
Neural Mechanisms of Language-Based Learning Impairments: Insights From Human Populations and Animal Models

R. Holly Fitch

University of Connecticut

Paula Tallal

Rutgers, The State University of New Jersey

The acquisition of speech perception and consequent expression of language represent fundamental aspects of human functioning. Yet roughly 7% to 8% of children who are otherwise healthy and of normal intelligence exhibit unexplained delays and impairments in acquiring these skills. Ongoing research has revealed several key features of language disability that may provide more direct insight into underlying anomalous neural functioning. For example, evidence supports a strong association between basic defects in processing rapidly changing acoustic information and emergent disruptions in speech perception, as well as cascading effects on other forms of language development (including reading). Considerable neurobiological research has thus focused on developmental factors that might deleteriously influence rapid sensory processing. Additional research focuses on mechanisms of neural plasticity, including how such brains might be "retrained" for improved processing of language. These and related findings from human clinical studies, electrophysiological studies, neuroimaging studies, and animal models are reviewed.

Key Words: developmental disability, speech processing, rapid auditory processing, dyslexia.

LANGUAGE LEARNING IMPAIRMENT (LLI): DEFINING THE PROBLEM

Developmental language and reading impairments have been the subject of clinical and neurological interest for many years, and more recently have become a focus of cognitive neuroscience research as well. Because language is one of the most complex of all human functions, it is not surprising to find that many genetic and environmental factors appear to influence its development. It is also not surprising that language-

related problems are among the most prevalent of developmental disabilities.

It is estimated that developmental disorders of language (which include deficits in both oral and written language) occur in approximately 20% of preschool- and school-age children (Beitchman, Nair, Clegg, Ferguson, & Patel, 1986). Language problems are typically associated with impairments such as hearing loss or paralysis of the speech musculature and tend to accompany higher order cognitive disorders such as general mental retardation, as well as pervasive developmental disorders such as infantile autism. Language problems also frequently characterize neurodevelopmental disabilities such as fragile X, Down's syndrome, and Klinefelter's syndrome, and are associated with neurological anomalies (such as intracranial bleeds of prematurity) and seizures. Importantly, language disabilities are not synonymous with speech-articulation (pronunciation) disorders. Although some children with language problems also demonstrate impaired development of speech articulation, others do not. Furthermore, speech articulation disorders may or may not be accompanied by problems with language itself (for diagnostic review, see Leonard, 1998).

Among the 20% of children with identifiable language-related problems, there is a subset of children whose disability cannot be attributed to any of the associated causes listed above. These children appear to be healthy and of normal intelligence but fail to progress through the normal language milestones at or near the expected age. A recent epidemiological study has dem-

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onstrated that after children with other identifiable deficits are excluded (e.g., hearing impairments, mental retardation, seizures, neurologic anomalies, or motor disabilities), approximately 7.4% of 5-year-olds can be shown to experience significant delays in language of unknown origin (1.25 or more standard deviations below the mean; see Tomblin et al., 1997). These impairments may manifest as disability in expressive language (with near normal receptive comprehension) or as disability in both receptive and expressive language (see American Psychiatric Association, 1994).

Historically, several different diagnostic classifications have been used to describe these language disorders of unknown origin, including developmental aphasia, congenital aphasia, developmental dysphasia, and specific language impairment (SLI; see Leonard, 1998). More recently, the phrase *language learning impairment* (LLI) has been used. This shift in terminology is based in part on research findings that demonstrate that the deficits characterizing children with LLI are expressed not only in the linguistic domain but seem to co-occur with a variable spectrum of related (and sometimes subtle) impairments (for review, see Tallal, Merzenich, Miller, & Jenkins, 1998). For example, children diagnosed with LLI are at increased risk for behavioral and emotional problems (Baker & Cantwell, 1987a, 1987b; Beitchman et al., 2001; Benasich, Curtiss, & Tallal, 1993). Accordingly, clinical research studies demonstrate that children referred to child guidance clinics for a variety of emotional and behavioral problems have a higher than expected incidence of LLI (Chess & Rosenberg, 1974; Grinnell, Scott-Hartnett, & Glassier, 1983). In one study, approximately 80% of juvenile delinquents sampled were found to have either a history of or concurrent diagnosis of LLI (Beitchman et al., 1986; Hall & Moats, 1999).

Evidence from longitudinal studies as well as family genetic studies demonstrates considerable overlapping etiology and co-occurrence between specific oral language impairments (Habib, 2000) and reading impairments, such as dyslexia (Catts, 1993; Flax et al., 2003; Leonard, 1998; Rissman, Curtiss, & Tallal, 1990; Snow, Burns, & Griffin, 1998). Taken together, longitudinal research shows a high rate of co-occurrence between early language impairments and a variety of behavioral and psychiatric problems. It is not uncommon for LLI to accompany attention deficit disorders, social and emotional problems, academic difficulties, and especially reading problems. Yet little is known about how these impairments are interrelated (including causality paths), or the neural mechanisms underlying their expression.

THE ETIOLOGY OF LLI: SPEECH-PROCESSING FROM THE BOTTOM UP

It is obvious from observing deaf children that dysfunction in the sensory registration of the auditory signal disrupts speech perception, giving rise to a global language disorder (as traditionally defined). What may be less obvious is that deafness is also likely to limit the acquisition of reading, even in individuals who are fluent in a visual sign language (e.g., see Rapin, 1978). This may be because to learn to perceive and produce an oral language, the acoustic waveform of speech must be chunked into individual phonemes (the smallest unit of sound that can change the meaning of a word), and these individual phonemes must acquire neural representation. Thus, to learn to decode print (and become a proficient reader), an individual must become aware that words can be broken down into smaller sounds and that these sounds (phonemes) can be related to letters (graphemes). Alphabetic languages such as English, in fact, require a proficiency with phonemic awareness to map the orthographic representations onto existing phonological representations (Shaywitz et al., 1998; Vellutino & Scanlon, 1987; for review, see Snow et al., 1998).

This, in turn, points to the important role that auditory/phonological mechanisms must play in the neural processes involved in developmental language and reading disorders. Accordingly, considerable research has focused on the neural mechanisms underlying phonological processing. In fact, one of the most prominent debates in the field of language research concerns whether phonological processing deficits, which have been shown to predict and characterize both oral and written language impairments (Bradley & Bryant, 1983; see also Ramus et al., 2003) are specific to linguistic systems or reflect constraints in more general purpose neural functions (such as attention, perception, sequencing, memory) on which all higher order processes must depend.

This debate encompasses, on one hand, a linguistic perspective—specifically, that speech is processed in a manner completely different from nonspeech acoustic information, and that speech and nonspeech processing are subserved by distinct neural pathways (see Chomsky, 1968; Fodor, 1983; Liberman, Cooper, Shankweiler, & Kennedy, 1967; Pinker, 1997). Evidence supporting this speech-specific perspective has been drawn from studies of categorical perception (i.e., the phenomenon that speech sounds can be discriminated only when they are identified as being linguistically different; for discussion, see Fitch, Miller, & Tallal, 1997), as well as studies of acquired brain lesions and cerebral asymmetry (which

show that specific areas of the brain—generally in the left hemisphere—are specialized for speech, language, and reading; Broadbent, 1958; Kimura, 1967; Liberman et al., 1967). Such findings have been substantiated by more recent neuroimaging studies showing activation in left hemisphere regions using speech stimuli (e.g., Shaywitz et al., 1995) and homologous right hemisphere regions for nonlinguistic acoustic discriminations (e.g., Zatorre, Evans, Meyer, & Gjedde, 1992). However, to directly test the notion that certain brain areas are truly specialized for speech, the comparison nonspeech stimuli must be acoustically identical to speech in every way except linguistic content. In other words, stimuli should contain the same basic spectral-temporal content, differing only along the dimension of linguistic relevance or meaning (for discussion, see Breier et al., 2001). In fact, when this kind of explicit control is employed, researchers have found highly overlapping neural activation patterns for speech and comparable nonspeech analogues (i.e., stimuli designed to mimic the temporal-spectral changes that characterize speech, but without the linguistic relevance; Belin et al., 1998; Binder et al., 2000; Fiez et al., 1995; Poldrack et al., 1998; Schwartz & Tallal, 1980; Scott, Blank, Rosen, & Wise, 2000; Temple et al., 2000). Such findings suggest that a critical parameter modulating the processing of speech within the cortex may involve not only linguistic relevance but spectral-temporal content as well. This, in turn, supports the view that neural mechanisms subserving the acoustic processing of speech and spectro-temporally complex nonspeech share common pathways even at the level of cortex. Thus, deficits in basic acoustic processing would be unlikely to spare speech processing. In fact, ongoing research in this field—including human neuroimaging using speech and comparable nonspeech stimuli, as well as electrophysiological studies of nonhuman primate auditory cortex—continues to uncover evidence of functional subdivisions in acoustic processing in cortex (such as anterior/posterior speech streams, what-and-where auditory pathways, and feature-based—acoustic-phonetic—versus articulatory-gestural pathways; see Giraud & Price, 2001; Kaas & Hackett, 1999, 2000; Rauschecker & Tian, 2000; Romanski et al., 1999; Scott & Johnsrude, 2003; Scott et al., 2000; Steinschneider, Volkov, Noh, Garell, & Howard, 1999; Wise, 2003; Wise et al., 2001; Zattore, 2003). Thus, convergent evidence from neuroimaging research may ultimately provide greater insight in understanding the specific pathways that are disrupted in developmentally language-impaired populations.

This leads to another perspective in the top-down versus bottom-up debate on language impairment—that developmental language impairments stem, at least in

part and in a subset of affected individuals, from basic (i.e., nonspeech-specific) auditory processing impairments. Considerable evidence has accumulated to support this view (Tallal, 1980; Tallal & Piercy, 1973a, 1973b, 1974, 1975; Tallal & Stark, 1981; Tallal, Stark, & Mellits, 1985; reviewed in Fitch et al., 1997; Tallal, Miller, & Fitch, 1993; see also Farmer & Klein, 1995; Hari & Kiesla, 1996; Kraus et al., 1996; McAnally & Stein, 1996, 1997; McCrosky & Kidder, 1980; Neville, Coffey, Holcomb, & Tallal, 1993; Robin, Tomblin, & Kearney, 1989; Wright et al., 1997; Witton et al., 1998). Admittedly, some researchers question the existence of nonlinguistic acoustic deficits, arguing that evidence supports a processing deficit more specific to linguistic information (e.g., see Mody, Studdert-Kennedy, & Brady, 1997). Other researchers question whether nonlinguistic acoustic processing deficits, even if they do exist, are either necessary or sufficient to lead to language disability (e.g., Bishop, Carlyon, Deeks, & Bishop, 1999; see also review by Ramus, 2003). Some failures to replicate auditory temporal processing deficits in LLI and reading-disabled populations can be attributed to subject selection issues (e.g., reporting a failure to find a deficit in children labeled as reading impaired, yet who are only slightly behind the norm in reading ability). Other interpretation issues arise from using tasks that are either too easy or too difficult, producing ceiling or floor effects on the given task. In addition, some researchers have argued that a failure to find auditory processing deficits in all clinically diagnosed dyslexic subjects within a sample (despite near 100% incidence of phonological difficulties), supports in itself a dissociation between basic auditory deficits and phonological problems (Ramus, 2003). If, however, one accepts that basic auditory processing deficits do not represent a sole causal pathway for language-based learning impairments, then such findings need not contradict coexisting evidence of highly significant relationships between early auditory processing and later language outcomes (see Benasich & Tallal, 2002). Interpretation difficulties also arise from comparing speech and nonspeech processing where the stimuli employed are not strictly comparable. Breier et al. (2001) addressed this issue, noting that to experimentally compare the “basic auditory processing deficit” versus “speech-specific” hypotheses, one must ensure that salient cues in nonspeech stimuli are “clearly analogous” to the speech stimuli used in a given experiment. Breier et al. assessed reading disabled (RD) children on just such a matched task (using voice-onset and tone-onset time variations) and determined that RD children exhibited difficulties on both tasks (although the authors could not speculate on any causal relationships between these effects).

In fact, the vast majority of research in this area supports an important role for auditory temporal-spectral processing deficits in the origin of language deficits, at least in a sizable subset of affected individuals. After extensively reviewing the literature on the etiology of LLI, Leonard (1998) stated that

the conclusion that children with SLI [i.e., LLI] have difficulty processing brief or rapidly presented stimuli seems indisputable. These findings are so consistent and demonstrable across task and stimulus variations that it is difficult to imagine that they are not an important piece of the SLI puzzle. (p. 145)

Accordingly, issues regarding the nature and neurobiology of auditory processing deficits—including whether they are specific to the auditory modality and whether they are causal to or merely co-occurring with linguistic deficits—continue to drive research in this field.

Studies addressing these questions have led to a variety of models of LLI, including: the rate-processing constraint hypothesis (for review, see Tallal, Merzenich, Miller, & Jenkins, 1998); the magnocellular deficit hypothesis (for review, see Stein, 2001 and Stein & Talcott, 1999); the cerebellar deficit hypothesis (for review, see Nicolson et al., 2000; Nicolson, Fawcett, & Dean, 2001); the double-deficit hypothesis (for review, see Wolf, 1986); and the attentional dwell time hypothesis (for review, see Hari, Vlata, & Uutela, 1999; Hari & Renvall, 2001). Importantly, all of these hypotheses have in common a constraint in the speed of information processing and/or production that is postulated to disrupt essential components of language learning, beginning with the acquisition of phonological representations. It is important to note that these hypotheses are not mutually exclusive but rather focus on different levels of analysis, including cognitive, anatomical, and physiological. Moreover, all of these hypotheses also begin with the premise that higher cognitive functions are built on more basic underlying neurobiological processes. Thus, if we are interested in ultimately understanding the neurobiological basis of language development and disorders, it is important to assess the integrity of the component acoustic processes critical in analyzing the complex waveform of speech.

A HISTORICAL PERSPECTIVE ON AUDITORY PROCESSING AND LLI

In 1973, Tallal and Piercy (1973a) developed an operant conditioning paradigm to test subjects on the detection, discrimination, and serial recall of sequentially pre-

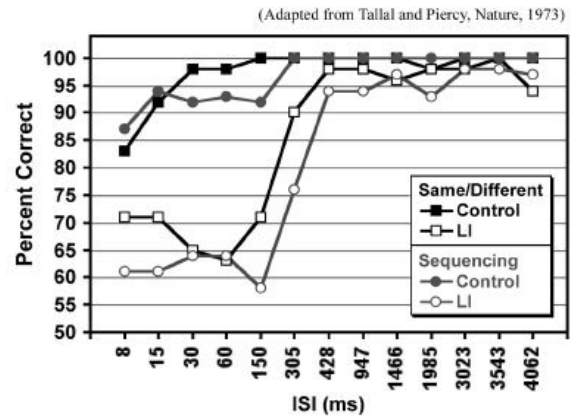


Figure 1: Children with language learning impairment (LLI) ($n = 12$) and age-matched controls ($n = 12$) were presented with two sequential tones separated by an interstimulus interval (ISI) of varying duration. In the same/different task, subjects were trained to press one button on a two-button response panel if the two were the same in frequency, and the other button if they were different. In the sequence task, subjects were trained to press one button for the higher frequency tone and the other for the lower tone. Next, they were presented with two-tone sequences of these tones and required to press the buttons in the order of stimulus presentation. Percentage correct is plotted as a function of ISI; duration of tones = 75 msec; Tone 1 fundamental frequency = 100 Hz; Tone 2 = 305 Hz.

sented discrete stimuli. Subjects were asked to respond by pressing panels on a response box in the order corresponding to stimulus presentation. Six- to 8-year-old children with LLI and matched controls were tested with this procedure using two 75 msec steady-state complex tones differing in fundamental frequency. In trials in which more than one tone was presented, the interstimulus-interval (ISI) was varied from 8 msec to 4062 msec. Figure 1 demonstrates that no significant differences were found between the performance of LLI and age-matched control children when the the ISI was 428 msec or longer. However, the performance of the children with LLI deteriorated rapidly at shorter ISIs. Although all controls were able to reach 75% correct performance at the ISIs of 8 msec or longer, no LLI subject reached a criteria of 75% correct at an ISI of 150 msec or shorter (Tallal & Piercy, 1973a, 1973b).

Tallal and Piercy (1973b) hypothesized that this apparent temporal integration dysfunction (seen for processing acoustic changes in the tens of msec time range) would probably be sufficient to disrupt phoneme perception, and subsequent aspects of language and reading that depend on discreet phoneme representations as well. To investigate this hypothesis, Tallal and Piercy (1974) developed two sets of computer-generated speech sounds. Figure 2 shows examples of the acoustic

waveform of these two classes of sounds. As can be seen in the sound spectrographs (which show frequency changes that occur over time), vowels are steady state (i.e., they transmit the same energy throughout the entire acoustic spectra), although stop-consonant-vowel (CV) syllables, such as /ba/ and /da/, have a transitional period between the release of the consonant and the initiation of the vowel. During this transition, the frequencies (called formants) change very rapidly over time (in the example shown, within 40 msec). Information carried within these brief formant transitions is, in turn, critical to syllable discrimination. Tallal and Piercy (1974) suggested that children with LLI may be specifically impaired in discriminating such brief and rapidly successive acoustic cues within speech but may be unimpaired in discriminating speech sounds characterized by steady-state or longer duration acoustic spectra (such as vowels). They tested this hypothesis by evaluating children with LLI, as well as controls. Stimuli were computer synthesized to provide explicit control of the temporal-spectral components within the acoustic waveform of the speech stimuli. Results showed that children with LLI were unimpaired in their ability to discriminate between steady-state vowels but were unable to discriminate the CV syllables incorporating 40 msec duration formant transitions.

To further determine whether these results were tied to the duration of the formant transitions (as opposed to linguistic properties of vowels vs. consonant-vowel syllables), an additional set of computer stimuli were synthesized. The same CV syllables (/ba/ vs. /da/) were used, but in this study, the duration of the formant transitions were extended from 40 msec to 80 msec. Once again, children with LLI were tested on their ability to identify and discriminate the stimuli. Results showed that the same children (who previously were unable to discriminate between the CV syllables with a formant transition of 40 msec) were now able to discriminate the same CV syllables presented with extended duration (80 msec) transitions (Tallal & Piercy, 1975). This demonstration that speech discrimination could be improved through computer manipulation of temporal-spectral stimulus parameters has led to the recent development of highly effective remediation strategies, specifically using acoustically modified speech to “train” individuals with speech, language, and reading deficits (Merzenich et al., 1996; Tallal et al., 1996; see discussion on Remediation, below). Subsequent studies assessing the ability of subjects with LLI to discriminate many different speech sound contrasts (with variations in numerous temporal and/or spectral cues) have added support to the view that these individuals are impaired in their ability to integrate brief acoustic components that occur within tens

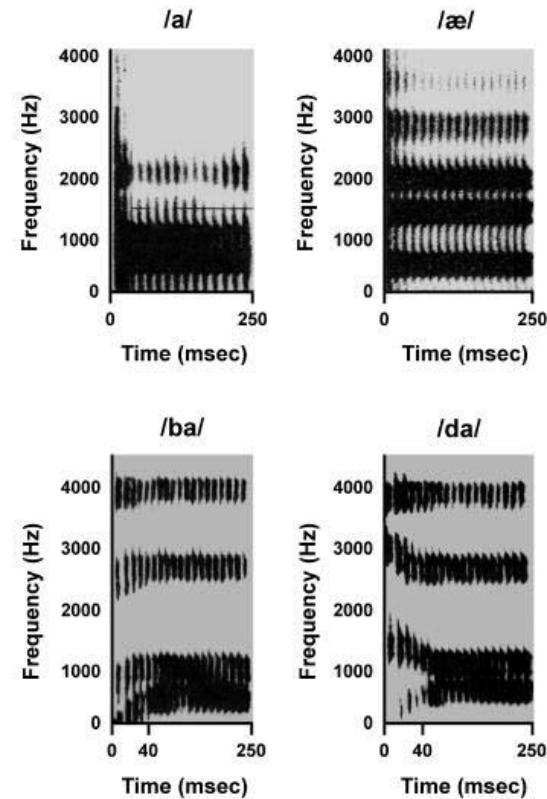


Figure 2: Spectrograms of vowel stimuli /a/ and /æ/, and consonant-vowel (CV) stimuli /ba/ and /da/.

of msec in the ongoing speech stream (e.g., see Stark & Tallal, 1988; Tallal et al., 1985).

Interestingly, spectrographic analyses of speech production data from children with LLI versus controls has shown a remarkable similarity between the pattern of temporal spectral-discrimination impairments and speech-production impairments (Stark & Tallal, 1979). This mirroring of specific temporal spectral constraints in both sensory and motor systems subserving speech has important implications for theories that pertain to neural mechanisms underlying speech in humans. Indeed, studies have demonstrated that temporal-processing deficits in language-disabled populations are not specific to the auditory modality. For example, Stark and Tallal (1988) used a comprehensive battery of non-verbal and verbal sensory and motor tasks designed to investigate visual, tactile, and cross-motor sensory integration, as well as rapid motor sequencing output of children with LLI. Results showed that children with LLI were impaired in their ability to discriminate, sequence, or remember any brief stimulus that was followed rapidly in succession (tens of msec) by a different stimulus,

regardless of the modality of stimulation. They found a similar pattern for the production of rapid, sequential oral or manual movements, again regardless of whether the stimuli were verbal or nonverbal. In a similar vein, evidence has shown that visual temporal integration thresholds are correlated with orthographic skills in normal (unimpaired) school-age children, indicating that temporal processing is apparently critical to language development in multiple sensory modalities (Talcott et al., 2000). The results of these behavioral studies show that some children with LLI exhibit a pervasive, pansensory-motor temporal processing deficit, and this deficit is likely to have profound implications for ongoing language development.

The degree of deficit in nonverbal integration characterizing LLI also appears to be significantly correlated with higher level aspects of linguistic processing—well beyond the phonemic level. For example, in one study of LLI, a significant correlation was found between degree of rapid processing impairment and overall degree of receptive language impairment (based on a comprehensive battery of standardized language tests; $R^2 = .85$, $p < .001$; Tallal et al., 1985). A correlation was also found between the degree of rapid auditory processing impairment and phonological decoding (as measured by the ability to read nonsense words; Tallal, 1980). These findings indicate that a primary inability to process basic acoustic information entering the nervous system in rapid succession may disrupt the development of phonological processes and subsequently lead to more global speech, language, and reading impairments (see also Catts, 1993; Reed, 1989). This developmental cascade model is also consistent with evidence that the phonological deficits that characterize dyslexia appear to be associated, at least in some subjects, with fundamental deficits in processing and integrating brief and rapidly successive transient signals (Farmer & Klein, 1995; Fitch et al., 1997; Hari & Renvall, 2001; Reed, 1989; Tallal, 1980; for review, see Stein, 1993).

PROSPECTIVE STUDIES OF INFANTS AT-RISK FOR LANGUAGE DISABILITIES

A particularly powerful method for studying the relationship between acoustic spectro-temporal processing abilities and language development has been employed by Benasich and colleagues. These researchers compared the abilities of infants born into families with a positive family history for LLI (HX+), as well as those with a negative family history (HX-). Benasich adapted the rapid auditory processing (RAP) methods developed by Tallal to derive individual RAP thresholds for 6-

to 9-month-old infants. In these studies, two brief (70 msec) complex tones differing in fundamental frequency (100 Hz vs. 300 Hz) were presented with interstimulus intervals (ISIs) varying from 500 msec to 8 msec. Infants were operantly conditioned using a two alternative force-choice procedure. This procedure shaped infants to look to a toy to the right of their midline when they heard stimulus sequence 1 (100 Hz followed by 300 Hz), and to a different toy to the left of their midline when they heard stimulus sequence 2 (100 Hz followed by 100 Hz). During the shaping and association phase, the tone pair for each stimulus was separated by a 500 msec ISI. In the variable ISI (test) phase, the ISIs varied from 8 msec to 300 msec. Rapid auditory processing (RAP) thresholds were established for each infant, using an adaptive staircase procedure (for discussion, see Benasich & Tallal, 1996). Initial assessments were obtained when infants were 7.5 months of age, and the sample was followed through age 36 months of age.

Results showed significantly higher mean RAP thresholds for infants born into families with a history of LLI (HX+) as compared to controls (Benasich & Leavers, 2002; Benasich & Tallal, 1996). Examination of relations between infant processing abilities and emerging language through 24 months of age also revealed that individual RAP thresholds at 7.5 months were the single best predictor of language outcome as measured by the Stanford Binet, as well as a standardized preschool language comprehension test. Interestingly, this proved to be the case for infants born into both HX+ as well as HX- families (see Figure 3). At 36 months, RAP thresholds established in infancy quite accurately identified children who were delayed (one *SD* below the mean) in language comprehension as well as on the verbal reasoning component of the Stanford-Binet, and also predicted language outcome for children developing language within the normal range. Importantly, none of the infant variables were capable of discriminating between children on the nonverbal portions of the Stanford-Binet, demonstrating the specificity of the relationship between early RAP thresholds and subsequent individual differences in language development (Benasich & Tallal, 2002).

This represents the first prospective, longitudinal study beginning in infancy demonstrating that (a) individual perceptual processing thresholds for brief, rapidly presented auditory cues can be determined in the first year of life, (b) individual differences in RAP thresholds can predict subsequent language outcomes in toddlers, and (c) auditory processing skills in the first year of life are not only significantly related to subsequent language achievement in at-risk children, but are remark-

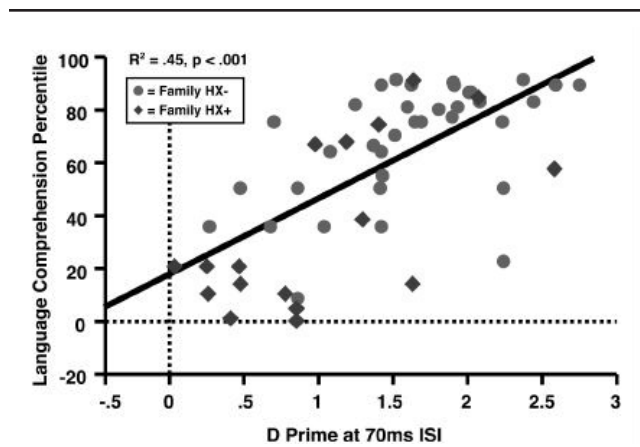


Figure 3: A bivariate plot showing the relationship between rapid auditory processing thresholds at 6 months (as measured by d' at 70ms ISI), and language comprehension percentile at 24 months (standardized Preschool Language Scale). Data shown for 33 control infants (HX-), and 17 infants with a family history of LLI (HX+).

NOTE: Adapted from Benasich and Leevers (2002). ISI = interstimulus interval.

ably accurate in predicting linguistic outcomes at the age of 36 months across a full range of individual differences (i.e., in normal children). These findings are consistent with retrospective evidence that early gap detection thresholds predict language outcome measures in normal children (Trehub & Henderson, 1996), as well as evidence that auditory event-related potentials (ERPs) from infants at risk for language problems differ from controls, and also predict later language outcomes (Leppänen & Lyytinen, 1997; Leppänen, Pihko, Eklund, & Lyytinen, 1999; Molfese & Molfese, 1997; Pihko et al., 1999). Convergent findings thus provide important insights into issues of precedence for auditory temporal processing versus phonological processing deficits in children with LLI. Specifically, temporal processing deficits can be shown preverbally—well before the age at which phonological deficits might be expected to arise. Although causality cannot be definitively established, these early indices are certainly predictive of later phonological and language problems.

Alternate interpretations of the above data can be derived from the fact that by 6 months of age, infants have begun to establish phonemic categories for their native language (a process that is thought to be complete by about 10 months of age; Best, 1984; Eimas, Siqueland, Jusczyk, & Vigorito, 1971; Kuhl, Williams, Lacerda, Stevens, & Lindblom, 1992). Therefore, it could be argued that individual experience in processing native phonological information contributes to differences in RAP thresholds, rather than the other way around. In fact, physiological studies with young infants have shown

that ERPs obtained using CV syllables (which incorporate rapid temporal spectral cues) are also highly predictive of language outcomes in early childhood (e.g., Leppänen et al., 1999; Molfese & Molfese, 1997). However, intercorrelations between these variables seem to suggest that basic acoustic processing, phonemic processing, and language development are all developmentally linked. Ultimately, additional studies will be needed to directly resolve issues of causality and to determine whether neurophysiological mechanisms subserving language development are, in fact, emergent from and dependent on general acoustic information pathways.

LLI: FUTURE RESEARCH DIRECTIONS

In a recent review, Wright, Bowen, and Zecker (2000) highlighted six major developments in the field of language development and LLI that they believed would significantly affect future research. These developments concern the perception of sequential sounds, sound-frequency discrimination, detection of target sounds in noise, the visual magnocellular-deficit hypothesis, individual differences, and remediation. They concluded that “there has been considerable new support for, and refinement of, the idea that the perception of sequential sounds is impaired in individuals with a reading or language disorder” (p. 482). Placing this literature into the framework of backward masking, Wright et al. (1997) demonstrated that, for individuals with LLI, detection of a brief tone presented before a burst of white noise is much more impaired than the detection of that same tone when presented after the noise. This masking is reduced if the noise does not contain the tone frequency. These data provide the first behavioral evidence that the interference between successively presented sounds is temporally asymmetric and frequency specific. This is an important refinement. Although Tallal and colleagues have focused on studies of rapid temporal processing in subjects with LLI (describing results as evidence of a temporal-processing impairment), their results generally derive from the discrimination of brief, rapidly successive frequency changes. Because the impaired perception of successive stimuli probably does not result from overall poor temporal resolution (because individuals with LLI have been shown to be normal in their ability to detect a brief silent gap in white noise; McAnally & Stein, 1996; Schulte-Korne, Deimel, Bartling, & Remschmidt, 1998), it is apparent that the parameters of the sequential information itself (as well as their temporal order and timing) are a part of what taxes the system. This inference is supported by data

from animal models (discussed below), which suggest stimulus complexity and general task demand influence the temporal parameters at which auditory processing deficits emerge.

In sum, although the expression of higher order language deficits is obviously symptomatic in bringing LLI children to clinical attention, the underlying etiology of these linguistic deficits remains a critical point of debate. Do language problems arise through a cascading snowball effect initially triggered by fundamental nonspeech-specific deficits in acoustic processing (bottom-up)? Or do they reflect higher order constraints in neural circuitry that is prespecialized solely for the processing of language (top-down)? Interestingly, populations with language problems have been shown to exhibit other higher order processing deficits that are not necessarily language specific, for example in sequencing or working memory (Mann & Liberman, 1984; Siegel & Ryan, 1989; Swanson, 1992, 1994; Swanson, Cochran, & Ewars, 1989). Generalized working memory deficits in these populations could certainly contribute to some of their phonological problems (see Bradley & Bryant, 1983; Brady, Shankweiler, & Mann, 1983). Importantly, such a causal pathway is not at odds with evidence of basic auditory processing deficits in these same populations, if one allows that multiple trajectories (which could stem from a common underlying cause) might contribute in additive or interactive ways to emergent language deficits.

For example, a recent study experimentally addressed the question of whether verbal working memory deficits or auditory processing deficits contribute more strongly to developmental language problems. Children who were extremely low birth weight (ELBW; with or without periventricular brain damage), and who are in turn at high risk for development of language and reading disabilities, were assessed on a variety of indices including speech discrimination, auditory temporal processing, working memory, phonological processing, and reading ability. Assessment indices were then fit to two competing statistical path models. One showed auditory temporal processing and working memory deficits contributing in parallel to phonological and reading deficits, and the other showed auditory temporal processing deficits as correlating with phonological deficits through a common underlying deficit in working memory. Results produced a much better fit for the model in which both auditory temporal processing and working memory contribute directly to phonological and reading deficits (Downie, Jakobson, Frisk, & Ushycky, 2002). Although this analysis does not directly substantiate issues of causality, the findings strongly suggest that auditory processing deficits observed in LLI and dyslexic

populations do not reflect simply a co-occurring but noncausal problem. Rather, basic auditory and higher order memory deficits might contribute to the development of phonological and reading difficulties through parallel (or even interactive) routes. Such a view is consistent with evidence that basic auditory processing deficits in children with LLI become more pronounced (i.e., are elicited at successively longer stimulus durations) when the working memory load of the acoustic sequencing task is increased (for example, by adding more elements and/or complexity to a stimulus; for review, see Stark & Tallal, 1988). Indeed, Downie et al. (2002) found a significant correlation between auditory processing and working memory, suggesting that some common factor—perhaps underlying neurophysiological disruption—could be affecting both indices.

NEUROIMAGING STUDIES AND LANGUAGE DISABILITIES

Advances in *in vivo* noninvasive neuroimaging technologies, including event-related potentials (ERP), structural magnetic resonance imaging (MRI), functional MRI (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) have all led to significant progress in understanding neurobiological substrates of language development and disorders. In 1991, Jernigan, Hesselink, Sowell, and Tallal reported the results of a volumetric MRI brain analysis on children with LLI and controls. The authors found a significant reduction in gray matter volume in subcortical structures (including striatum and thalamus) in children with LLI, as well as bilateral reduction in cortical structures known to subserve language. Aberrant patterns of cerebral lateralization were also demonstrated both in prefrontal and parietal regions. Similar volumetric and asymmetry differences have been reported in other MRI studies of individuals with language problems, including a lack of the normal left greater than right pattern in the planum temporale (located in Broca's area), and aberrant asymmetry in the parietal and frontal regions (Cowell, Jernigan, Denenberg, & Tallal, 1995; Larsen, Høien, Lundberg, & Odegaard, 1990; Leonard et al., 1993). Decreased physiological activation in these same regions has been reported for children with LLI using evoked potential recording (Neville et al., 1993). Functional neuroimaging techniques (PET, fMRI) have also been used to assess adult dyslexics and have consistently shown reduced activity in left perisylvian regions as compared to controls during a variety of phonological processing tasks (Hagman et al., 1992; Paulesu et al., 1996; Rumsey et al., 1992, 1997; Shaywitz et al., 1998).

Recently, Temple et al. (2000) used fMRI to examine the neural response to rapidly changing nonlinguistic auditory stimuli in dyslexic adults as compared to normal reading adults. Stimuli comprised computer synthesized nonspeech analogs (originally designed by Belin et al., 1998), which incorporated rapid or slow acoustic transitions at the beginning and end of a steady-state stimulus (i.e., the spectral/temporal acoustic changes that characterize CVC syllables). Importantly, these stimuli had no linguistic relevance (see Figure 4). Subjects performed a pitch discrimination task while alternating between blocks of stimuli incorporating rapid (40 ms) or slow (200 ms) formant transitions. The pitch discrimination task was unrelated to the manipulation of temporal acoustic changes, so any differences in neural activation would reflect differential response to rapid acoustic change rather than an explicit discrimination based on frequency. Statistical analysis of the fMRI data demonstrated that the largest area of activation for normal readers was in the left prefrontal region, between the middle and superior frontal gyri in Brodmann area 46/10/9. Analysis of the dyslexic readers revealed no left frontal response to the rapidly, as compared to slowly, changing stimuli (see Figure 5). Individual analysis revealed that 9 of 10 normal readers exhibited a left frontal response to the rapidly as compared to slowly changing stimuli, whereas only 2 of the 8 dyslexic readers exhibited differential left frontal activity for this comparison (Temple et al., 2000).

Functional neural imaging studies with dyslexic children and adults have also shown disruption in the neural responses to both phonological and nonlinguistic transient auditory stimuli. For phonological processing, both dyslexic adults and children failed to show activation in posterior language brain regions but did show activation in left frontal language areas. During rapid auditory processing, dyslexic children and adults failed to show activity in left prefrontal brain areas. This atypical neural processing in both frontal and posterior areas of the language network in the left hemisphere led to the hypothesis that developmental dyslexia could be described as a “disconnection” syndrome (Paulesu et al., 1996). This hypothesis was tested directly in two PET studies (Paulesu et al., 1996; Rumsey et al., 1992), which showed that dyslexic adults exhibit a decreased correlation in functional activity between temporal parietal and frontal brain areas.

WHITE MATTER AND LANGUAGE DISRUPTION

In general, so-called disconnection deficits suggest a disruption of white matter because myelinated fiber tracts typically interconnect functionally related brain

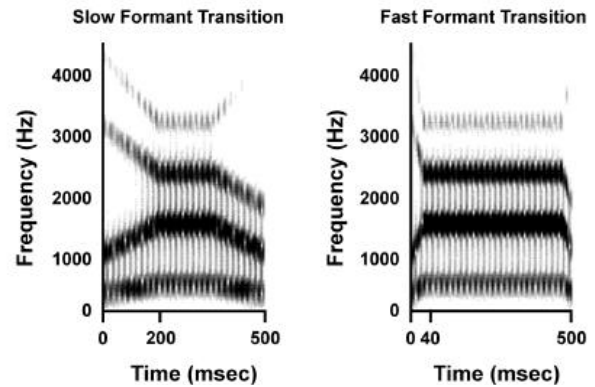


Figure 4: Nonspeech analogues. Spectrograms of stimuli are shown with frequency (Hz) on the vertical axis and time (ms) on the horizontal axis. The spectro-temporal structure of the nonspeech analogues with fast formant transitions was similar to that of consonant-vowel-consonant speech syllables (i.e., rapid acoustic changes occurring over 40 ms and surrounding a 520 ms steady-state period). In the slow formant transition stimuli, the duration of the acoustic transitions were extended to 200 msec.

NOTE: Adapted from Temple et al. (2000).

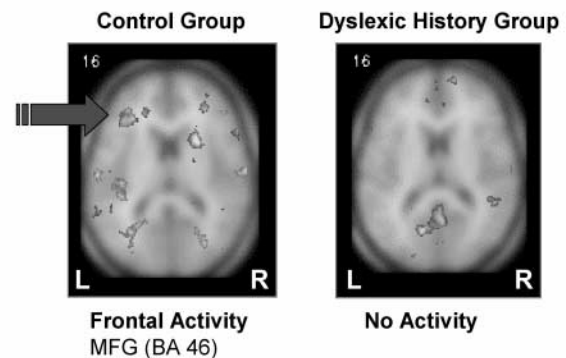


Figure 5: fMRI response to rapid auditory stimuli in normal ($n = 10$) and dyslexic ($n = 8$) readers. Normal readers show a significant frontal activity difference between rapid and slow nonspeech analogues. Dyslexic readers show (on the smoothed averaged anatomies of dyslexic readers) no differential left frontal response to rapid versus slow stimuli.

NOTE: Adapted from Temple et al. (2000).

areas. Accordingly, white matter organization was recently studied in individuals with dyslexia using a relatively new imaging technique called diffusion tensor imaging (DTI). This method provides information regarding white matter microstructure (e.g., see Klingberg et al., 2000). In this study, dyslexic adults were found to exhibit disruption in temporal parietal white matter, a region of white matter connecting left hemi-

sphere language regions to more frontal and posterior brain areas. Interestingly, the degree to which the left temporal parietal white matter was disorganized was significantly correlated with reading ability, suggesting that the organization of this white matter plays a critical role in reading. Klingberg et al. (2000) hypothesized that the disruption in white matter in the left hemisphere language areas, connecting frontal and posterior brain regions, might play a specific role in the rapid transmission of sensory information between these brain regions. They further hypothesized that disruptions in white matter microstructure in dyslexic individuals may compose a part of the neural substrate linking rapid temporal-spectral processing deficits with phonological deficits known to characterize dyslexic readers (see also Golestani, Paus & Zatorre, 2002).

Ultimately, increasingly refined neuroimaging studies performed during auditory processing tasks will lead to a more detailed understanding of patterns of functional deficits associated with language disability, as well as anatomical underpinnings for these effects. Indeed, cutting-edge neuroimaging and electrophysiological studies have recently revealed evidence of functional subdivisions in normative cortical processing of acoustic stimuli, in both humans and nonhuman primates (see Giraud & Price, 2001; Kaas & Hackett, 1999, 2000; Rauschecker & Tian, 2000; Romanski et al., 1999; Scott & Johnsrude, 2003; Scott et al., 2000; Steinschneider et al., 1999; Wise, 2003; Wise et al., 2001; Zattore, 2003). Such findings suggest that acoustic processing subsystems could be differentially affected in impaired individuals.

NEUROMIGRATIONAL ANOMALIES AND LANGUAGE DISABILITY

Another possible etiology for anomalous neurocircuitry associated with developmental disorders of language involves neuronal migrational disorders (Barth, 1987). Neuronal migrational disorders occur when control mechanisms regulating the final positioning of newly generated migrating neural cells are disrupted. This can occur via global/regional factors (e.g., regional hypoxia/ischemia, systemic teratogenic or genetic factors) as well as focal factors (e.g., focal ischemia and/or excitotoxic activity), and can result in permanent cellular/structural anomalies including agyria/pachygyria, microgyria, dysplasia, and neuronal and leptomeningeal heterotopias and focal ectopias (for review, see Barth, 1987).

In 1979, Galaburda and Kemper reported on a post-mortem cellular analysis of the brain of an adult dyslexic male. This subject was characterized by normal intelli-

gence, but delayed speech development, in the pre-school period, and difficulties reading and spelling in elementary school. Findings included the presence of cortical dysplasias and polymicrogyria in the left temporal lobe, and cortical dysplasias throughout the left hemisphere.

Subsequently, Galaburda, Sherman, Rosen, Aboitiz, and Geschwind (1985) published an account of three additional brains obtained postmortem from adult male dyslexics. One of these subjects exhibited delayed speech development followed by reading difficulties in school, and the others exhibited early childhood learning disabilities followed by reading difficulties. Again, numerous cellular anomalies including neuronal ectopias and cortical dysplasias were observed, primarily in left perisylvian/temporal (language) regions. The authors ascribed these cellular anomalies to focal disruption of neocortical neuronal migration, which probably arose during the prenatal period (for review, see Galaburda, 1994).

More recently, the same brains that had shown focal cortical disruption were further analyzed and found to also show disruption at the thalamic level. Specifically, analysis of the lateral geniculate (visual) nucleus (LGN) (Livingstone, Rosen, Drislane, & Galaburda, 1991) revealed that the dyslexic brains had significantly smaller magnocellular (large) LGN cells (28% smaller in surface area) but no size differences in parvocellular (small) LGN neurons, as compared to controls. Concurrent electrophysiological evidence showed that healthy adult dyslexics exhibited anomalies in neural activation during performance of tasks known to depend on the magnocellular system. Livingstone and colleagues suggested that the focal cortical anomalies seen in dyslexics may be linked to disruptions of thalamic development, including the magnocellular pathways of the LGN responsible for transmission of low spatial frequency, low luminance contrast, high rate-of-change information (see also Lehmkuhle, Garzia, Turner, Hash, & Baro, 1993; Lovegrove, Garzia, & Nicholson, 1990; Slaghuis, Lovegrove, & Freestun, 1992; Stein & Talcott, 1999). Interestingly, evidence of thalamic anomalies has also been seen in the auditory (medial geniculate) nucleus (MGN). Specifically, dyslexics exhibit a significant shift toward more small and fewer large cells in the left MGN as compared to controls (Galaburda, Menard, Rosen, & Livingstone, 1994). Although the functional relevance of these findings remains unclear, they have been viewed in light of concurrent data demonstrating that language-disabled subjects exhibit deficits in processing rapidly changing auditory information.

THE NEUROBIOLOGY OF LLI: WHERE ARE WE TODAY?

In summary, convergent data support a hypothesis that focal cortical neuromigrational anomalies, thalamic (sensory) anomalies, and/or delayed or disrupted myelination may contribute to a neurobiological lattice underlying anomalous cortical activation patterns seen during speech and language processing in impaired individuals. Moreover, in addition to linguistic deficits, individuals with LLI may also be characterized by deficits in rapid sequential auditory processing, transient visual processing, attention, and working memory. These findings are also supported by neurobehavioral studies of animal models with similar neuromigrational anomalies (discussed below).

Support for this model also includes prospective, longitudinal studies with infants (Benasich & Tallal, 2002), as well as studies showing that sensory integration thresholds in the auditory modality are predictive of verbal IQ, even in normally developing children, and are correlated with phonological awareness components of reading in school-age children (Talcott et al., 2000). Collective data suggest that individual differences in temporal integration thresholds play a highly significant role both in normal development of—and disorders of—various components of speech, language, and reading, and that basic sensory integration thresholds may be driving developmental trajectories from very early in life (Benasich & Tallal, 1996, 2002; Lepänen & Lyytinen, 1997; Leppänen et al., 1999; Molfese & Molfese, 1997).

Still, the neurobiological features of this hierarchical system remain unclear. According to Hebb (1949), mechanisms probably operate to increase the connection strengths between “nearly simultaneously” excited neurons within cortical networks (creating in turn “cortical cell assemblies”). The duration over which “nearly simultaneous” information is chunked is, in turn, likely to have a highly significant affect on the fidelity and selectivity of perceptual representations. However, we know very little about the neural mechanisms that determine individual differences governing what is considered “nearly simultaneous.” Although we accept the premise that neurons that fire together wire together, we know considerably less about what drives individual differences in what the nervous system will bind together as “nearly simultaneous.” In fact, there are numerous potential prenatal and postnatal candidate processes (including genetic and environmental mechanisms) that could affect individual differences in neural chunking rates. Given that it is important to investigate the neurobiological basis for these differences, advances in this field would clearly benefit from the use of animal models. Unfortunately, speech, language, and reading

are species specific. However, although animals do not learn to talk or read, evidence from many other areas of cognitive neuroscience research shows that animal models can be extremely informative in understanding the neurobiological basis for lower level processes that subserve higher cortical functions. Furthermore, there is little empirical evidence to date to suggest that the neural systems involved in the basic acoustic analysis of the complex waveform of speech operate substantially differently from those involved in comparable acoustic analysis of nonspeech signals. As such, these systems should be amenable to study in animal models.

MICROGYRIA, AUDITORY PROCESSING AND THALAMIC MORPHOLOGY IN RATS

Fortuitously, neuromigrational anomalies similar to the ones seen in human dyslexic brains can be studied in rodent species (e.g., spontaneous neural ectopias in mice and induced cerebrocortical microgyria in rats and mice; Humphreys, Rosen, Press, Sherman, & Galaburda, 1991; Rosen, Burstein, & Galaburda, 2000; Rosen, Galaburda, & Sherman, 1989; Rosen, Press, Sherman, & Galaburda, 1992; Rosen, Sherman, Richman, Stone, & Galaburda, 1992; Sherman, Galaburda, Behan, & Rosen, 1987; Sherman, Galaburda, & Geschwind, 1985; Sherman, Rosen, Stone, Press, & Galaburda, 1992). By comparing intact and anomalous subjects on a variety of tasks, animal models may provide an opportunity to experimentally bridge the neurobiological and behavioral evidence obtained from human language disabled populations in a way that is often not possible when studying living human subjects.

Following the discovery of cellular developmental anomalies in the brains of dyslexics, rodent models were developed to simulate these anomalies through perinatal intervention. For example, Humphreys and colleagues (1991) found that focal freezing lesions on the skull of postnatal Day 1 (P1) rats produced neocortical microgyria with striking histological similarity to those seen in dyslexic humans (see also Dvorak & Feit, 1977; Dvorak, Feit, & Juránková, 1978; Rosen, Press, et al., 1992). The next step was to assess the behavioral profile of subjects with induced microgyria. Accordingly, Fitch, Tallal, Brown, Galaburda, and Rosen (1994) adapted an operant conditioning paradigm to test auditory processing in rats, training subjects to perform a target-identification of a two-tone sequence. The temporal parameters of the two-tone stimuli (i.e., total stimulus duration) were shortened across days of testing so that subjects were tested at long as well as short stimulus duration conditions. Results showed that microgyric male rats exhibited auditory processing deficits only at short stimulus durations (see Figure 6). This deficit was strik-

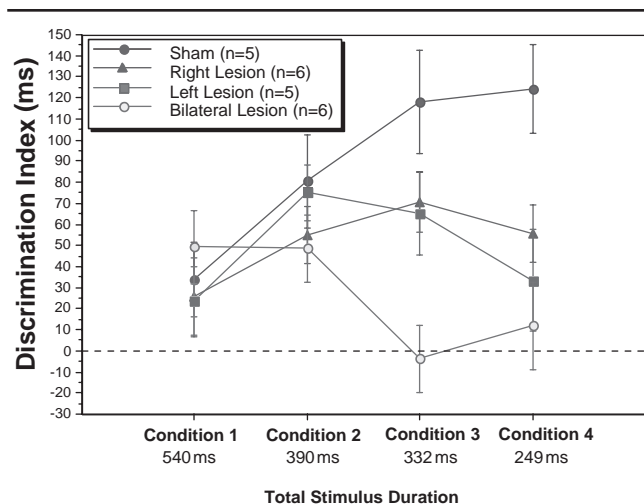


Figure 6: Discrimination indices for sham and microgyric rats tested in a two-tone sequence target identification task as a function of treatment group and total stimulus duration. For discrimination indices, zero represents chance, whereas positive values reflect discrimination of the target.

NOTE: Adapted from Fitch, Tallal, Brown, Galaburda, and Rosen (1994).

ingly similar to that seen in children with LLI, using a similar two-tone sequence discrimination task (Tallal & Piercy, 1973a, 1973b).

These results provided evidence of a link between a known neuropathological correlate of dyslexia and a known behavioral deficit associated with language disability. Moreover, the results contradict the notion that the effects occurred via direct (local) disruption of cortex (e.g., through local hyperexcitability associated with increased seizure activity as seen in slice studies of microgyric cortex; see Jacobs, Gutnick, & Prince, 1996; Jacobs, Morgensen, Warren, & Prince, 1999). Indeed, many colleagues and reviewers have expressed surprise over the fact that focal freezing lesions were induced in primary sensory-motor cortex (SM-I)—not temporal cortex—and that these SM-I lesions somehow led to rate-specific auditory processing deficits. Interestingly, it has been shown in multiple studies that bilateral P1 freezing lesions placed in the sensory-motor, occipital and frontal cortices of male rats all lead to significant auditory processing deficits in adulthood (Herman, Galaburda, Fitch, Carter, & Rosen, 1997; see also Clark, Rosen, Tallal, & Fitch, 2000b). Moreover, in these same studies, male rats with neonatally induced microgyria also exhibited morphological changes in the medial geniculate nucleus (MGN)—specifically, a significant shift toward more smaller and fewer large cells (Herman et al., 1997)—much like that seen in the MGN of human dyslexic brains (Galaburda et al., 1994). Again, this effect was seen regardless of focal lesion location in cortex.

In sum, these collective results support the view that developmental focal damage of the male rat cortex exerts pervasive reorganizational effects, which ultimately may be associated with anomalies in auditory thalamic (MGN) morphology. The mechanisms underlying this effect may involve developmental propagation from disrupted cortex to the thalamus, potentially via descending projections that develop postnatally in rodents (e.g., Miller, Chou, & Finlay, 1993; see also Goldman-Rakic & Rakic, 1978; Rosen et al., 2000; Schneider, 1981). These MGN anomalies, in turn, appear to be associated with severely deleterious effects on auditory processing of stimuli that incorporate rapid sequential change. In language-disabled humans, similar anatomical and behavioral effects are seen. We can hypothesize that anatomically based defects in auditory processing may exert cascading effects on phonological perception and, potentially, the development of language and reading skills (for further discussion, see Fitch, Miller, et al., 1997; Fitch, Read, & Benasich, 2000).

More recently, the above rodent model has been adapted to an acoustic startle reduction (reflex modification) paradigm. The startle reduction paradigm does not require motivation or attention, and data can be collected from the first day of testing (e.g., Wecker, Ison, & Foss, 1985). This paradigm utilizes a loud (105dB-110 dB) 50 ms burst of white noise, presented at random intervals unpredictable to the subject (for reviews, see Hoffman & Ison, 1980; Ison & Hoffman, 1983). When the noise bursts are presented, large-amplitude motor responses (startle responses) occur. These movements are measured by placing subjects on load-sensing platforms, which transduce and transmit movement information that can be recorded, quantified, and analyzed. In a simple version of the acoustic startle paradigm, some trials include a 75 dB prepulse cue (such as a tone) that immediately precedes the noise burst. If the prepulse stimulus (or cue) is detected, this cue produces a significant attenuation of the startle response on that trial (i.e., startle reduction or reflex modification). More complex versions of this paradigm include the presentation of a silent gap embedded in low-level background white noise as the prepulse cue (e.g., Ison, 1982; Ison, O'Connor, Bowen, & Bocirnea, 1991; Ison & Pinckney, 1983; Leitner et al., 1993). Response attenuation data can then be analyzed to provide an index of prepulse stimulus detectability. The startle-reduction paradigm has also been adapted to incorporate a repeating background of two-tone sequences, paired with the presentation of a reverse sequence (oddball) immediately before the noise burst on cued trials. Such a format derives from the oddball stimulus presentation design used in electrophysiological research (e.g., Clark, Rosen, Tallal, &

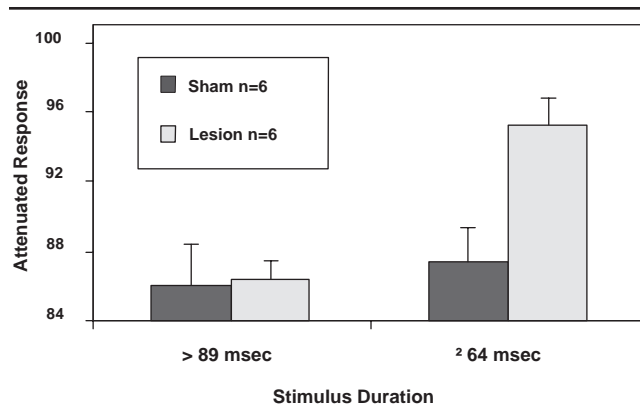


Figure 7: Attenuated startle response as a function of stimulus duration, for sham and microgyric male rats (from Clark, Rosen, Tallal, & Fitch, 2000a). Responses at/near 100% indicate lack of stimulus discrimination.

Fitch, 2000a; Kraus, McGee, Littman, Nicol, & King, 1994). Assessment of sham and microgyric male rats using this paradigm showed (a) a highly significant reduction in subjects' startle response on cued (oddball) trials for both groups using a two-tone sequence separated by 350 ms (indicating that all subjects were able to detect the oddball [deviant] two-tone sequence as different from the background two-tone sequence) and (b) significant sham/microgyric differences for stimuli of total duration less than 89 ms (with microgyric males showing significantly less response attenuation for "short" duration stimuli; Clark et al., 2000a, see Figure 7).

Because identical acoustic stimuli were used in both the operant target ID auditory discrimination task and the startle-reduction paradigm, a comparison could be made between the stimulus properties that elicited processing deficits in microgyric animals as a function of these different test paradigms. This provides an important comparison because the operant task is a fairly demanding task that requires subjects to learn a target, listen to a stimulus, make a comparison, and then determine if that stimulus is the subject's target. The startle-reduction paradigm, in contrast, requires only the passive recognition of a stimulus change and is thus considerably less demanding. Interestingly, although two-tone sequences of 249 ms duration have been found to elicit highly significant processing deficits in microgyric animals in the operant paradigm, the startle-reduction paradigm (in which the same tone sequences were presented but in a passive oddball detection format) showed that only tone sequences shorter than 89 ms total duration would elicit response differences between control and microgyric animals. This suggests, in turn, that cognitive demand or load may interact, in some fashion, with basic auditory processing deficits evi-

denced in the microgyric group. The notion of parallel (and possibly interactive) deficits in auditory processing and, for example, working memory, is discussed further below.

Finally, Clark, Tallal, Rosen, Peiffer, and Fitch (2000) tested synthetic speech processing in sham and microgyric male rats. Results showed that (a) neither group exhibited significant discrimination of the synthetic syllables /da/ versus /ga/ on any day, but (b) microgyric subjects were significantly impaired relative to shams in the discrimination of /ba/ from /wa/ on Day 1 of testing. The latter stimuli are discriminable based solely on differences in the duration of formant transitions. These preliminary findings have also been replicated in young (P20–35) sham and microgyric male rats (Thomas, Clark, Benasich, & Fitch, 2001). Such findings further support the relationship between malformations of the cerebral cortex and deficits in rapid auditory and speech processing and validate the continued assessment of the behavioral consequences of cerebrocortical microgyria in the rat as a tool in understanding the etiology of developmental language disabilities.

SEX DIFFERENCES IN THE BEHAVIORAL AND MORPHOLOGICAL CONSEQUENCES OF MICROGYRIA

In 1990, Humphreys, Kaufmann, and Galaburda assessed the postmortem brains of three dyslexic women and suggested that the anomalies characterizing dyslexic female brains may differ from those seen in dyslexic males. Although the sample size was too small to empirically assess the sex difference, considerable related data supports the existence of fundamental sex differences in brain organization and development (Bachevalier, Brickson, Hagger, & Mishkin, 1990; Bachevalier & Hagger, 1991; Beatty, 1992; Breedlove, 1992; Clark & Goldman-Rakic, 1989; Fitch, Brown, O'Connor, & Tallal, 1993; Kimura & Harshman, 1984; Kulynych, Vlader, Jones, & Weinberger, 1994; McGlone, 1980; Raz, Lauterbach, Hopkins, Glogowski, & Porter, 1995; Shaywitz et al., 1995). To address potential sex differences in response to early brain injury, the Fitch et al. (1994) operant study was repeated using both male and female rats with P1 bilateral freezing lesions of SM-I, or sham surgery. A substantial sex difference was found. Behavioral deficits at rapid rates of stimulus presentation were replicated in males but were not seen in females. Female rats with induced microgyria showed no deficits in auditory discrimination performance at any condition (Fitch, Brown, Tallal, & Rosen, 1997; see Figure 9). Subsequent anatomical analyses found that lesioned females also had no aberrant morphology of the medial geniculate nucleus (MGN), although male

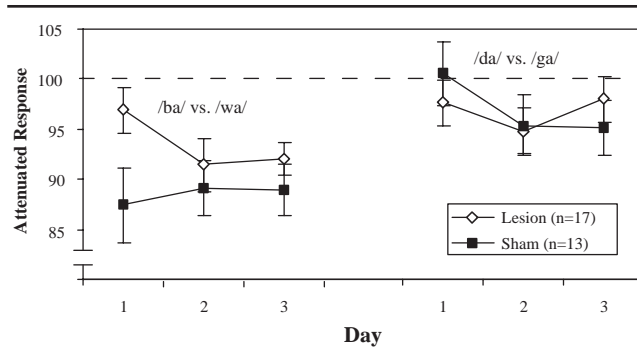


Figure 8: Attenuated response to synthetic speech stimuli in an adapted oddball startle reduction paradigm, for sham and microgyric adult male rats (from Clark, Tallal, Rosen, Peiffer, & Fitch, 2000). Responses at or near 100% indicate failure to discriminate the stimulus.

littermates with identical cortical lesions did show significant changes in the distribution of cell size within the MGN (Herman et al., 1997). Subsequent analyses of the MGN in microgyric male, female, and testosterone-treated female rats revealed that these sex effects appear to be mediated by interactions between response to early injury and exposure to testosterone (Rosen, Herman, & Galaburda, 1999).

The factors underlying a female advantage in response to focal developmental cortical damage remain unclear. However, we have previously reported a sex difference in functional organization of the rat brain, with males exhibiting greater asymmetry than females for rapid auditory processing (Fitch et al., 1993). In humans, sex differences in language recovery following left-hemisphere damage have been consistently observed, with females showing significantly better recovery (McGlone, 1980). Sex differences in the magnitude of the right ear advantage (REA) for the discrimination of verbal material have also been reported, with males showing a larger and more consistent REA (Kimura & Harshman, 1984). Sex differences have been reported in the pattern of cerebral blood flow during the performance of verbal tasks (Wood, Flowers, & Naylor, 1991), in asymmetry as measured by fMRI during verbal tasks (Shaywitz et al., 1995), and in structural asymmetry of the right and left plenum temporale as measured by MRI (Kulynych et al., 1994). These results all support the notion of sex differences in the pattern of cerebral organization, particularly for language-related functions. Such findings speak, in turn, to a possible hormonal role in establishing cerebral organization of language functions and possibly in mediating behavioral response to focal injury (for discussion, see Lambe, 1999). Animal studies support this assertion by demonstrating hormonally mediated differences in the maturation rate

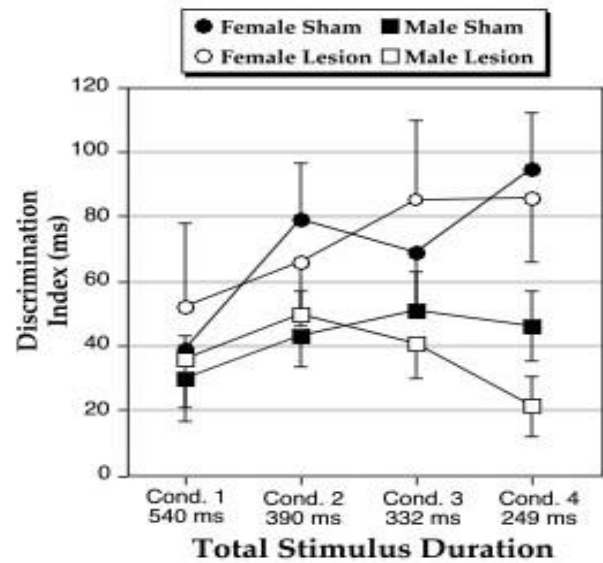


Figure 9: Discrimination indices in a two-tone sequence target identification task as a function of sex, treatment group, and total stimulus duration. For discrimination indices, zero indicates chance, positive indices indicate discrimination.

NOTE: Adapted from Fitch, Brown, Tallal, and Rosen (1997).

of specific cortical regions, which, in turn, critically influence the behavioral effects of lesioning these regions (e.g., Bachevalier et al., 1990; Bachevalier & Hagger, 1991; Clark & Goldman-Rakic, 1989; Kolb & Cioe, 1996). Geschwind and Galaburda (1985) postulated that differential androgen exposure in utero may influence the development of cerebral organization, particularly for language, and further suggested that exposure to androgens may render the male brain more susceptible to adverse effects following developmental injury. Other studies suggest that female hormones may protect the brain from the deleterious consequences of cortical damage (e.g., see Roof, Duvdevani, & Stein, 1993).

It is thus possible that sex differences in early hormonal exposure, neural maturation, brain organization, and response to focal brain injury may relate to our finding that male but not female rats exhibit behavioral and morphological defects in response to P1 cortical injury (Fitch, Brown, et al., 1997). These collective data may further relate to reports of a higher incidence of language and reading impairments among males as compared to females (Finucci & Childs, 1983; Flannery & Liederman, 1996; Flannery, Liederman, Daly, & Schultz, 2000; Gualtieri & Hicks, 1985; Liederman & Flannery, 1995; Niels & Aram, 1986), although the sex difference in incidence of language disability has been attributed to referral bias and is not universally supported (Shaywitz, Shaywitz, Fletcher, & Escobar, 1990).

AUDITORY PROCESSING DEFICITS IN ECTOPIC MICE

Studies have also been performed to examine auditory processing in mice that exhibit spontaneously forming focal malformations of cortex (ectopias). Results show clear evidence of auditory processing deficits similar to those seen in the microgyric rat model, in ectopic subjects of both the BXSb/MpJ and NZB/B1NJ mouse strains.

In the case of BXSbs, ectopic male mice were found to be significantly worse than nonectopics in detecting the shortest detectable silent gap presented in a background of white noise (Clark, Sherman, Bimonte, & Fitch, 2000; see Figure 10). These behavioral data were paralleled by auditory evoked response potential (AERP) data from adult male BXSb mice. AERP results showed that ectopic male BXSb had a smaller negative deflection for the onset of a second acoustic stimulus following a short, but not long, inserted tone (Frenkel, Sherman, Bashan, Galaburda, & LoTurco, 2000). Interestingly, a similar result was found for dyslexic as compared to control adults using MEG (Nagarajan et al., 1999).

NZB mice that exhibit spontaneously forming ectopias were also assessed. Again, ectopic male mice demonstrated evidence of impaired auditory processing as compared to nonectopics for short duration stimuli (see Figure 11) and, again, AERP recordings from a subset of these same animals confirmed that ectopic subjects displayed a reduced negative deflection to the onset of a second acoustic stimulus following a short, but not long, inserted tone (Peiffer et al., 2001; see Figure 12).

Recent findings also continue to support the existence of sex differences in the behavioral consequences of focal malformations, specifically showing that ectopic male but not ectopic female BXSb mice exhibit deficits in processing rapidly occurring auditory stimuli (Peiffer, Rosen, & Fitch, 2003).

These convergent findings from humans and animal models have critical implications for the robust relationship between focal malformations of cortex and temporally specific auditory processing deficits, which are evident across species, for different types of malformations, in different cortical locations, on divergent types of auditory assessment tasks, and appear to be influenced across species by a sex difference.

COGNITIVE AND MEMORY EFFECTS IN ECTOPIC MICE

Data obtained by Denenberg and colleagues have also shown differential patterns of learning and memory for ectopic as compared to nonectopic mice of the BXSb/MpJ and NZB/B1NJ strains (Balogh, Sherman,

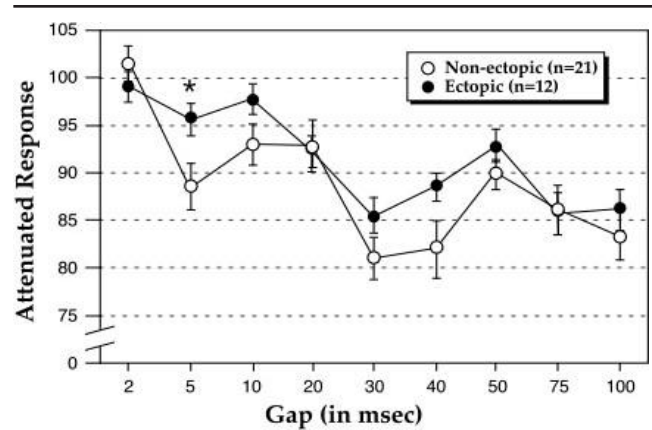


Figure 10: Attenuated startle response (vertical axis) as a function of gap duration (horizontal axis), for ectopic and nonectopic BXSb mice. Responses at or near 100% indicate lack of discrimination of the stimulus. The * indicates a significant difference between ectopics and controls for the 5 ms gap (from Clark, Sherman, Bimonte, & Fitch, 2000).

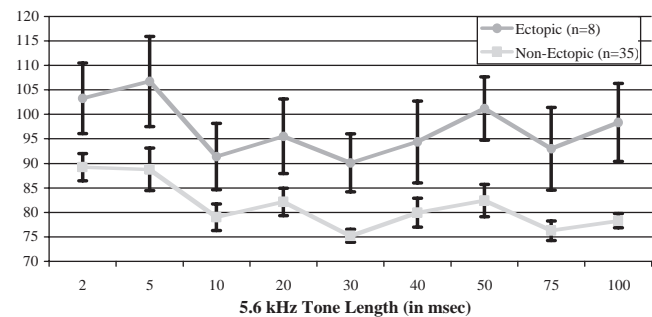


Figure 11: Attenuated startle response (vertical axis) as a function of embedded 5.6 KHz tone duration (horizontal axis) for ectopic and nonectopic NZB mice. Responses at or near 100% indicate lack of discrimination (evident for ectopic NZB at 2 and 5 ms embedded tones). Nonectopic NZB did show significant discrimination of 2 ms and 5 ms embedded tones. In addition, the ectopic NZB were, overall, significantly worse than nonectopics at detecting all durations (from Peiffer et al., 2001).

Hyde, & Denenberg, 1998; Boehm, Sherman, Hoplight, et al., 1996; Boehm, Sherman, Rosen, et al., 1996; Denenberg, Sherman, Schrott, Rosen, & Galaburda, 1991; Denenberg et al., 1996; Hyde, Sherman, Hoplight, & Denenberg, 2000a, 2000b; Schrott et al., 1992). In this important series of studies, Denenberg and colleagues showed that (a) the presence of cortical ectopias has a significant impact on learning and memory measures in both strains of mice that were studied, including a significant working memory deficit associated with the presence of ectopias in frontal cortex and (b) ectopia effects

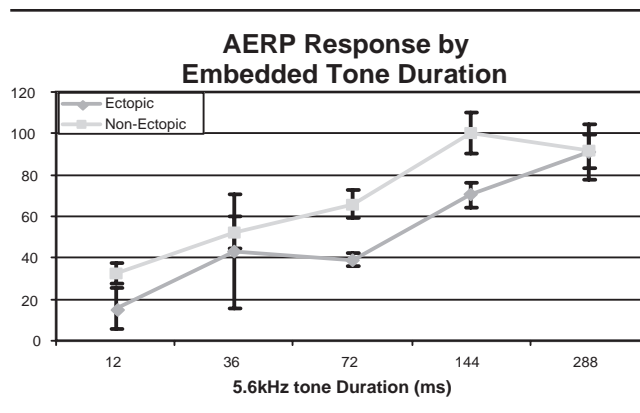


Figure 12: Ratio of peak AERP to first and second onsets of 10.5 kHz tone ($A2/A1 \times 100$, vertical axis), with an inserted 5 kHz tone of variable duration (horizontal axis). Data from ectopic and nonectopic NZB mice. Results show that groups were the same at long durations (288 ms), whereas at shorter durations (144 and 72 ms), NZB ectopics respond significantly less to the second onset than NZB nonectopics. $A2$ = AERP amplitude to second onset; $A1$ = AERP amplitude to first onset (from Peiffer et al., 2001).

on learning and memory processes appear to be more sensitive to cortical ectopia location, (i.e., effects differ for the two strains studied). That is, the effects of frontal versus SM-I ectopias on learning/memory appear to be quite different. This location sensitivity contrasts directly with the location-insensitive effects of cortical malformations on auditory processing deficits and suggests that different neurodevelopmental pathways may underlie these effects. It has been suggested, for example, that working memory deficits associated with frontal ectopias might be mediated through local alterations in cortical circuitry (e.g., see Gabel & LoTurco, 2001). Auditory deficits associated with these malformations, on the other hand, are more likely the result of reorganizational changes at the thalamic level initiated by cortical malformations, and appear to be insensitive to cortical lesion location (e.g., Herman et al., 1997).

ANIMAL MODELS OF SENSORY TRAINING AND PLASTICITY

In addition to animal models of auditory processing deficits, an intriguing series of animal studies has demonstrated that sensory experience can alter not only sensory processing thresholds but also physiological indices of sensory processing in the brain. For example, the acoustic frequency maps in temporal cortex in nonhuman primates can be altered by sound experience with particular frequencies (Kilgard & Merzenich, 1998; Recanzone, Schreiner, & Merzenich, 1993). Importantly, these effects can be seen in adult animals, suggest-

ing a heretofore unimagined level of plasticity in the adult cortex with respect to sensory processing (for reviews, see Merzenich & Jenkins, 1995 and Merzenich, Tallal, Peterson, Miller, & Jenkins, 1999). Similar effects have been seen at the behavioral and neurophysiological level in humans (Karni & Sagi, 1991; Karni et al., 1995), suggesting that similar organizational changes might be induced (with the right experience) in the brains of language-disabled humans.

DEVELOPMENTAL LANGUAGE DISORDERS AND REMEDIATION

In humans, it has been convincingly demonstrated that phonological systems must be developed through experience-dependent exposure to native language (Kuhl et al., 1992). As part of this exposure, an infant hears a continuous speech stream from the environment. This rapidly changing stream must, in turn, be segmented into reliable chunks that activate consistent neuronal firing patterns. Hebbian learning principles would suggest that the neuronal firing patterns most consistently activated in response to the acoustic chunks derived from the incoming speech waveform will, in turn, come to be represented as the building blocks (phonemes) of the native language (Hebb, 1949).

Neurophysiologists have further shown that within each sensory modality, the features that represent the physical world come to be mapped in the CNS in a highly organized fashion. Although it was previously thought that these neural maps had to be established during critical periods of development (as set by early environmental exposure), recent research has challenged that view by demonstrating changes in sensory thresholds as well as neurophysiological sensory maps in adult humans and nonhuman primates (Buonomano & Merzenich, 1998; Karni et al., 1995; Karni & Sagi, 1991; Kilgard & Merzenich, 1998; Merzenich & Jenkins, 1995). Whether these maps are set during critical periods of development or can be altered throughout life, it is hypothesized that neuroplasticity is driven by Hebbian mechanisms that operate to increase the connection strengths between nearly simultaneously firing of neurons within cortical networks to create cortical cell assemblies (Hebb, 1949) or neural groups (Finkel & Edelman, 1985). These neural groups may be strengthened progressively through explicit training, resulting in increasingly stronger positive coupling, with the neuronal cell assemblies responding increasingly more synchronously in time (for review, see Merzenich et al., 1999).

The results of neuroplasticity based training studies in animals (discussed above) have recently been applied to training programs aimed at ameliorating the deficits that characterized LLI. It was posited that if language

learning problems are characterized by a basic processing constraint in the way in which incoming sensory information is segmented and represented, and also are affected by the frequency and obligatory nature of phonological and morphological structures within a language (see Leonard, 1998), then these factors should drive the design of any remediation strategy. Tallal and colleagues (Tallal, Merzenich, et al., 1998) hypothesized that Hebbian learning principles, shown in studies with monkeys to drive neuroplasticity, might be adapted to the treatment of auditory processing constraints in children with LLI. A hierarchy of computer-based neural training exercises was, therefore, developed to (a) drive neural processing of rapidly successive acoustic stimuli to faster and faster rates and (b) improve speech perception, phonological analysis, phonological awareness, and language and reading comprehension by providing intensive training exercises within obligatory linguistic contexts (phonological, morphological, semantic, and syntactic). These exercises utilized speech stimuli that had been acoustically modified to amplify and temporally extend the brief, rapidly successive intrasyllabic acoustic cues (within ongoing speech) using a computer algorithm (for a detailed description of the speech-modification algorithm, see Nagarajan et al., 1998). Exercises were developed in the form of computer games that were programmed to be individually adaptive. The goal was to find for each subject a level of acoustic and linguistic functioning that elicited a high rate of accuracy through the use of acoustically modified speech. Once established, the exercises were programmed to adaptively change, based on each individual's trial-by-trial responses. As training progressed, the training became more difficult (moving toward more rapid and less amplified speech in response to correct responses), or less difficult (moving to more acoustically modified speech following incorrect responses). The goal was to drive the performance of each individual from a reliance on acoustically modified speech toward competence with natural speech. Adaptive training was also performed to directly drive temporal integration thresholds for rapidly successive acoustic frequency sweep tones (within the range of formant transitions in speech), again to improve performance into the processing range necessary for normal speech perception.

Two laboratory studies demonstrated dramatic success with this training method (Merzenich et al., 1996; Tallal et al., 1996; Tallal, Merzenich, et al., 1998). Results (see Figure 13) showed that intensive daily training resulted in highly significant improvements in temporal integration rates, speech discrimination, language processing, and grammatical understanding. Importantly, a well-matched group of children with LLI served as a comparison group. This comparison group received

essentially identical language training, but using natural, unmodified speech. In addition, they played computer games for equivalent periods of time, but these games were visual (rather than auditory) and were not temporally adaptive. Both groups received the same amount of training, reinforcement, and rewards for performance. Both groups of subjects with LLI performed comparably on measures of nonverbal intelligence and language before training. After training, the group that received language training with acoustically modified speech, as well as explicit training aimed at decreasing temporal integration thresholds for rapidly successive nonlinguistic acoustic stimuli, showed significantly greater improvements in language than the comparison group (Merzenich et al., 1996; Tallal et al., 1996).

These results demonstrate that basic temporal thresholds are remarkably plastic, well beyond early critical periods of development. They also demonstrate that phonological processing, as well as higher level aspects of linguistic processing, can be driven toward improvement through the use of training aimed at ameliorating low-level temporal-spectral processing constraints. These data suggest that when successive inputs are delivered to the same cortical processing channels at progressively higher speeds, they drive stronger positive coupling of cooperative cell assemblies that lead to increased precision in acoustic analyses critical for building up sharp (categorical) phonological representations, which, in turn, represent the building blocks of both oral language and reading.

The experiments described above were prompted by physiological studies with animals demonstrating that neuroplastic changes in sensory cortical maps can be induced through behavioral training (Kilgard & Merzenich, 1998; Recanzone et al., 1993). It was therefore of interest to determine if training-induced changes in neural activation could also be observed in subjects with LLI (as measured pre-training and post-training by fMRI). It has been well documented that the neural response to rapidly changing nonspeech analogues is disrupted in dyslexia (e.g., see Temple et al., 2000). Therefore, a study was performed to assess whether this neural signature could be altered after training with Fast ForWord (a commercially available set of neuroplasticity-based training exercises described in Merzenich et al., 1996 and Tallal et al., 1996). Three adult dyslexic subjects (two of whom showed significantly elevated temporal integration thresholds, and one who showed a threshold within the normal range) were scanned before and after training with Fast ForWord. Recall that this training program was explicitly designed to improve rapid successive processing of nonspeech as well as speech stimuli. The training did not include exposure to the nonspeech analogs or tasks used

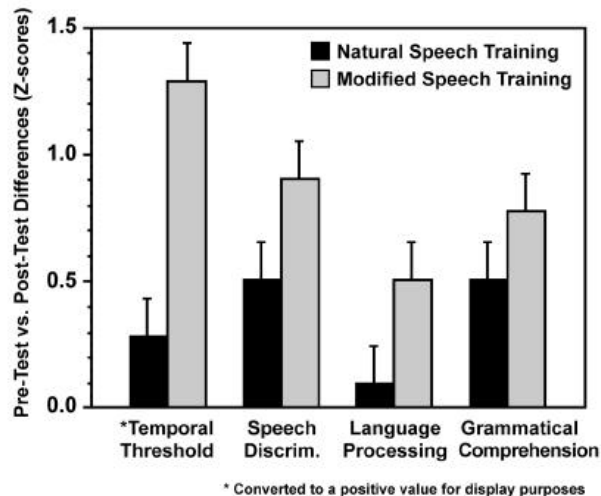


Figure 13: Post-training minus pre-training difference (z-scores) are shown for subjects with language impairment (LLI) who received training either with natural speech or acoustically modified speech. Raw scores on standardized test measures were converted to z-scores on the basis of the pretraining performance of all subjects for each individual test. Mean and standard error values for each standardized test measure demonstrated that significantly greater improvement was achieved by the LLI children who received training with acoustically modified speech (gray bars) as compared to those who received the same training with natural speech (black bars).

NOTE: Adapted from Tallal et al. (1996).

in the fMRI experiment itself. When fMRI patterns to rapid nonspeech analogs were compared before and after training, results showed that the two subjects characterized by rapid auditory processing and auditory language comprehension deficits before training exhibited (a) anomalous activation patterns to rapid stimuli prior to training and (b) significantly increased activity in left prefrontal cortex after training. The individual with normal acoustic thresholds before training did not show increased activity in left frontal cortex and also did not show behavioral improvements. These preliminary data were among the first results to show both behavioral and neurophysiological effects of neuroplasticity-based training in individuals with language disability.

As a follow-up to this study, a much larger group of children with dyslexia received behavioral testing and neural imaging studies before and after Fast ForWord training (Temple et al., 2003). One goal of this study was to determine whether the characteristic neural signature showing decreased activation in left posterior language regions (temporal parietal cortex) during phonological tasks in adult dyslexic subjects could be replicated in dyslexic children, and if so, could then be ameliorated via Fast ForWord training. Twenty dyslexic children and 12 normal reading children performed a

letter-rhyme (phonological) task in the scanner, both before and after Fast ForWord training. Prior to training, the normal reading children showed activity in both left frontal (inferior frontal, BA 44-6) and left temporal parietal (middle temporal and angular gyrus, BA 39) brain regions during the rhyming task. The dyslexic children, in a manner similar to dyslexic adults, showed more diffuse left frontal activity and no significant left temporal parietal response during this same task. Next, the 20 dyslexic children completed 6 to 8 weeks of Fast ForWord training. After the training, the dyslexic children showed significantly improved performance on standardized reading measures assessing single word reading, nonword reading, and passage comprehension (see Figure 14). Similarly, the dyslexic children showed substantial normalization of brain activation after Fast ForWord training, including a less diffuse area of activation in the left prefrontal cortex. In addition, whereas before training the children with dyslexia had shown a complete failure to activate the left temporal parietal region, after 6 to 8 weeks of training with Fast ForWord, the dyslexic children showed significantly increased left temporal parietal activation during the phonological processing (letter rhyming) task (Temple et al., 2003; see Figure 15). Finally, significant correlations were also evident between behavioral improvement and activation changes in dyslexics; such effects were not seen for control children (who received a postscan after 6 to 8 weeks with no intervention).

CONCLUSIONS AND FUTURE DIRECTIONS

Animal models have proven to be invaluable in studying the neurobiology of sensory, perceptual, and motor systems. Such models have also opened dramatic new avenues of investigation in the study of neurobiological systems underlying learning and memory. However, higher cognitive systems such as speech, language, and reading (that are particular to humans) have resisted study from the perspective of cellular and systems neuroscience, due in large part to the perceived lack of amenability to animal modeling.

With the advent of noninvasive in vivo neuroimaging technologies came an accompanying increase in our ability to explore the neural substrates underlying higher cognitive abilities in humans. While these technologies have proven particularly beneficial in advancing our understanding of the gross neuroanatomical substrates subserving language learning systems, they remain insensitive to the study of finer grain neurobiological circuitry. Yet, evidence indicates that individual differences in processing of relatively fine-grain information (e.g., rapidly successive acoustic signals) appear not only to be disrupted in many individu-

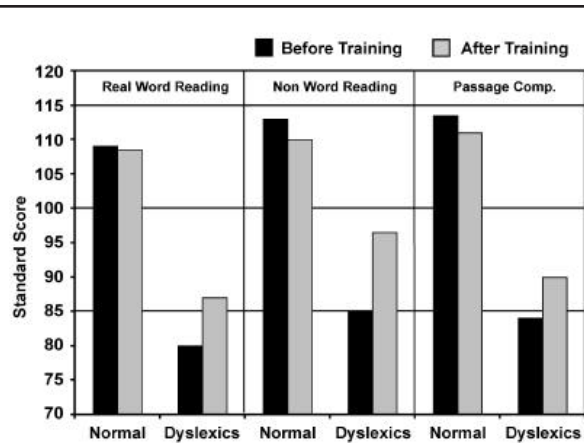


Figure 14: Standard scores on the three subtests of the Woodcock-Johnson Reading Mastery Test-Revised for normal ($n = 12$) as compared to dyslexic readers ($n = 20$) before (black bars) and after (gray bars) training with Fast ForWord. Mean = 100; $SD = 15$; 85 = below average. NOTE: Adapted from Temple et al. (2003).

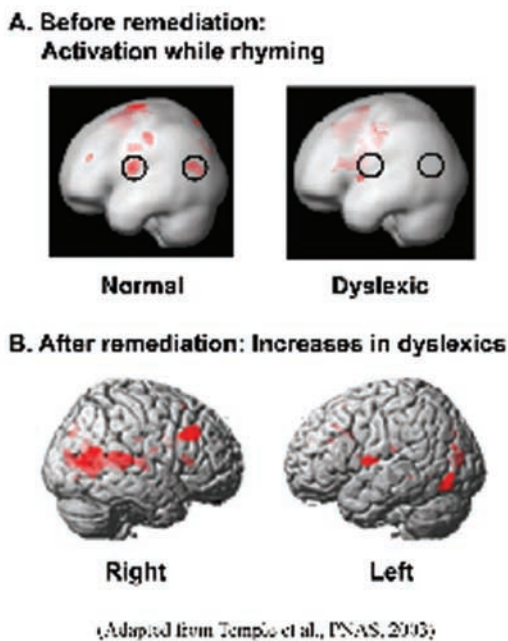


Figure 15: A = Left hemisphere activations of normal readers and dyslexic readers during rhyming (as compared to matching) letters. B = Areas showing increased activation during phonological processing in dyslexic readers after remediation with Fast ForWord. Black circles highlight left temporo-parietal and frontal regions that are disrupted in dyslexic children and significantly affected by remediation. NOTE: Adapted from Temple et al. (2003).

als with LLI but also to predict individual differences across the normal range of language learning. As such, the study of the fine-grain neurobiological circuitry subserving these processing systems would enhance under-

standing of both normal and impaired language development. Fortunately, more recent animal models have provided a window through which to investigate these neurobiological substrates.

It is important to point out that there are likely many different potential causes for language learning deficits, and indeed, many different types of LLI. Although a high percentage of young children presenting with significant oral language delay and/or disorders subsequently may develop reading, writing, spelling, and/or other academic achievement problems, as well as one or more of the negative emotional or psychiatric sequelae that often accompany such school failure, others will not. Similarly, although some dyslexic children may have concurrent or historical phonological processing, phonological awareness, and/or other oral language deficits, others will not. Finally, there is clearly substantial evidence that LLI segregates in families and that there are likely multiple genes that may be involved in the development of speech, language, and reading systems. Yet, more than 40% of children with LLI are the only member of their family ever to be affected with a language learning disorder.

To further complicate issues, language learning clearly is experience-dependent and, above all, developmental. The considerable confusion, and indeed controversy, that has characterized the theoretical assumptions driving this field of research may result, to a large extent, from a failure to study the neural basis of language systems within a developmental framework. Historically, our knowledge pertaining to the brain basis of language and other higher cognitive functions has derived from studies of adult patients who have lost specific functions after sustaining discrete brain damage. Such observations in adult patients (i.e., apparently encapsulated, modular, functional systems) largely fail to match the effects of similar brain injuries sustained early in life. Similarly, patterns of impairment (including correlations between nonlinguistic and linguistic indices) observed in young children with particular types of developmental language impairments may or may not match observations of older children or adults with a life-long history of a similar disability and consequent acquisition of compensatory strategies.

In this review, we focus on one particular line of research that has proven particularly fertile in the study of neural substrates underlying language learning systems. It is important to emphasize that by doing so, we are not suggesting that this is the only potential model of LLI worthy of study. Although auditory processing clearly plays an important role in the development of phonological systems that form the building blocks for both oral and written language, this does not imply that other nonlinguistic or linguistic specific systems are not

also important contributors to language development and disorders. We focus here specifically on reviewing the literature pertaining to the role of rapid auditory processing in language development and disorders because there is now a broad body of data to bring to bear on questions of particular interest to behavioral and cognitive neuroscientists that have been, and more importantly, may become, increasingly amenable to future research on the neurobiological substrates of language learning.

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