyslexia and controls. Within 200-400 msec. following stimulus onset, the left temporal lobe, including Wernicke's area, became involved in controls but not in individuals with dyslexia. The individuals with dyslexia initially activated the left inferior frontal cortex (suggesting involvement of Broca's area). Interestingly this area has been reported to be involved when normal subjects are required to perform a silent noun generation task. The authors suggested that individuals with reading impairment, in order to compensate for their underdeveloped phonological skills, try to guess the word from whatever other limited information there may be available to them.

The usefulness of various electrophysiological and magnetoencephalographic measurement techniques is variable and a function of the type of technique employed as well as how well the targeted behavior or cognitive process, under study, has been operationally defined. Although many of the research studies can be criticized for methodological problems, there is no question that the advances made in the measurement of higher cognitive functions over the past two decades have been impressive. Generally, those methodologically sound studies which have examined discrete skills in carefully selected subtypes of people with learning disabilities, have yielded results consistent with neuroanatomical and neuroimaging data. This converging evidence further strengthens the position that learning disabilities have a basis in neurobiology.

EEG COHERENCE ANALYSES

In order to understand how the brain, particularly the cerebral cortex, is involved in complex cognitive processes, it is necessary to develop measures that reflect the degree to

which activity in different cortical areas represents functional linkages. Two areas that receive information from either subcortical generator or another cortical region may be linked not only to those areas but also linked together because of this relationship.

Typically, EEG activity measured from two different electrode sites employing either a common reference (e.g., linked ears) or a bipolar configuration, can be compared by their relative amplitude or power spectra as a function of frequency. These measures represent the degree to which they have a similar amplitude or power (amplitude squared) distribution within the typical range of EEG frequencies (approx. 0.5 - 40 Hz).

Another measure of functional linkage between brain regions is coherence. Electroencephalographic (EEG) coherence has been suggested to be an index of the connectivity of the brain. It represents the coupling between two EEG signals from different brain areas and is mathematically analogous to a cross-correlation in the frequency domain. Coherence provides a quantitative measure of the association between pairs of signals as a function of frequency. The importance of coherence estimates in the study of functional organization of the cortex was first emphasized by Shaw and Ongley (1972). Coherence measures have found a strong foothold in electroencephalographic research, with increasing literature on the use of coherence as a measure of abnormality in clinical medicine (Cantor *et al*. 1982; Flor-Henry *et al.,* 1982; O'Conner *et al*. 1979; Shaw *et al.,* 1977) and as a correlate of cognitive processing (Beaumont *et al.,* 1978; Busk and Galbraith, 1975; Shaw *et al.,* 1977; Thatcher *et al.,* 1983; Tucker *et al.,* 1982).

According to Thatcher (1992), coherence reflects a number of synaptic connections between recording sites and the strength of these connections. Thatcher

(1992) and Nunez (1995) argue that high coherence indicates integration of function while low coherence indicates differentiation of function. Coherence shares some of the characteristics of a correlation coefficient in that it is a value, which varies between 0 and 1. High coherence occurs during epileptic seizures, for example, in 3 Hz wave discharges associated with absence seizures. Coherence is also increased after closed head injury and in mental retardation (Thatcher, 1991). Low coherence can also be a sign of inappropriate brain function, particularly following penetrating wounds of the brain where cortical-cortical connections have been physically severed.

Although a formal understanding of coherence requires complex mathematics, an excellent non-mathematical description of coherence was provided by Shaw (1981). Shaw explained that coherence could be considered as a measure of the degree to which two signals at a given frequency maintain a phase-locked relationship over time. Regardless of the phase angle difference between the signals at a specific frequency, if it is constant, the coherence will be 1.0. If signals have an entirely random phase relationship, coherence will be 0. The degree to which a phase relationship is maintained over time between two signals of the same frequency at two locations in the cortex appears to be a measure of the degree to which they are either functionally linked, or working together to carry out some kind of processing task. As Shaw points out, coherence is independent of the amplitude of the signals over the epochs considered, and dependent on their pattern of fluctuation.

Brain functioning can be indexed by the electroencephalogram (EEG), which measures electrical activity of the brain. The EEG is composed of many cyclic signals of different frequencies, and spectral analysis is often used to quantify the contribution of

these signals. With spectral or Fourier analysis, the signals are transformed from the time domain to the frequency domain, and a number of parameters can be obtained. A widely used parameter is the power spectrum (i.e., the amount of variance explained by each frequency component in the spectrum). However, the association of EEG power with either behavior or cognition has not been unequivocal (Gale and Edwards, 1986; Anokhin and Vogel, 1996). In addition, the neural mechanisms generating the surface EEG remain enigmatic. It would be desirable to use EEG parameters that more closely reflect anatomical and neurophysiological parameters, such as axonal sprouting, synaptogenesis, myelination, and pruning of synaptic connections.

Recent evidence suggests that a second parameter obtained by spectral analysis, EEG coherence, may be used to index such processes (Kaiser and Gruzelier, 1996). EEG coherence is the squared cross-correlation between signals from two scalp locations for each component in the frequency domain. It has been suggested to measure the number of corticocortical connections and synaptic strength of connections between two brain areas (Thatcher *et al.*, 1986, 1987; Thatcher, 1991, 1994a, b). Based on the structural properties of the human cortex Thatcher and colleagues (1986) proposed a "two compartmental" model of EEG coherence. EEG generating cells in the neocortex are either (1) pyramidal cells with long-distance loop connections (e.g., frontooccipital) of an excitatory nature or (2) highly branched stellate cells with only short-distance connections (e.g., intercolumnar) of both an excitatory and an inhibitory nature (Braitenberg, 1978; Szentagothai, 1978). The pyramidal cells act in two compartments: compartment A is composed of the basal dendrites that receive input primarily from the axon collaterals from neighboring or short-distance pyramidal cells, while compartment

B is composed of the apical dendrites of cortical pyramidal cells that receive input primarily from long distance intracortical connections. Short-distance coherence between electrodes for as far as 14 cm apart can be influenced by the short fiber system, while longer-distance coherence is influenced only by the long-distance fiber system, which represent the majority of white matter fibers.

In children, short-distance coherence has been found to be higher for subjects with cognitive dysfunctions compared to controls. Gasser and colleagues (1987) showed that 10- to 13-year-old mildly retarded children had higher coherences than controls. Higher short-distance coherences were also found in dyslectics (Leisman and Ashkenazi, 1980; Leisman, 2002) and in Down's syndrome (Schmid *et al.*, 1992). In a population of normal children, Thatcher *et al.* (1983) showed that a negative correlation exists between full-scale IQ and short-distance coherences. Therefore, low coherence seems to be the most preferred situation. A possible explanation for these findings is that, in a normal brain, selective synaptic pruning leads to less dispersion of neural signals and, thus, lowers short-distance coherences. Intelligence may be reflected in a greater specificity of short-distance corticocortical connections, thus further lowering coherence.

The difference in coherence between adolescents and children suggests that both short- and long-range coherences decrease with increasing cognitive maturation. We chose to study the genetic architecture of EEG coherence, because it has been empirically associated with cognitive abilities and because clear theoretical notions have been put forward to link this trait to structural aspects of the brain. The interpretation of EEG coherence in terms of corticocortical connectivity is based largely on a nonlinear mathematical wave model by Nunez (1981) that attempts to describe the synchronicity

between neural generators in terms of anatomical parameters, such as synaptic delays, conduction velocity, and corticocortical fiber length.

This model has been integrated by Thatcher *et al.* (1986; Thatcher, 1994a; 1994b) with specific knowledge about the structure of the human neocortex. He distinguished a short-distance fiber system, which gradually becomes less important with increasing distance, and a long-distance fiber system. Kaiser and Gruzelier (1996) hypothesized that changes in short-range coherence are associated with changes in synaptic density: further differentiation of local neural circuitry through pruning leads to a smaller dispersion of neural signal and thus increased coherence. Long-range coherence, on the other hand, would be lower if the number of synaptic contacts is smaller, although this may be offset by a larger degree of myelination. In spite of its theoretical elegance, the evidence for the existence of separate compartments influencing coherence is incomplete.

EEG coherence can be regarded as an index for both structural and functional brain characteristics, but can also be influenced by task-related aspects (French and Beaumont, 1984). The structural baseline depends on the anatomical features of the brain, that is, the number and synaptic strength of corticocortical connections. However, the actual "state" of coherence can change according to the demands of the task or the emotional state of the subject.

A further concern in the interpretation in coherence is the confounding by volume conduction. Coherence can be due in part to conductivity through other tissue than axonal fibers, such as skull or blood. Although skull is a poor conductor, blood may serve as a good conductor (Nunez, 1981). Coherence would thus become a function of skull size and blood supply. However, when volume conduction is responsible for coherence

between two scalp locations, phase differences between these signals will be zero. When signals are transported via the much slower medium of myelinated axonal fibers, phase differences will reflect the velocity of this electric transport and will become larger than zero. Phase differences were always nonzero for the intrahemispheric coherences reported here.

In the following section, we will report on the attempt to examine the nature of hemispheric interaction in dyslexia employing electrophysiologic means and to evaluate the frequency distribution and coherence values at a variety of scalp locations while performing a number of tasks. In this study, the power distribution and coherence at different frequencies are evaluated.

MATERIAL AND METHODS

SUBJECTS

Twenty dyslexic between 7 and 10.9 years of age, and (X = 7.6; S.D. = 1.8; 19 boys, 1 girl) were selected. The dyslexic subjects attended the Institute for Learning Development at the Eye Institute of New Jersey. The dyslexics were those whose full-scale WISC-R IQs ranged between 90-124 ($\bar{X}$ =104.23; S.D. =7.54); Verbal I.Q. scores ranged between 96-116 ($\bar{X}$ = 98.28; S.D. = 7.24); Performance I.Q. scores ranged between 89-134 ($\bar{X}$ = 104.41; S.D. = 8.76). Each subject demonstrated one of Boder's (1973) subtypes and had better than 20/30 Snellen acuity as well as no evidence of ocular pathology or eye movement abnormality. None of the subjects demonstrated mental retardation, cerebral palsy, or other overt neurological signs. Each of the subjects was two or more years deficient in reading ability in relation to mental age (on Stanford

Achievement or Spache Reading Tests). In addition, each subject was administered Denkla and Rudel's (1976) tests of rapid automatized naming of colors, objects, numbers, and letters.

A second group of twenty normal subjects was also selected (7 to 11.11 years of age; $\bar{X}$ = 8.2 years; S.D. = 2.3; 16 male, 4 female). Each of the subjects read at grade level or better and demonstrated WISC-R full scale IQs ranging from 90-128 ($\bar{X}$ = 103.9; S.D. = 8.01); verbal range 88-131 ($\bar{X}$ = 101.69; S.D. = 6.98); performance range 84-117 ($\bar{X}$ = 98.47; S.D. = 9.24). None of the subjects demonstrated evidence of overt neurologic, ocular-pathologic, or eye movement disorder. Denkla and Rudel's (1976) tests were administered.

PROCEDURE

EEG was recorded from each of the subjects employing the 10-20 montage and ordinary silver/silver chloride skin electrodes. The data were subjected to and subjected to time series, cross series spectral estimation, and coherence analyses to determine the amount of sharing between two wave trains (Bendat & Piersol, 1971; Leisman & Ashkenazi, 1980).

The EEG activity was recorded under each of the following experimental conditions: rest-eyes closed and rest-eyes open while undergoing continuous performance tests (Leisman, 1973; 1974). Recordings were also obtained as subjects viewed projected items from the Stanford-Binet in which latencies for confrontation naming were also recorded (Leisman & Ashkenazi, 1980) and while subjects were also presented with grade appropriate paragraphs from the Spache Tests (1966) Diagnostic Reading Tests.

The EEG was recorded on an eight channel Grass model 7 polygraph (T.C. = 0.15 Hz. Filters out, 50 μV = 5 mm). The raw EEG was stored on a Hewlett-Packard 1330A instrumentation tape recorder and was simultaneously A-D converted and ultimately processed by BMDX92 and BMD07M programs (Dixon, 1970). The EEG analyses were performed over 20 epochs of 5 sec, each of which were set by means of a pulse delivered by a Digitimer signal generator. The sampling rate was set at 256 samples/sec. The effective bandwidth of what turned out to be the critical P_3-O_1/P_4-O_2 electrode monitored frequencies was 0.5 Hz and the power was computed logarithmically (0db = 0.06 μV^2/Hz) with the 0.05 confidence limit being 0.22 dB. Statistical tests for uncorrelated EEG data were also applied.

For coherences, the *Z*-transformed values of 2.0 corresponded to a coherence of 0.96 with the 0.05 confidence on this scale being approximately 0.4.

The computer program read the power spectral density (PSD) values over frequency bands 0-32 Hz in steps of 1 Hz; computed statistically standardized normal distributions for a frequency spectrum of interest. Then a frequency associated with each PSD value was computed utilizing the following equations:

$$F_k = BW/4 \div (k-1) \times BW/2 \qquad k = 1,2,.... N \tag{1}$$

where: F_k = associated frequency; BW = bandwidth utilized in computation of PSD values. The value BW was obtained from the header record on the PSD tape; N = number of PSD values contained in the data file. The frequency values were computed in a programmed iteration in which k varied from 1 to N in integer steps and computed frequency values were then stored in an array. To determine the amount of power at any

frequency, the input PSD values were converted to power values of volts^2. Computation of power utilized the following equation:

$$P_k = \mathrm{PSD}_k \times \Delta f_k \qquad k = 1,2,.... N \tag{2}$$

where: P_k = power in volts^2; $\mathrm{PSD_k}$ = PSD values in volts^2/unit bandwidth $\Delta f = BW/2$ (Eq. (1)). Following computation of the power values, a subroutine averaged the power values over selected frequency bands in the following way:

$$\bar{P}_k = \sum_{i=1/n}^{m} P_i \qquad k = 1,2,.... L \tag{3}$$

where: P_k = average power in volts^2;

Pi = power values in selected band

i = 1,2,…m

n = number of power values in selected band

L = number of bands selected

The final calculations performed were the standard deviation calculations from 1 to L bands. The following equation was used to calculate the standard deviation of each band:

$$\sigma_k = \sum_{i=1}^{N} P_i^2 - (N \times \bar{P}_k^{\,2}) \qquad \mathrm{k} = 1,2,....\mathrm{L} \tag{4}$$

where: σ_k = standard deviation; P_i = power values in the selected band; N = number of power values in the selected band; P = average power in the selected band.

A standardized normal distribution computation (Bendat & Piersol, 1971) was used to accomplish a test of uncorrelated data:

$$D = \left[Nf\left(\frac{2}{n_1} \div \frac{2}{n_2} \right) \right]^{1/2} \sum_{i=1}^{Nf} \log_{10} \frac{\hat{G}_1(f_i)}{\hat{G}_2(f_i)} \quad (5)$$

where: D = standardized normal distribution; $N = BW/B_e$; BW = bandwidth in Hz (Eq. (1)); B_e = resolution bandwidth (i.e. spectrum of interest) input via program header; n_1 = number of PSD values in the numerator time epoch; n_2 = number of PSD values in the denominator time epoch $\hat{G}_1$ = PSD values in the numerator time epoch; $\hat{G}_2$ = PSD values in the denominator time epoch. The statistic D has a standardized normal distribution, Z. That is, $D = y(0,1) = Z$. The region of acceptance for the hypothesis that $\hat{G}_1(f) = \hat{G}_2(f)$ is $(-Z_{\alpha/2} \leq D \leq Z_{\alpha/2})$ where α is the level of significance of the test.

RESULTS

The program selected the autospectral density pattern over the left parieto-occipital region (P_3-O_1) as the most consistent discriminating feature between dyslexic and normals under the rest-eyes closed condition (F (8,19) = 3.75, $p<0.01$). None of Boder's (1973) clinical subtypes demonstrated any significant difference in EEG spectral data under any condition ($p<0.10$). The dyslexic data were, therefore pooled in this respect.

INSERT TABLE I ABOUT HERE

The analyses provided quantitative data concerning the maximum and average power in the dominant frequencies, their bandwidths, the values of their coherences, and the left-right asymmetries (*cf.* Table I). Dyslexics (Fig. 3) demonstrated greater energy in the 3-7 Hz bands and in the 16-28 Hz bands than did normals with peaks appearing at around 6, 10, 17, and 24 Hz. Normals, on the other hand, demonstrated greater energy in the 9-12 Hz band than did dyslexics with a well developed peak in the alpha band at around 10 Hz. Simple effects and the Neuman-Keuls tests revealed no significant differences between groups by task ($p<0.10$) other than the data obtained under the rest-eyes closed condition at the P_3-O_1 locations. The between groups frequency spectrum differences noted suggest that the functional organization of the parieto-occipital regions is different in dyslexics than in normals.

INSERT FIGURE 3 ABOUT HERE

The coherence values (Table I) demonstrated that the normals have greater shared activity between hemispheres at symmetrical locations whereas dyslexics demonstrate greater coherence *within* the same hemisphere during all tasks, but especially during the rest-eyes closed condition over P_3-0_1 locations (F (8,19) = 3.67, $p<0.01$). The diagonal coherences between hemispheres and sensory cortical areas other than parieto-occipital regions did not significantly differ ($p<0.10$) for or between normals and dyslexics. For normals, the largest coherences occurred between homologous leads over each hemisphere. Intrahemispheric coherences were largest for dyslexics over the left hemisphere under rest-eyes closed conditions, but not for dyslexics. In only two of the twenty dyslexic records was bilateral coherence present, with the coherence at a given frequency being less than that of the background activity.

There were also indications that the spectral EEG differences found between normals and dyslexics persist into adolescence and adulthood although there may be some degree of behavioral improvement (Fig. 4).

INSERT FIGURE 4 ABOUT HERE

While Boder (1973) and Mattis *et al.*, (1975) among others have reported on different forms that dyslexia may manifest, no significant differences were noted between dyslexics subtypes in the spectral EEG data although collectively, the dyslexics were significantly different from the normals.

The left parieto-occipital leads produced a frequency spectrum in the dyslexic, which appears consistently different from the data obtained from normals. This suggests that the functional organization of this area may be different in dyslexics than in normals.

The coherence values indicated that normals had greater shared activity *between* hemispheres at symmetrical locations, but significantly at the P_3-O_1/P_4-O_2 locations and the dyslexics demonstrated greater coherence within the same hemisphere during all tasks, but significantly during the rest-eyes closed situation and at the P_3-O_1 location.

Denkla and Rudel (1976) had indicated dyslexic subjects that they had studies with tests requiring rapid automatized naming of colors, objects, letters, and words demonstrated what they called “below-age expectation signs.” The response latency of these subjects was significantly greater than for either their normal or non-dyslexic learning disabled. Denkla had Rudel had claimed that the automatization deficits that they found were not separable from deficits in visual-verbal association reflecting the “adequacy of specific neuroanatomical connections.”

More specifically, Denkla and Bowen (1973) had indicated that in individuals with left temporal-occipital lobectomies, the direct visual route to automatized word recognition and reading is impaired. These findings along with those of Hanley and Sklar (1976) and others (Leisman, 1978; Leisman & Ashkenazi, 1980; Leisman & Zenhausern, 1982; Witelson, 1976; 1977) implicate inadequate lateralization for the observed language dysfunction. This places the problem of dyslexia in an aphasiological context, with the difficulties manifested on the part of dyslexics in both expressive and receptive language as well as in spatial perception and processing. The right seems to be more autonomous in dyslexics, or perhaps equivalent to the left in some respects. The data become more impressive when taken in the light of Witelson's (1977) thoughts on the equivalence of the two cerebral hemispheres in dyslexia.

One can, therefore, say that normals seem to have greater sharing (perhaps communication) between the two cerebral hemispheres and that dyslexics lack this sharing. One might explain the phenomena in terms of the master-slave relationship between the left and right hemispheres and that, the right is "slaved" to the left with respect to language. Dyslexia may be the result of objection to that slavery.

FIGURE LEGEND

Figure 1. Cortical hemispheric anatomy.

Figure 2. (A) Sagittal projection of the left hemisphere VOI where there was a significant difference in anisotropy between the poor readers and the control group. The contour and the superimposed grid represents the standard anatomical space. AC = anterior commissure; PC = posterior commissure. The VOI had a volume of 960 mm3, and was located within x = (-36 to -26), y = (-50 to -10), z = (0 to 32) mm relative the to anterior commissure. (B & C) Axial slices from an anisotropy image of one control subject. Left hemisphere is to the left in the image. (B) z = 20 mm, and (C) z = 24 mm above the anterior-posterior commissure line. For the gray scale, lighter colors represent higher anisotropy. Green = voxels significant in both the between-group analysis and the Word ID correlation analysis; yellow = voxels significant only in the between-group analysis; blue = voxels significant only in the correlation analysis. The cluster from the correlation analysis had a volume of 670 mm3, of which 52 percent overlapped with the cluster from the between-group comparison. (D and E) Part of the image in Fig. 2B and 2C shown at higher magnification. Shown in red is a two dimensional representation of the primary eigenvector of diffusion within each voxel, which is the main direction of diffusivity and thus can be interpreted as representing the main direction of the axons within a voxel.

Figure 3: Mean values of EEG autospectral density by frequency recorded from P_3-O_1 electrode placements for normal and dyslexic subjects.

Figure 4: EEG autospectral density for normal subject J.R. (aged 8.2 years), dyslexic subject A.P. (aged 18.4 years), dyslexic subject P.T. (aged 7.9 years), and normal subject M.L. (aged 26.7 years), recorded from P_3-O_1 electrode placements.

Table 1. Average frequency (in Hz), power (in dB), left-right asymmetry of power (in dB) between hemisphere and within hemisphere coherence values at P_3-O_1/P_4-O_2 locations for dyslexics and normals.

	Dyslexic					Normal				
S	Freq (Hz)	Power (dB)	L-R (dB)	Bilat. Coher.	W/in Coher.	Freq (Hz)	Power (dB)	L-R (dB)	Bilat. Coher.	W/in Coher.
1	09.2	12	-03	--	1.1	09.2	28	--	--	0.8
2	10.4	21	-04	--	1.8	10.8	24	--	2.4	--
3	11.7	22	10	--	2.4	12.7	18	--	1.9	--
4	09.8	18	04	--	1.6	10.9	20	-4	1.3	--
5	10.8	17	03	--	1.4	08.6	16	--	1.9	--
6	10.6	24	-01	--	0.8	08.9	08	--	1.8	--
7	10.6	28	-05	--	1.5	11.2	11	--	2.4	--
8	11.2	12	-07	--	2.1	11.7	13	-2	1.5	1.8
9	12.0	19	-04	--	1.9	10.0	12	--	1.3	--
10	09.8	14	--	0.7	0.6	10.7	15	-1	1.3	0.9
11	10.8	25	-02	--	1.0	10.6	11	--	1.2	1.4
12	11.7	22	--	1.0	--	12.0	09	--	0.8	1.1
13	08.7	13	-01	--	0.9	11.7	07	--	1.0	--
14	09.0	27	08	--	2.1	08.9	11	--	1.9	--
15	10.7	13	-04	--	2.4	09.5	10	--	1.7	0.6
16	10.3	08	-06	--	1.8	08.8	11	-2	2.1	--
17	09.5	22	-07	--	2.0	08.6	14	--	1.4	--
18	12.2	20	-07	--	1.9	09.3	09	--	1.8	--
19	11.9	09	-01	--	0.9	12.4	12	--	1.9	--
20	08.4	15	-04	--	1.6	11.6	10	--	0.9	--

Figure 1

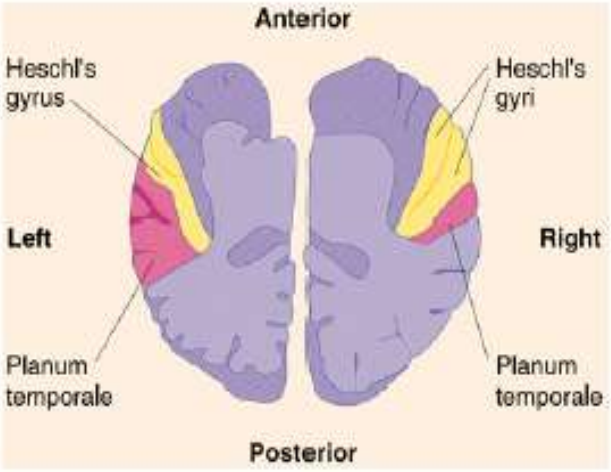

Anterior
Heschl's gyrus
Heschl's gyri
Left
Right
Planum temporale
Planum temporale
Posterior

Figure 2:

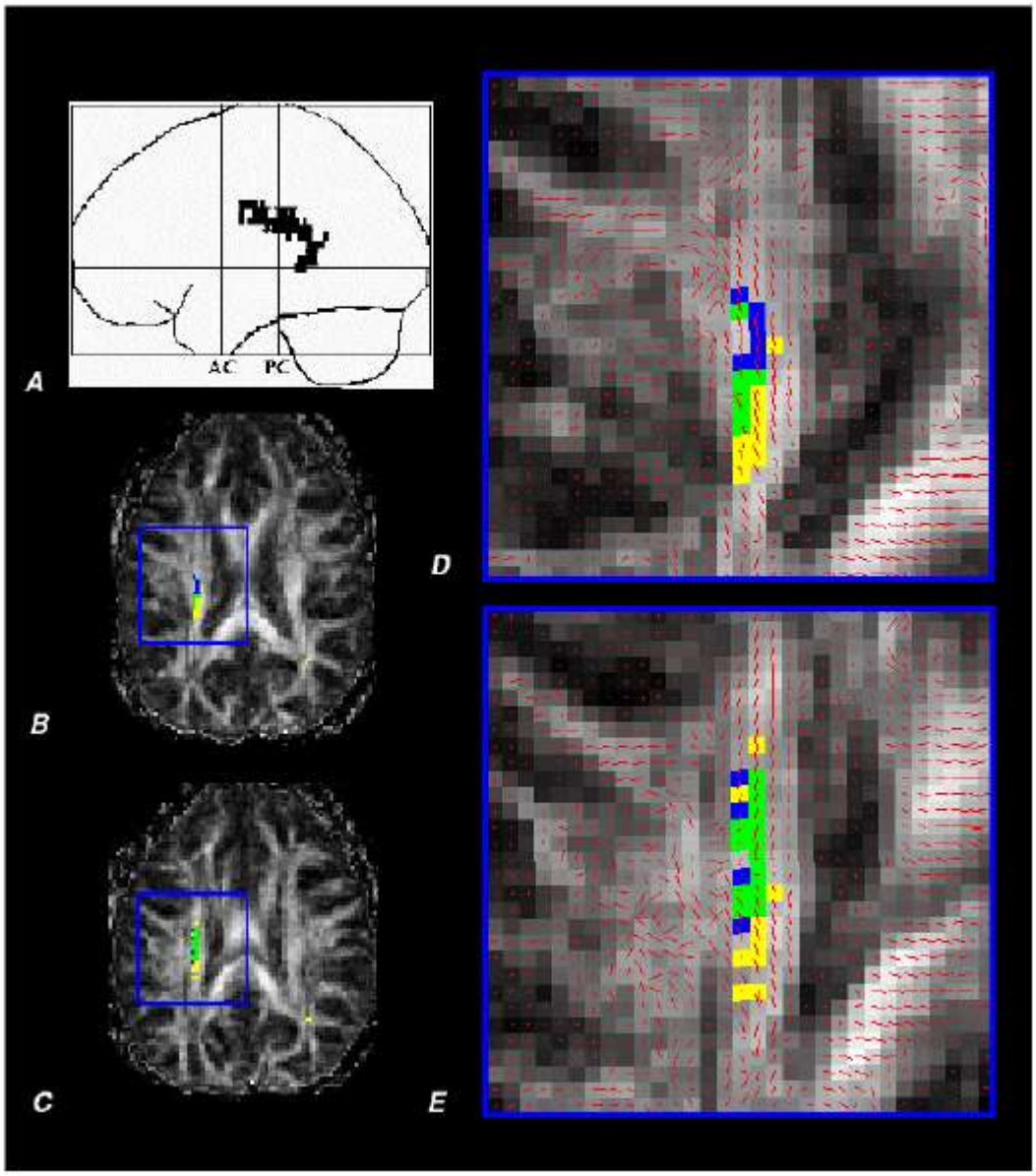


Figure 3:

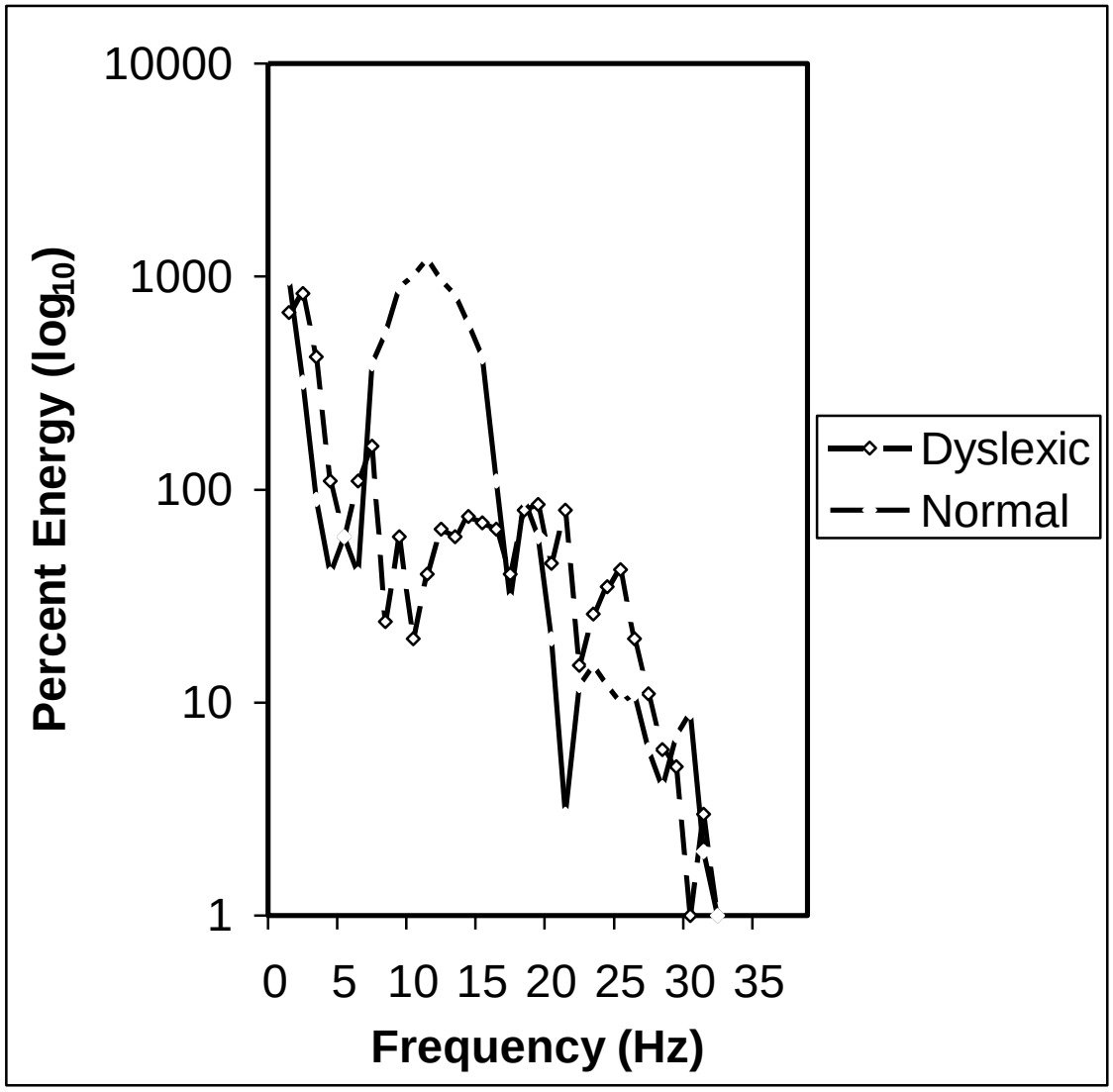
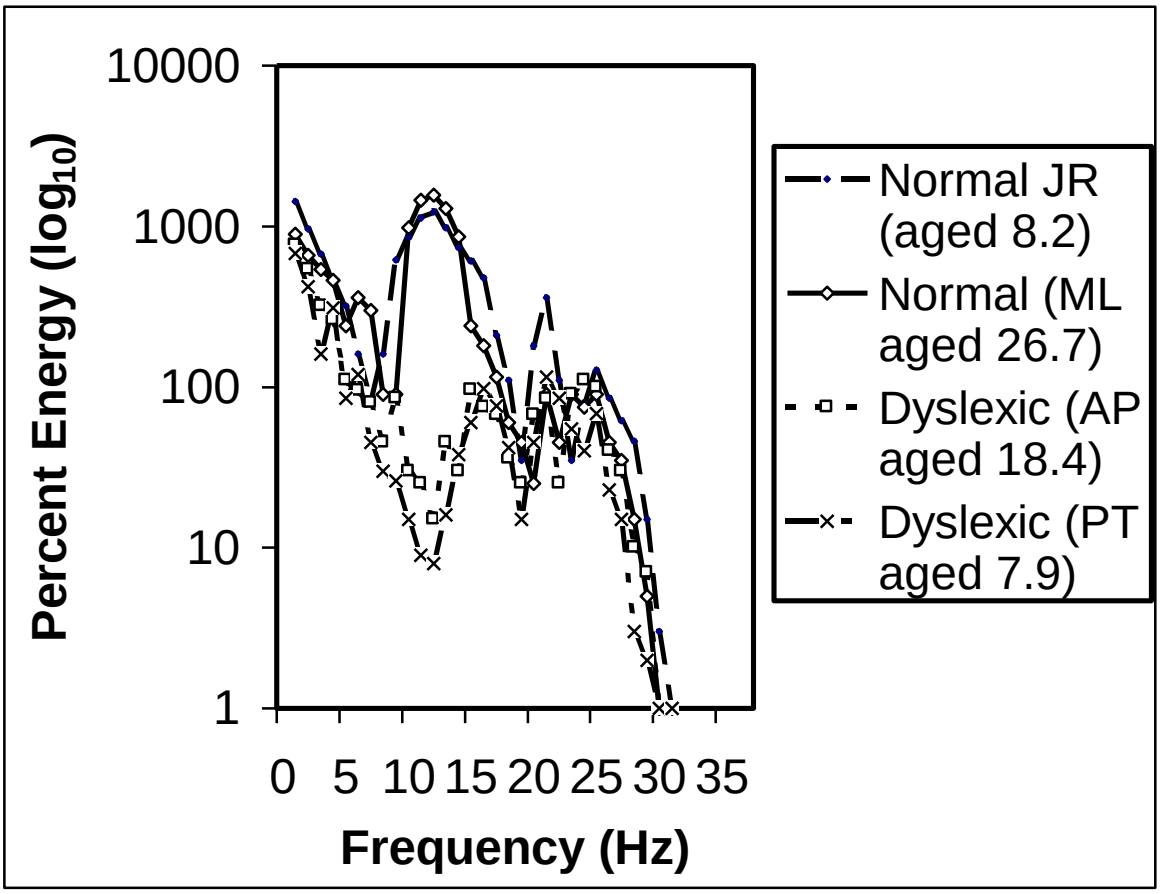

10000
1000
100
10
1
Percent Energy (log10)
0 5 10 15 20 25 30 35
Frequency (Hz)
Dyslexic
Normal

Figure 4:


10000
1000
100
10
1
Percent Energy (log10)
0 5 10 15 20 25 30 35
Frequency (Hz)
Normal JR (aged 8.2)
Normal (ML aged 26.7)
Dyslexic (AP aged 18.4)
Dyslexic (PT aged 7.9)

REFERENCES

Ackerman, P. T., Dykman, R. A., & Oglesby, D. M. (1994). Visual event-related potentials of dyslexic children to rhyming and nonrhyming stimuli. *Journal of Clinical and Experimental Neuropsychology, 16* (1), 138-154.

Ackerman, P. T., Dykman, R. A., Oglesby, D. M., & Newton, J. E. O. (1995). EEG power spectra of dysphonetic and nondysphonetic poor readers. *Brain and Language, 49,* 140-152.

Anokhin, A., and Vogel, F. (1996). EEG alpha rhythm frequency and intelligence in normal adults. *Intelligence.* 23: 1-14.

Ashcraft, M. H., Yamashita, T. S., & Aram, D. M. (1992). Mathematics performance in left and right brain-lesioned children and adolescents. *Brain and Cognition, 19,* 208-252.

Atkins, C. M., & Sweatt, J. D. (1999). Reactive oxygen species mediate activity dependent neuron-glia signaling in output fibers of the hippocampus. *Journal of Neuroscience, 19*(17), 7241-7248.

Bakker, D. J. (1992). Neuropsychological classification and treatment of dyslexia. *Journal of Learning Disabilities, 25(2),* 102-109.

Beaumont, J.G., Mayes, A.R., and Rugg, M.D. (1978) Asymmetry in EEG alpha coherence and poser: effects of task and sex. *Electroencephalography and Clinical Neurophysiology, 45*: 393-401.

Beaumont, J.G., Mayes, A.R., and Rugg, M.D. (1978) Asymmetry in EEG alpha coherence and poser: effects of task and sex. *Electroencephalography and Clinical Neurophysiology, 45*: 393-401.

Been, P. H. (1994). Dyslexia and irregular dynamics of the visual system. In K. P. van den Bos, L. S. Siegel, D. J. Bakker, & D. L. Share (Eds.), *Current directions in dyslexia research*. Lisse, The Netherlands: Swets & Zeitlinger, pp. 91-116.

Bendat, J.S. & Piersol, A.G. (1971). *Measurement and analysis of random data*. New York: NY: Wiley.

Best, M., & Demb, J. B. (1999). Normal planum temporale asymmetry in dyslexics with a magnocellular pathway deficit. *Neuroreport, 10(3),* 607-612.

Boder, E. (1971). Developmental dyslexia: Prevailing diagnostic concepts and a new approach. In H. Myklebust (Ed.), *Progress in learning disabilities.* New York, NY: Grune and Stratton, pp. 293-321.

Boder, E. (1973). Developmental dyslexia: a diagnostic approach based on three atypical reading-spelling patterns. *Developmental Medicine and Child Neurology*, *15*, 683-687.

Bouma, H. & Legein, C. (1980). Dyslexia: a specific recoding deficit? an analysis of response latencies for letters and words in dyslexic and average readers. *Neuropsychologia*, *18*, 285-298.

Booth, J. A., Perfetti, C. A., MacWhinney, B., & Hunt, S. B. (2000). The association of rapid temporal perception with orthographic and phonological processing in children and adults with reading impairment. *Scientific Studies of Reading, 4*, 101-132.

Braitenberg, V. (1978). Cortical architectonics: General and areal. In: M. Brazier, and H. Petsche, H. (Eds.), *Architectonics of the cerebral cortex, New York, NY:* Academic Press, pp. 443-465.

Brunswick, N. & Rippon, G. (1994). Auditory event-related potentials, dichotic listening and handedness as indices of lateralisation in dyslexic and normal readers. *International Journal of Psychophysiology, 18*, 265-275.

Burgel, U., Schormann, T., Schleicher, A., & Zilles, K. (1999). Mapping of histologically identified long fiber tracts in human cerebral hemispheres to the MRI volume of a reference brain: position and spatial variability of the optic radiation. *Neuroimage, 10*(5), 489-499.

Broca, P. (1865). Du siège de la faculté du langage articulé dans l'hémisphère gauche du cerveau. *Bulletin de la Société d''Anthropologie,* tome VI: 377-393.

Busk, J. & Galbraith, G.C. (1975) EEG correlates of visual-motor practice in man. *Electroencephalography and Clinical Neurophysiology*, *38*: 415-422.

Byrne**,** J.M., Dywan, C.A. & Connolly, J.F. (1995). An innovative method to assess the receptive vocabulary of children with cerebral palsy using event related brain potentials. *Journal of Clinical and Experimental Neuropsychology,* 17(1): 9-19.

Cantor, D.S., Thatcher, R.W., McAlaster, R., Lester, M.L. & Horst, R.L. (1982) Topographic distribution of EEG hemispheric coherence related to cognitive functioning in children. *Southeastern Conf. on Human Development,* [abstr].

Cardon, L. R., Smith, S. D., Fulker, D. W., Kimberling, W. J., Pennington, B. F., & DeFries, J. C. (1994). Quantitative trait locus for reading disability on chromosome 6. *Science, 266*(5183), 276-279.

Chase, C. H. (1996). A visual deficit model of developmental dyslexia. In: C. H. Chase, G. D. Rosen, & G. F. Sherman (Eds.), *Developmental dyslexia: Neural, cognitive, and genetic mechanisms.* Baltimore, MD: York Press, pp. 127-156.

Chase, C., & Jenner, A. R. (1993). Magnocellular visual deficits affect temporal processing of dyslexics. *Annals of the New York Academy of Sciences, 682,* 326-329.

Chi, J.G., Dooling, E.C., & Gilles, F.H. (1977). Left-right asymmetries of the temporal speech areas of the human fetus. *Archives of Neurology*, *34*(6): 346-8.

Cohen, J. & Breslin, P.W. (1984). Visual evoked-responses in dyslexic children. *Annals of the New York Academy of Sciences*, *425*, 338-343.

Crichley, M. (1973). *The dyslexic child (2nd edition*). London: Heinemann.

Cohen, M., Town, P., & Buff, A. (1988). Neurodevelopmental differences in confrontational naming in children. *Developmental Neuropsychology, 4(1),* 75-81.

Condor, A., Anderson, V. & Sailing, M. (1995). Do reading disabled children have planning problems? *Developmental Neuropsychology, 11(4),* 485-502.

Cunningham D.J. (1892). *Surface anatomy of the cerebral hemispheres*, London, UK: Williams & Norgate.

Curley, J. F., & Ginard, R. J. (1990). A computerized visual-search task as a measure of cerebral dysfunction and organization. *Perceptual and Motor Skills, 71*, 895-904.

Dalby, M. A., Elbro, C., & Stodkilde-Jorgensen, H. (1998). Temporal lobe asymmetry and dyslexia: an *in vivo* study using MRI. *Brain and Language, 62,* 51-69.

Demb, J. B., Boynton, G. M., & Heeger, D. J. (1998). Functional magnetic resonance imaging of early visual pathways in dyslexia. *Journal of Neuroscience*, *18*(17), 6939-6951.

Demb, J. B., Poldrack, R. A., & Gabrieli, J. D. E. (1999). Functional neuroimaging of word processing in normal and dyslexic readers. In: R. Klein & P. McMullen (Eds.), *Converging methods for understanding reading and dyslexia*. Cambridge, MA: MIT Press, pp. 243-305.

Denkla, M.B. & Bowen, F.P. (1973). Dyslexia after left occipito-temporal lobectomy: a case report. *Cortex*, *9*, 321-328.

Denkla, M.B. & Rudel, R.G. (1976). Rapid "automatized" naming (R.A.N.): dyslexia differentiated from other learning disabilities. *Neuropsychologia*, *14*, 471-479.

Dixon, W. J. (1970). Biomedical computer programs X-series supplement. Berkeley, CA: University of California Press.

Doehring, D. G., (1978). The tangled web of behavioral research on developmental dyslexia. In: A. L. Benton & D. Pearl (Eds.), *Dyslexia: An appraisal of current knowledge*. New York, NY: Oxford University Press, pp. 123-135.

Doehring, D. G., & Hoshko, I. M. (1977). Classification of reading problems by the Q-technique of factor analysis. *Cortex, 13*, 281-294.

Doehring, D. G., Trites, R. L., Patel, P., & Fiedorowicz, C. (1981). *Reading disabilities: The interaction of reading, language and neuropsychological deficits.* New York, NY: Academic Press.

Dougherty, R. F., Cynader, M. S., Bjornson, B. H., Edgell, D., & Giaschi, D. E. (1998). Dichotic pitch: a new stimulus distinguishes normal and dyslexic auditory function. *Neuroreport, 14*, 3001-3005.

Duane, D.D. (1989). Commentary on dyslexia and neurodevelopmental pathology. *Journal of Learning Disabilities, 22*, 219-220.

Duara, R., Kushch, A., Gross-Glenn, K., Barker, W. W., Jallad, B., Pascal, S., & Loewenstein, D. A. (1991). Neuroanatomic differences between dyslexic and normal readers on magnetic resonance imaging scans. *Archives of Neurology*, 48(4): 410-6.

Eden, G. F., Stein, J. F., Wood, M. H., & Wood, F. B. (1993). Dyslexia: A study of preserved and impaired visuospatial and phonological functions. *Annals of the New York Academy of Sciences, 682*, 335-338.

Eden, G. F., Stein, J. F., Wood, H. M., & Wood, F. B. (1995a). Temporal and spatial processing in reading disabled and normal children. *Cortex, 31*, 451-468.

Eden, G. F., Stein, J. F., Wood, H. M., & Wood, F. B. (1995b). Verbal and visual problems in reading disability. *Journal of Learning Disabilities, 28(5),* 272-290.

Eden, G. F., VanMeter, J. W., Rumsey, J. M., Maisog, J. M., Woods, R. P., & Zeffiro, T. A. (1996). Abnormal processing of visual motion in dyslexia revealed by functional brain imaging. *Nature, 382*(6586), 66-69.

Farmer, M. E., & Klein, R. M. (1995). The evidence for a temporal processing deficit linked to dyslexia: A review. *Psychonomic Bulletin & Review, 2*(4), 460-493.

Fawcett, A. J., Chattopadhyay, A. K., Kandler, R. H., Jarratt, J. A., Nicolson, R. I., & Proctor, M. (1993). Event-related potentials and dyslexia. *Annals of the New York Academy of Sciences, 682*, 342-345.

Fawcett, A. J., Nicolson, R. I., & Dean, P. (1996). Impaired performance of children with dyslexia on a range of cerebellar tasks. *Annals of Dyslexia, 46*, 259-283.

Fein, G. Galin, D., Yingling, C.D., Johnstone, J. Davenport, L, & Herron, J. (1986). EEG spectra in dyslexic and control boys during resting conditions. *Electroencephalography and Clinical Neurophysiology, 63*(2), 87-97.

Fiedorowicz, C. (1986). Training of component reading skills. *Annals of Dyslexia, 36,* 318-334.

Fiedorowicz, C., & Trites, R. L. (1991). From theory to practice with subtypes of reading disabilities. In: B. P. Rourke (Ed.), *Neuropsychological validation of learning disability subtypes.* New York, NY: Guilford Press.

Fitch, R. H., Tallal, P., Brown, C. P., & Galaburda, A. M. (1994). Induced microgyria and auditory temporal processing in rats: A model for language impairment? *Cerebral Cortex, 4*(3), 260-270.

Flor-Henry, P., Kiles, Z.J. & Tucker, D.M. (1982) Studies in EEG power and coherence (8-13Hz) in depression mania and schizophrenia compared to controls. *Advances in Biological Psychiatry, 9*: 1-7.

Flowers, D. L. (1993). Brain basis for dyslexia: A summary of work in progress. *Journal of Learning Disabilities, 26(9),* 575-582.

Flowers, D. L., Wood, F. B., & Naylor, C. E. (1991). Regional cerebral blood flow correlates of language processes in reading disability. *Archives of Neurology, 48,* 637-643.

French, C., & Beaumont, J. (1984). A critical review of EEG coherence studies of hemispheric function. *International Journal of Psychophysiology, 1*:241-254.

Fried, P.A., Watkinson, B., & Gray, R. (1992). A follow-up study of attentional behavior in 6-year-old children exposed prenatally to marijuana, cigarettes, and alcohol. *Neurotoxicology and Teratology, 14,* 299-311.

Galaburda, A. M. (1988). The pathogenesis of childhood dyslexia. *Research in Nervous and Mental Disorders, 66,* 127-138.

Galaburda, A. M. (1989). Ordinary and extraordinary brain development: Anatomical variation in developmental dyslexia. *Annals of Dyslexia, 39,* 67-80.

Galaburda, A. M. (1993). Neuroanatomical basis of developmental dyslexia. *Neurologic Clinics, 11(1),* 161-173.

Galaburda, A. M. (1994). Developmental dyslexia and animal studies: At the interface between cognition and neurology. *Cognition, 50,* 133-149.

Galaburda, A. M. (1997). Neurobiology of developmental dyslexia: Results of a ten year research program. *Learning Disabilities, 8(1),* 43-50.

Galaburda, A., & Livingstone, M. (1993). Evidence for a magnocellular defect in developmental dyslexia. *Annals of the New York Academy of Sciences, 682,* 70-82.

Galaburda, A. M., Menard, M. T., & Rosen, G. D. (1994). Evidence for aberrant auditory anatomy in developmental dyslexia. *Proceedings of the National Academy of Sciences of the U S A, 91,* 8010-8013.

Galaburda, A., & Sanides F. (1980). Cytoarchitectonic organization of the human auditory cortex. *Journal of Comparative Neurology, 190*(3): 597-610.

Galaburda, A. M., Sherman, G. F., Rosen, G. D., Aboitiz, F., & Geschwind, N. (1985). Developmental dyslexia: four consecutive patients with cortical anomalies. *Annals of Neurology, 18*(2), 222-233.

Gale, A., and Edwards, J. (1986). *Physiological Correlates of Human Behavior, Vol. 3. Individual Differences and Psychopathology,* Academic Press, Orlando, FL.

Gasser, T., Jennen-Steinmetz, C., and Verleger, R. (1987). EEG coherence at rest and during a visual task in two groups of children. *Electroencephalography and Clinical Neurophysiology, 67*:151-158.

Gross-Glenn, K., Duara, R., Barker, W. W., Loewenstein, D., Chang, J.Y., Yoshii, F., Apicella, A. M., Pascal, S., Boothe, T., Sevush, S., Jallad, B. J., Novoa, L., & Lubs, H. A. (1991). Positron emission tomographic studies during serial word-reading by normal and dyslexic adults. *Journal of Clinical and Experimental Neuropsychology, 13(4),* 531-544.

Gross-Tsur, V., Shalev, R. S., Manor, O., & Amir, N. (1995). Developmental right hemisphere syndrome: Clinical spectrum of the nonverbal learning disability. *Journal of Learning Disabilities, 28(2),* 80-86.

Gayan, J., Smith, S. D., Cherny, S. S., Cardon, L. R., Fulker, D. W., Brower, A. M., Olson, R. K., Pennington, B. F., & DeFries, J. C. (1999). Quantitative-trait locus for specific language and reading deficits on chromosome 6p. *American Journal of Human Genetics, 64*(1), 157-164.

Geschwind, N., & Behan, P. (1982). Left-handedness: association with immune disease, migraine, and developmental learning disorder. *Proceedings of the National Academy of Sciences of the U S A, 79*(16), 5097-5100.

Geshwind, N. & Levitsky, W. (1968). Left-right asymmetries in temporal speech region. *Science, 161,* 186-187.

Gilger, J. W., Pennington, B. F., Harbeck, R. J., DeFries, J. C., Kotzin, B., Green, P., & Smith, S. (1998). A twin and family study of the association between immune system dysfunction and dyslexia using blood serum immunoassay and survey data. *Brain and Cognition, 36*(3), 310-333.

Hagman, J. O., Wood, F., Buchsbaum, M. S., Tallal, P., Flowers, L., & Katz, W. (1992). Cerebral brain metabolism in adult dyslexic subjects assessed with positron emission tomography during performance of an auditory task. *Archives of Neurology, 49,* 734-739.

Hanley J. & Sklar, B. (1976). Electroencephalographic correlates of developmental reading dyslexias: computer analysis of recordings from normal and dyslexic children. In: G. Leisman (Ed.), *Basic visual processes and learning disability*. Springfield, IL: Charles C. Thomas pp. 217-253.

Harnadek, M. C. S., & Rourke, B. P. (1994). Principal underlying features of the syndrome of nonverbal learning disabilities in children. *Journal of Learning Disabilities, 27*(3), 144-154.

Harter, M. R., Anllo-Vento, L., & Wood, F. B. (1989). Event-related potentials, spatial orienting, and reading disabilities. *Psychophysiology, 26*(4), 404-421.

Harter, M.R., Diering, & Wood, F. B. (1988). Separate brain potential characteristics in children with reading disabilities and attention deficit disorder: Relevance-independent effects. *Brain and Cognition, 7,* 54-86.

Heilman, K. M., Voeller, K., & Alexander, A. W. (1996). Developmental dyslexia: A motor-articulatory feedback hypothesis. *Annals of Neurology, 39,* 407-412.

Herman, A. E., Galaburda, A. M., Fitch, R. H., Carter, A. R., & Rosen, G. D. (1997). Cerebral microgyria, thalamic cell size and auditory temporal processing in male and female rats. *Cerebral Cortex, 7*(5), 453-464.

Hinshelwood, J. (1896). A case of dyslexia: A peculiar form of word-blindness. *Lancet, 2,* 1451-1454.

Horwitz, B., Rumsey, J. M., & Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences of the United States of America. 95(15),* 8939-8944.

Hugdahl, K., Heiervang, E., Nordby, H., Smievoll, A. I., Steinmetz, H., Stevenson, J., & Lund, A. (1998). Central auditory processing, MRI morphometry and brain laterality: applications to dyslexia. *Scandinavian Audiology. Supplementum. 49,* 26-34.

Humphreys, P., Kaufmann, W. E., & Galaburda, A. M. (1990). Developmental dyslexia in women: neuropathological findings in three patients. *Annals of Neurology, 28*(6), 727-738.

Humphreys, P., Kaufmann, W. E., & Galaburda, A. M. (1990). Developmental dyslexia in women: Neuropathological findings in three patients. *Annals of Neurology, 28*, 727-738.

Huppi, P. S., Maier, S. E., Peled, S., Zientara, G. P., Barnes, P. D., Jolesz, F. A., & Volpe, J. J. (1998). Microstructural development of human newborn cerebral white matter assessed in vivo by diffusion tensor magnetic resonance imaging. *Pediatric Research, 44*(4), 584-590.

Hynd, G. W., Hall, J., Novey, E. S., Eliopulos, D., Black, K., Gonzalez, J. J., Edmonds, J. E., Riccio, C., & Cohen, M. (1995). Dyslexia and corpus callosum morphology. *Archives of Neurology, 52*, 32-38.

Hynd, G. W., Marshall, R. M., & Semrud-Clikeman, M. (1991). Developmental dyslexia, neurolinguistic theory and deviations in brain morphology. *Reading & Writing: An Interdisciplinary Journal, 3(3-4)*, 345-362.

Hynd, G.W., Semrud-Clikeman, M., (1989). Dyslexia and neurodevelopmental pathology: relationships to cognition, intelligence, and reading skill acquisition. *Journal of Learning Disabilities, 22*, 204-216.

Hynd, G.W., Semrud-Clikeman,, M., Lorys, A.R., Novety, E.S., & Eliopulos, D. (1990). Brain morphology in developmental dyslexia and attention deficit disorder/hyperactivity. *Archives of Neurology, 47*, 919-926.

Iovino, I., Fletcher, J. M., Breitmeyer, B. G., & Foorman, B. R. (1998). Colored overlays for visual perceptual deficits in children with reading disability and attention deficit/hyperactivity disorder: are they differentially effective?. *Journal of Clinical and Experimental Neuropsychology. 20 (6)*, 791-806.

Jenner, A. R., Rosen, G.D., & Galaburda, A.M. (1999). Neuronal asymmetries in primary visual cortex of dyslexic and nondyslexic brains. *Annals of Neurology. 46(2)*, 189-196.

Johnstone, J., Galin, D., Fein, G., Yinglling, C., Herron, J., & Marcus, M. (1984). Regional brain activity in dyslexic and control children during reading tasks: Visual probe event-related potentials. *Brain and Language, 21*, 235-254.

Kaiser, J., and Gruzelier, J. (1996). Timing of puberty and EEG coherence during photic stimulation. *International Journal of Psychophysiology, 21*:135-149.

Kaufman, W.E. & Galaburda, A.M. (1989). Cerebrocortical microgenesis in neurologically normal subjects - a histopathological study. *Neurology*, *39*, 257-269.

Katz, J., & Smith, P. S. (1991). The staggered spondaic word test: A ten-minute look at the central nervous system through the ears. *Annals of the New York Academy of Sciences, 620*, 233-251.

Kershner, J. (1977). Cerebral dominance in disabled readers, good readers, and gifted children: Search for a valid model. *Child Development, 48*, 61-67.

Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J. D., Moseley, M. E., & Poldrack, R. A. (2000). Microstructure of temporo-parietal white matter as a basis for reading ability: evidence from diffusion tensor magnetic resonance imaging. *Neuron, 25*(2), 493-500.

Klingberg, T., Vaidya, C. J., Gabrieli, J. D., Moseley, M. E., & Hedehus, M. (1999). Myelination and organization of the frontal white matter in children: A diffusion tensor MRI study. *Neuroreport, 10*(13), 2817-2821.

Kujala, T., Myllyviita, K., Tervaniemi, M., Alho, K., Kallio, J., & Naatanen, R. (2000). Basic auditory dysfunction in dyslexia as demonstrated by brain activity measurements. *Psychophysiology, 37(2)* 262-266.

Kusch, A., Gross-Glenn, K., Jallad, B., Lubs, H., Rabin, M., Feldman, E., & Duara, R. (1993). Temporal lobe surface area measurements on MRI in normal and dyslexic readers. *Neuropsychologia, 31(8),* 811-821.

Lambe, E. K. (1999). Dyslexia, gender, and brain imaging. *Neuropsychologia. 37(5),* 521-536.

Larsen, J. P., Høien, T., Lundberg, I., & Ødegaard, H. (1990). MRI evaluation of the size and symmetry of the planum temporale in adolescents with developmental dyslexia. *Brain and Language, 39,* 289-301.

Larsen, J. P., Höien, T., & Ødegaard, H. (1992). Magnetic resonance imaging of the corpus callosum in developmental dyslexia. *Cognitive Neuropsychology, 9(2),* 123-134.

Leavell, C., & Lewandowski, L. (1990). Neurolinguistic deficits and the left hemisphere in the reading disabled. *Developmental Neuropsychology, 6(4),* 319-337.

Leisman, G. (1973). Conditioning variables in attentional handicaps. *Neuropsychologia, 11,* 199- 205.

Leisman, G. (1974). The relationship between saccadic eye movements and the alpha rhythm in attentionally handicapped patients. *Neuropsychologia, 12,* 201-210.

Leisman, G. (1976). The role of visual processes in attention and its disorders. In G. Leisman (Ed.), *Basic visual processes and learning disability*. Springfield, IL: Charles C. Thomas, pp. 7-123.

Leisman, G. (1978). Ocular-motor system control of position anticipation and expectation: Implications for the reading process. In J.W. Senders, D.F. Fisher, & R.A. Monty (Eds.), *Eye movements and the higher mental functions.* Hillsdale, NJ: Lawrence Erlbaum & Associates, pp.195-207.

Leisman, G. (2002). Coherence of hemispheric function in developmental dyslexia. *Brain and Cognition*, *48*(2-3): 425-31.

Leisman, G. & Ashkenazi, M. (1980). Aetiological factors in dyslexia: IV. Cerebral hemispheres are functionally equivalent. *International Journal of Neuroscience*, *11*, 157-164.

Leisman, G. & Schwartz, J. (1976). Ocular-motor variables and reading disorders. In: R.M. Knights & D. J. Bakker (Eds.), *The neuropsychology of reading disorders: theoretical approaches*. Baltimore, MD: University Park Press, pp. 333-348.

Leisman, G. & Schwartz, J. (1977). Ocular-motor function and visual information processing implications for the reading process. *International Journal of Neuroscience, 8*, 7-16.

Leisman, G. & Zenhausern R. (1982). Integratory systems deficits in developmental dyslexia In: R.N. Malatesha & L. Hartlage (Eds.), *Neuropsychology and cognition*. Amsterdam, The Netherlands: Elsevier, pp. 479-506.

Lennerstrand, G., Ygge, J., & Jacobsson, C. (1993). Control of binocular eye movements in normals and dyslexics. *Annals of the New York Academy of Sciences, 682*, 231-239.

Leonard, C. M., Voeller, K. K. S., Lombardino, L. J., Morris, M. K., Hynd, G. W., Alexander, A. W., Andersen, H. G., Garofalakis, M., Honeyman, J. C., Mao, J., Agee, F., & Staab, E. V. (1993). Anomalous cerebral structure in dyslexia revealed with magnetic resonance imaging. *Archives of Neurology, 50,* 461-469.

Livingstone, M. (1993). Parallel processing in the visual system and the brain: Is one subsystem selectively affected in dyslexia? In: A. M. Galaburda (Ed.), *Dyslexia and development: Neurobiological aspects of extra-ordinary brains*. Cambridge, MA: Harvard University Press, pp. 237-256.

Livingstone, M. S., Rosen, G. D., Drislane, F. W., & Galaburda, A. M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. *Proceedings of the National Academy of Sciences of the U S A, 88,* 7943-7947.

Logan, W. J. (1996). Neuroimaging and functional brain analysis. In J. H. Beitchman, N. J. Cohen, M. M. Konstantareas, & R. Tannock (Eds.), *Language, learning, and behavior disorders: Developmental, biological, and clinical perspective.* Cambridge, UK: Cambridge University Press pp. 297-314.

Lou, H. C. (1992). Cerebral single photon emission tomography (SPECT) and positron emission tomography (PET) during development and in learning disorders. In: I. Rapin & S. J. Segalowitz (Eds.), *Handbook of neuropsychology, Vol. 6: Child neuropsychology*. Amsterdam, The Netherlands: Elsevier, pp. 331-338.

Lovegrove, W. (1993). Weakness in the transient visual system: A causal factor in dyslexia? *Annals of the New York Academy of Sciences, 682*, 57-69.

Makris, N., Meyer, J. W., Bates, J. F., Yeterian, E. H., Kennedy, D. N., & Caviness, V. S. (1999). MRI-Based topographic parcellation of human cerebral white matter and nuclei II. Rationale and applications with systematics of cerebral connectivity. *Neuroimage, 9*(1), 18-45.

Makris, N., Worth, A. J., Sorensen, A. G., Papadimitriou, G. M., Wu, O., Reese, T. G., Wedeen, V. J., Davis, T. L., Stakes, J. W., Caviness, V. S., Kaplan, E., Rosen, B. R., Pandya, D. N., & Kennedy, D. N. (1997). Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging. *Annals of Neurology, 42*(6), 951-962.

Marcel, T. & Rajan, P. (1975). Lateral specialization for recognition of words and faces in good and poor readers. *Neuropsychologia*, *13*, 489-497.

Mattis, S., French, J.H., & Rapin, I. (1975). Dyslexia in children and young adults: three independent neuropsychological syndromes. *Developmental Medicine and Child Neurology, 17*, 150-163.

Mattson, A. J., Sheer, D. E., & Fletcher, J. M. (1992). Electrophysiological evidence of lateralized disturbances in children with learning disabilities. *Journal of Clinical and Experimental Neuropsychology, 14(5),* 707-716.

McAnally, K. I., & Stein, J. F. (1996). Auditory temporal coding in dyslexia. *Proceedings of the Royal Society, London, B Biological Science, 263*(1373), 961-965.

Melillo, R. & Leisman, G. (2003). Neurobehavioral disorders of childhood: An evolutionary perspective. New York, NY: Kluwer.

Mentis, M., & Lundgren, K. (1995). Effects of prenatal exposure to cocaine and associated risk factors on language development. *Journal of Speech and Hearing Research, 38*, 1303-1318.

Merrill, J. E., & Scolding, N. J. (1999). Mechanisms of damage to myelin and oligodendrocytes and their relevance to disease. *Neuropathology and Applied Neurobiology, 25*(6), 435-458.

Molfese, D. L., & Molfese, V. J. (1997). Discrimination of language skills at five years of age using event-related potentials recorded at birth. *Developmental Neuropsychology, 13,* 135-156.

Moseley, M. E., Cohen, Y., Kucharczyk, J., Mintorovitch, J., Asgari, H. S., Wendland, M. F., Tsuruda, J., & Norman, D. (1990). Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. *Radiology, 176*(2), 439-445.

Nagarajan, S., Mahncke, H., Salz, T., Tallal, P., Roberts, T., & Merzenich, M. M. (1999). Cortical auditory signal processing in poor readers. *Proceedings of the National Academy of Sciences of the U S A, 96*(11), 6483-6488.

Nicolson, R. I., Fawcett, A. J., Berry, E. L., Jenkins, I. H., Dean, P., and Brooks, D. J. (1999). Association of abnormal cerebellar activation with motor learning difficulties in dyslexic adults. *Lancet, 353,* 1662-1667.

Njiokiktjien, C. (1994). Dyslexia: A neuroscientific puzzle. *Acta Paedopsychiatrica, 56,* 157-167.

Njiokiktjien, C., de Sonneville, L., & Vaal, J. (1994). Callosal size in children with learning disabilities. *Behavioral and Brain Research, 64,* 213-218.

Nunez, P.L. (1995) *Neocortical dynamics and human EEG rhythm*. New York: Oxford University Press.

O'Conner, K.P., Shaw, J.C. and Ongley, C.O. (1979) The EEG and differential diagnosis in psychogeriatrics. *British Journal of Psychiatry, 135:* 156-162.

Ogden, J. A. (1996). Phonological dyslexia and phonological dysgraphia following left and right hemispherectomy. *Neuropsychologia, 34(9),* 905-918.

Ortiz, T., Exposito, F. J., Miguel, F., Martin-Loeches, M., & Rubia, F. J. (1992). Brain mapping in dysphonemic dyslexia: In resting and phonemic discrimination conditions. *Brain and Language, 42,* 270-285.

Pandya, D. N., & Kennedy, D. N. (1997). Morphometry of in vivo human white matter association pathways with diffusion-weighted magnetic resonance imaging. *Annals of Neurology , 42*(6), 951-962.

Paulesu, E., Frith, U., Snowling, M., Gallagher, A., Morton, J., Frackowiak, R. S. J., & Frith, C. D. (1996). Is developmental dyslexia a disconnection syndrome? Evidence from PET scanning. *Brain, 119,* 143-157.

Paus, T., Zijdenbos, A., Worsley, K., Collins, D.L., Blumenthal, J., Giedd, J.N., Rapoport, J.L., & Evans, A.C. (1999). Structural maturation of neural pathways in children and adolescents: in vivo study. *Science, 283* (5409):1908-11.

Pennington, B. F. (1999). Toward and integrated understanding of dyslexia: Genetic, neurological, and cognitive mechanisms. *Development and Psychopathology, 11,* 629-654.

Pennington, B. F., Smith, S. D., Kimberling, W. J., Green, P. A., & Haith, M. M. (1987). Left-handedness and immune disorders in familial dyslexics. *Archives of Neurology, 44*(6), 634-639.

Pfeiffer, R.A. (1936). Pathologie der Horstrahlung der corticalen Horsphare. In: Bumke, O., & Forster, O., (eds.) *Handbuch der Neurologie*. Berlin: Springer; pp. 533-626.

Pham-Dinh, D., Mattei, M. G., Nussbaum, J. L., Roussel, G., Pontarotti, P., Roeckel, N., Mather, I. H., Artzt, K., Lindahl, K. F., & Dautigny, A. (1993). Myelin/oligodendrocytes glycoprotein is a member of a subset of the immunoglobulin superfamily encoded within the major histocompatibility complex. *Proceedings of the National Academy of Sciences of the U S A, 90*(17), 7990-7994.

Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance Medicine, 36*(6), 893-906.

Pirozzolo, F. & Rayner, K. (1979). Cerebral organization and reading disability. *Neuropsychologia, 17,* 485-492.

Porac, C. & Coren, S. (1981). *Lateral preferences and human behavior*. New York, NY: Springer.

Pugh, K. R., Mencl, W. E., Shaywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Constable, R. T., Skuldarski, P., Marchione, K. E., Jenner, A. R., Fletcher, J. M., Liberman, A. M., Shankweiler, D. P., Katz, L., Lacadie, C., & Gore, J. C. (2000). The angular gyrus in developmental dyslexia: Task-specific differences in functional connectivity within posterior cortex. *Psychological Science, 11*, 51-56.

Rapin & S. J. Segalowitz (Eds.), *Handbook of neuropsychology, Vol. 6: Child neuropsychology* (pp. 331-338). Amsterdam, The Netherlands: Elsevier Science.

Rosen, G. D., Burstein, D., & Galaburda, A. M. (2000). Changes in efferent and afferent connectivity in rats with induced cerebrocortical microgyria. *Journal of Comparative Neurology, 418*(4), 423-440.

Rosen, G. D., Sherman, G. F., & Galaburda, A. M. (1993). Dyslexia and brain pathology: Experimental animal models. In: A. M. Galaburda (Ed.), *Dyslexia and development: Neurobiological aspects of extra-ordinary brains*. London: Harvard University Press, pp. 89-111.

Rosenberger P.B. & Hier, D. (1980). Cerebral asymmetry and verbal intellectual deficits. *Annals of Neurology, 8,* 300-304.

Rourke, B.P. (Ed.). (1995). *Syndrome of nonverbal learning disabilities: Neurodeveopmental manifestations.* New York: Guilford Press.

Rourke, B. P., & Fuerst, D. R. (1992). Psychosocial dimensions of learning disability subtypes: Neuropsychological studies in the Windsor laboratory. *School Psychology Review, 21,* 361-374.

Rourke, B. P., & Fuerst, D. R. (1995). Cognitive processing, academic achievement, and psychosocial functioning: A neurodevelopmental perspective. In D. Cicchetti & D. J. Cohen (Eds.), *Developmental psychopathology Vol. 1: Theory and methods* (pp. 391-423). New York: John Wiley & Sons.

Rourke, B. P., & Fuerst, D. R. (1996). Psychosocial dimensions of learning disability subtypes. *Assessment, 3(3),* 277-290.

Rumsey, J. M. (1996). Neuroimaging in developmental dyslexia: A review and conceptualization. In G. R. Lyon & J. M. Rumsey (Eds.). *Neuroimaging,* Baltimore, MD: Paul H. Brookes pp. 57-77.

Rumsey, J.M., Andreason, P., Zametkin, A.J., Aquino, T., King, A.C., Hamburger, S.D., Pikus, A., Rapoport, J.L., & Cohen RM. (1992). Failure to activate the left temporoparietal cortex in dyslexia. An oxygen 15 positron emission tomographic study. *Archives of Neurology, 49*(5): 527-34.

Rumsey, J. M., Casanova, M., Mannheim, G. B., Patronas, N., DeVaughn, N., Hamburger, S. D., & Aquino, T. (1996). Corpus callosum morphology, as measured with MRI, in dyslexic men. *Biological Psychiatry, 39,* 769-775.

Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K. L., Maisog, J. M., & Andreason, P. (1999). A functional lesion in developmental dyslexia: left angular gyral blood flow predicts severity. *Brain and Language, 70*(2), 187-204.

Rumsey, J.M., Nace, K., Donohue, B., Wise, D., Maisog, J.M., & Andreason, P. (1997). A PET study of impaired word recognition and phonological processing in dyslexic men. *Archives of Neurology, 54,* 562-578.

Schulte-Körne, G., Deimel, W., Bartling, J., & Remschmidt, H. (1998). Auditory processing and dyslexia: evidence for a specific speech processing deficit. *Neuroreport. 9*(2) 26 January 337-340.

Schultz, R. T., Cho, N. K., Staib, L. H., Kier, L. E., Fletcher, J. M., Shaywitz, S. E., Shankweiler, D. P., Katz, L., Gore, J. C., Duncan, J. S., & Shaywitz, B. A. (1994). Brain morphology in normal and dyslexic children: The influence of sex and age. *Annals of Neurology, 35,* 732-742.

Schmid, R., Tirsch, W., Rappelsberger, P., Weinmann, H., and Poppl, S. (1992). Comparative coherence studies in healthy volunteers and Down's syndrome patients from childhood to adult age. *Electroencephalography and Clinical Neurophysiology, 83*:112-123.

Shapleske, J., Rossell, S. L., Woodruff, P. W. R., & David, A. S. (1999). The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance. *Brain Research Reviews, 29,* 26-49.

Shaw, J.C., O'Conner, K.P. and Ongley, C.O. (1977) EEG coherence as a measure of cerebral functional organization. In: M.A.B. Brazier & H. Petsche (Eds.). *Architectonics of the cerebral cortex*, New York, NY: Raven Press, pp. 245-256.

Shaw, J.C. and Ongley, C. (1972) The measurement of synchronization. In: H. Petsche and M.A.B. Brazier, (Eds.), *Synchronization of EEG activities in epilepsies*, New York, NY: Springer, pp. 204-214.

Shaw, J. C. (1981) An introduction to the coherence function and its use in EEG signal analysis. *Journal of Medical Engineering & Technology*, 5, 279-288.

Shaywitz, S. E., Escobar, M. D., Shaywitz, B. A., Fletcher, J. M., & Makuch, R. (1992). Evidence that dyslexia may represent the lower tail of a normal distribution of reading ability. *New England Journal of Medicine, 326*(3), 145-150.

Shaywitz, S.E., Shaywitz, B.A., Pugh, K.R., Fulbright, R.K,, Constable, R.T., Mencl, W.E., Shankweiler, D.P., Liberman, A.M., Skudlarski, P., Fletcher, J.M., Katz, L., Marchione, K.E., Lacadie, C., Gatenby, C., & Gore, J.C. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proceedings of the National Academy of Sciences of the USA, 95*(5): 2636-41.

Sherman, G. F., Galaburda, A. M., & Geschwind, N. (1985). Cortical anomalies in brains of New Zealand mice: a neuropathologic model of dyslexia? *Proceedings of the National Academy of Sciences of the U S A, 82*(23), 8072-8074.

Sklar, B., Hanley, J., & Simmons, W.W., (1972). An EEG experiment aimed toward identifying dyslexic children. *Nature, 15,* 240 (5381), 414-416.

Sklar, B., Hanley, J., & Simmons, W.W., (1973). A computer analysis of EEG spectral signatures from normal and dyslexic children. *IEEE Transactions in Biomedical Engineering, 20*(1) 20-26. .

Slaghuis, W. L., Lovegrove, W. J., & Davidson, J. A. (1993). Visual and language processing deficits are concurrent in dyslexia. *Cortex, 29,* 601-615.

Slaghuis, W. L., Twell, A. J., & Kingston, K. R. (1996). Visual and language processing disorders are concurrent in dyslexia and continue into adulthood. *Cortex, 32*, 413-438.

Smith, G. E. (1907). A new topographical survey of the human cerebral cortex, being an account of the anatomically distinct cortical areas and their relationship to the cerebral sulci. *Journal of Anatomy, 41*: 237-254.

Spache, G. (1966). *Diagnostic reading scales*. New York, NY: McGraw Hill.

Spafford, C. S., & Grosser, G. S. (1993). The social misperception syndrome in children with learning disabilities: Social causes versus neurological variables. *Journal of Learning Disabilities, 26*(3), 178-189, 198.

Stein, J. F. (1994). Developmental dyslexia, neural timing and hemispheric lateralisation. *International Journal of Psychophysiology, 18*, 241-249.

Stein, J. F. (1996). Visual system and reading. In C. H. Chase, G. D. Rosen, & G. F. Sherman (Eds.), *Developmental dyslexia: Neural, cognitive, and genetic mechanisms*. Baltimore, MD: York Press, pp. 107-125.

Steinmetz, H., & Galaburda, A. M. (1991). Planum temporale asymmetry: In-vivo morphometry affords a new perspective for neuro-behavioral research. *Reading & Writing: An Interdisciplinary Journal, 3(3-4),* 331-343.

Stelmack, R.M., Saxe, B.J., Noldy-Cullum, N., Campbell, K.B., & Armitage, R. (1988). Recognition memory for words and event-related potentials. A comparison of normal and disabled readers. *Journal of Clinical and Experimental Neuropsychology, 10,* 185-200.

Stevens, B., & Fields, R. D. (2000). Response of Schwann cells to action potentials in development. *Science, 287*(5461), 2267-2271.

Studdert-Kennedy, M., & Mody, M. (1995). Auditory temporal perception deficits in the reading-impaired: A critical review of the evidence. *Psychonomic Bulletin and Review, 2,* 508-514.

Sutton, J.P., Whitton, J.L., Topa, M. & Moldofsky, H. (1986). Evoked potentials maps in learning disabled children. *Electroencephalography and Clinical Neurophysiology, 65*, 399-404.

Szentagothal, J. (1978). The neural network of the cerebral cortex: A functional interpretation. *Proceedings of the Royal Society, London, 201*:219-248.

Talcott, J. B., Witton, C., McLean, M. F., Hansen, P. C., Rees, A., Green, G. G., & Stein, J. F. (2000). Dynamic sensory sensitivity and children's word decoding skills. *Proceedings of the National Academy of Sciences of the U S A, 97*(6), 2952-2957.

Tallal, P. (1980). Auditory temporal perception, phonics, and reading disabilities in children. *Brain and Language, 9*(2), 182-198.

Tallal, P. & Katz, W. (1989). Neuropsychological and neuroanatomical studies of developmental language/reading disorders: recent advances. In: C. vonEuler, I. Landberg, & G.G. Lennenstrand (Eds.), *Brain and reading*. London, UK: Macmillan, pp. 494-507.

Tallal, P., Miller, S., & Fitch, R. H. (1993). Neurobiological basis of speech: A case for the preeminence of temporal processing. *Annals of the New York Academy of Sciences, 682*, 27-47.

Tallal, P., & Piercy, M. (1973). Defects of non-verbal auditory perception in children with developmental aphasia. *Nature, 241*(5390), 468-469.

Taylor, M. J., & Keenan, N. K. (1990). Event-related potentials to visual and language stimuli in normal and dyslexic children. *Psychophysiology, 27(3),* 318-327.

Temple, E., Poldrack, R. A., Protopapas, A., Nagarajan, S., Salz, T., Tallal, P., Merzenich, M. M., & Gabrieli, J. D. E. (2000). Disruption of the neural response to rapidly transient acoustic stimuli in dyslexia: evidence from fMRI. *Proceedings of the National Academy of Sciences of the U S A,* 97(25): 13907-13912.

Temple, E., Poldrack, R. A., Salidis, J., Deutsch, G., Merzenich, M. M., Tallal, P., & Gabrieli, J. D. E. (2001). Disrupted Neural Responses to Phonological and Orthographic Processing in Dyslexic Children: An fMRI Study. *Neuroreport*. 2001, *12*(2): 299-307.

Thatcher, R. (1991). Maturation of the human frontal lobes: Physiological evidence for staging. *Developmental Neuropsychology, 7*:397-419.

Thatcher, R.W. (1992) Cyclic cortical reorganization during early childhood. *Brain and Cognition, 20*: 24-50.

Thatcher, R. (1994a). Psychopathology of early frontal lobe damage: Dependence on cycles of development. *Developmental Neuropsychology, 6:565*-596.

Thatcher, R. (1994b). Cyclic cortical reorganization, origins of human cognitive development. IN: Dawson, G., and Fischer, K. (Eds.), *Human behavior and the developing brain*, New York, NY: Guilford Press, pp. 232-266.

Thatcher, R.W., Cantor, D.S., McAlaster, R. & Geisler, F. (1991). Comprehensive predictions of outcome in closed head-injured patients: The development of prognostic equations. *Annals of the New York Academy of Sciences, 620*: 82-101.

Thatcher, R., Krause, P., & Hrybyk, M. (1986). Cortico-cortical associations and EEG coherence: A two-compartmental model. *Electroencephalography and Clinical Neurophysiology, 64:123*-143.

Thatcher, R.W., McAlaster, R., Lester, M.L., Horst, R.L. and Cantor, D.S. (1983) Hemispheric EEG asymmetries related to cognitive functioning in children. In: A. Perecman (Ed.), *Cognitive processing in the right hemisphere*, New York, NY: Academic Press, pp.125-146.

Thatcher, R., Walker, R., and Guidice, S. (1987). Human cerebral hemispheres develop at different rates and ages. *Science,* 236:1110-1113.

Tootell, R, B. H., & Taylor, J. B. (1995). Anatomical evidence for MT and additional cortical visual areas in humans. *Cerebral Cortex, 5*, 39-55.

Tranel, D., Hall, L. E., Olson, S., & Tranel, N. N. (1987). Evidence for a right hemisphere developmental learning disability. *Developmental Neuropsychology, 3(2),* 113-127.

Trites, R. L., & Fiedorowicz, C. (1976). Follow-up study of children with specific (or primary) reading disability. In: R. M. Knights & D. J. Bakker (Eds.), *The neuropsychology of learning disorders: Theoretical approaches.* Baltimore, MD: University Park Press.

Tucker, D.M., Dawson, S.L., Roth, D.L., Blair, T.B. and Sawler, B.G. (1982) Regional changes in power and coherence during cognition: longitudinal study of individuals. In: *International Neuropsychology Society, Pittsburgh, PA*. [abstr].

Von Bonin, G. (1962). Anatomical asymmetries of the cerebral hemispheres. In: V. B. Mounteastle (Ed.) *Interhemispheric relations and cerebral dominance.* Baltimore, MD: Johns Hopkins Univ. Press,

Werring, D. J., Clark, C. A., Barker, G. J., Thompson, A. J., & Miller, D. H. (1999). Diffusion tensor imaging of lesions and normal-appearing white matter in multiple sclerosis. *Neurology, 52*(8), 1626-1632.

Wimberger, D. M., Roberts, T. P., Barkovich, A. J., Prayer, L. M., Moseley, M. E., & Kucharczyk, J. (1995). Identification of "premyelination" by diffusion-weighted MRI. *Journal of Computer Assisted Tomography, 19*(1), 28-33.

Witelson, S. F. (1976). Abnormal right hemisphere functional specialization in developmental dyslexia. In: R. M. Knights & D. J. Bakker (Eds.) *The neuropsychology of reading disorders: theoretical approaches*. Baltimore, MD: University Park Press, pp. 233-255.

Witelson, S. F. (1977). Developmental dyslexia: two right hemispheres and non left. *Science, 195*, 309-311.

Witelson, S. F., & Pallie, W. (1973). Left hemisphere specialisation for language in the newborn: Neuroanatomical evidence of asymmetry. *Brain, 96,* 641-646.

Witton, C., Talcott, J. B., Hansen, P. C., Richardson, A. J., Griffiths, T. D., Rees, A., Stein, J. F., & Green, G. G. (1998). Sensitivity to dynamic auditory and visual stimuli predicts nonword reading ability in both dyslexic and normal readers. *Current Biology, 8*(14), 791-797.

Wright, B. A., Bowen, R. W., & Zecker, S. G. (2000). Nonlinguistic perceptual deficits associated with reading and language disorders. *Current Opinion in Neurobioogy, 10*(4), 482-486.

Yeni-Komshian, G. H., Isenberg, P., & Goldberg, H. (1975). Cerebral dominance and reading disability: left visual field deficit in poor readers. *Neuropsychologia, 13,* 83-94.