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CHAPTER 4

NEUROBIOLOGY OF (CENTRAL) AUDITORY PROCESSING DISORDER AND LANGUAGE-BASED LEARNING DISABILITY

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(Central) auditory processing disorder (abbreviated here APD) is defined as a deficit in the processing of auditory information, despite normal hearing thresholds, that primarily involves the auditory modality (ASHA, 2005; Jerger & Musiek, 2000). This umbrella definition encompasses a wide variety of perceptual and cognitive manifestations. APD thus cannot be reduced to a single anatomic site or impaired process in the auditory system. The question of whether such a nonspecific definition can really benefit research, diagnosis, and treatment notwithstanding, in this chapter we will focus on the physiologic processes thought to underlie the perception of auditory aspects that fall within the realm of APD. We will review evidence for specific physiologic processes and anatomic sites contributing to normal and abnormal auditory processing. In particular we review studies of the physiology and anatomy of: (1) auditory temporal processing, (2) auditory perception in noise, (3) representation and discrimination of acoustic features and (4) binaural processing. We also present evidence for (5) training-related neural plasticity of these processes where such evidence exists, focusing on training studies aimed at populations with symptoms of APD. The physiologic processes reviewed here with their accompanying perceptual correlates are summarized in Table 4–1. To our knowledge, physiologic and anatomic studies of APD diagnosed populations have been rare. On the other hand, many studies have focused on auditory processing in populations diagnosed with language-based learning disabilities (e.g., specific language impairment [SLI] and

Table 4–1. Auditory Processing Deficits: Perception and Neurophysiology

Perceptual Difficulty	Proposed Neurophysiological Correlates
Temporal Processing	
Temporal resolution	Delayed onset of auditory brainstem response (ABR) to speech
Temporal order judgment[1]	Abnormal cortical representation of sound under temporal stress
Backward masking detection	Delayed ABR wave V in masked conditions
Modulation detection	Reduced amplitude aodulation following response (AMFR)
Auditory Perception in Noise	
Processing of speech in noise[1]	Abnormal suppression of otoacoustic emissions (OAE), speech-evoked ABR; cortical representation of speech in noise,[2] frequency following response (FFR) magnitude.[2]
Representation and Discrimination of Acoustic Features (Speech and Nonspeech)	
Discrimination of acoustic features[1]	Abnormal cortical representation of sound; immature cortical responses;[2] abnormal mismatch negativity response (MMN).[2]
Speech perception[1]	Delayed speech-evoked ABR onset; reduced magnitude of the FFR in F1 frequency range; abnormal cortical lateralization and N1 responses.
Speech discrimination[1]	Abnormal MMN[2] and P3 (not reviewed here)
Binaural Processing	
Sound localization, dichotic listening[1]	Abnormal binaural interaction components (BIC)
Training Related Plasticity	
[1]Improve with training and [2]Exhibit training related plasticity in the LLD population	

dyslexia) in which symptoms of APD are often present. Throughout the chapter we will use the general term LLD (language-based learning disorder) to refer to this population. The principles we present here derive, therefore, from our understanding of the normal auditory system as applied to a wide array of studies in clinical populations intersecting with APD.

Temporal Processing

Temporal processing in the auditory system is defined, broadly, as the ability of the auditory system to represent and process changes in the acoustic signal that occur over time (e.g., the temporal envelope of the signal), and to its ability to process brief transient acoustic events (e.g., sound onset and consonants). Adequate auditory perception requires good temporal resolution on the time scale of microseconds for the processing of binaural cues, milliseconds for processing of temporal synchrony, tens of milliseconds for the processing of speech transients and voicing information and hundreds of milliseconds to seconds for the processing of prosodic and suprasegmental cues. In addition, in order to make sense of our environment, the intact auditory system needs to be sensitive to the order in which acoustic events occur (e.g., "on" vs. "no") and be able to transition between those time scales and integrate information from all the time scales to create a unitary auditory percept. Indeed, evidence suggests that encoding of temporal information into a coherent form begins as early as the cochlear nucleus and continues up to the auditory cortex (Frisina, 2001; Griffiths, Uppenkamp, Johnsrude, Josephs, & Patterson, 2001).

The measurement of auditory evoked potentials provides a window into temporal processing, providing information about neural timing with fractions of a millisecond precision. Available recording techniques enable the study of timing along the ascending auditory pathway from the XIIIth nerve to the auditory cortex and indeed most of our information on temporal processing in humans comes from such studies. Additional information, in particular regarding cortical temporal processing comes from studies of patients with cortical lesions. However, it should be noted that due to the complex pattern of connectivity in the auditory pathway (e.g., massive feedback connections), and the relative nature of perception (i.e. its dependence on context) it is hard to attribute a specific perceptual deficit to a specific anatomic location along the pathway without additional information (Eggermont & Ponton, 2002; Phillips, 1995).

Temporal Resolution

Of particular interest here is the brainstem's response to sound. Transient acoustic events evoke a pattern of voltage changes in the auditory brainstem. The resulting waveform provides information about brainstem nuclei along the ascending auditory pathway (see Hood, 1998; Jacobsen, 1985 for reviews). Converging evidence suggests that learning-impaired populations show normal click-evoked auditory brainstem responses (ABR) (Grontved, Walter, & Gronborg, 1988a, 1988b; Jerger, Martin, & Jerger, 1987; Lauter & Wood, 1993; Mason & Mellor, 1984; McAnally & Stein, 1997; Purdy, Kelly, & Davies, 2002), yet about a third of all individuals diagnosed with language-based learning problems manifest reduced temporal synchrony at the level of the upper brainstem (i.e., lateral lemniscus, inferior colliculus) in response to speech sounds (Banai, Nicol, Zecker, & Kraus, 2005; Cunningham, Nicol, Zecker, Bradlow, & Kraus, 2001; King, Warrier, Hayes, & Kraus, 2002; Wible, Nicol, & Kraus, 2004) and backward masked signals (Marler & Champlin, 2005).

The speech-evoked ABR may be conceptualized as the neural code of a speech syllable (reviewed in Johnson, Nicol, & Kraus, 2005). To a consonant-vowel syllable, the onset response (waves V, A) represents the burst onset of a voiced consonant, whereas later portions likely represent the offset of the onset burst or the onset of voicing (wave C) and the offset of the stimulus (wave O). The harmonic portion of the speech stimulus gives rise to the frequency-following response (FFR, waves D, E, and F) (Galbraith, Arbagey, Branski, Comerci, & Rector, 1995; Krishnan, 2002). The FFR is characterized as a series of transient neural events phase locked to the periodic information within the stimulus (Marsh & Worden, 1968; Sohmer & Pratt, 1977). Disruption of either the onset or the FFR is likely to result in impaired representation of important segmental and suprasegmental information, respectively, within the speech sound thus degrading the input into higher levels of the auditory system (Kraus & Nicol, 2005). A characteristic brainstem response to the speech syllable /da/ is shown in Figure 4–1. Like the familiar click-evoked ABR, speech-evoked ABRs can be obtained from an individual subject with relative ease, making it an objective biological marker of auditory processing (Johnson et al., 2005; Russo, Nicol, Musacchia, & Kraus, 2004).

Using this measure in large groups of normal learning children and children

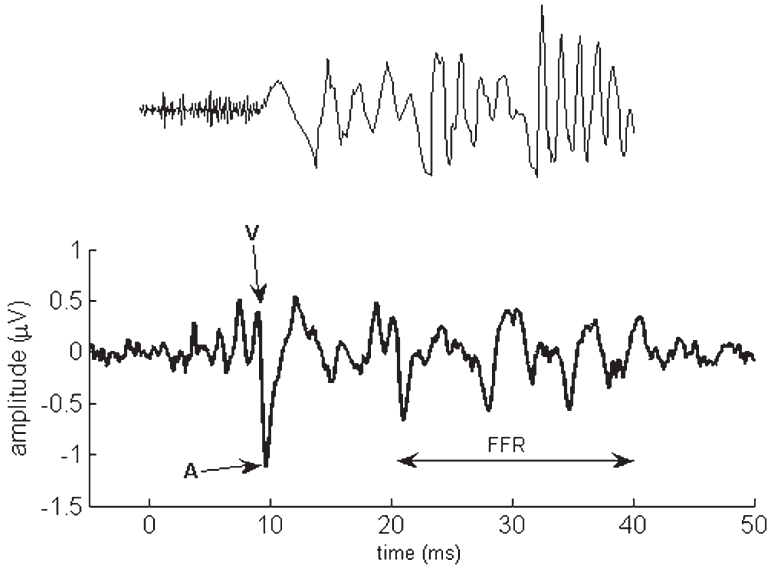

Figure 4–1. *Top:* Stimulus waveform (amplitude vs. time) of the speech syllable /da/. The first 10 ms correspond to the consonant portion whereas the larger amplitude portion from 10 to 40 ms corresponds to the vowel portion of the syllable. *Bottom:* the corresponding brainstem evoked response (speech-ABR) recorded from a typically developing 9-year-old child. Waves V and A marked on the response waveform correspond to the brainstem's response to the initial portion of the syllable, whereas the FFR corresponds to the vowel.

diagnosed with LLD has shown that children with LLD present abnormalities of both the onset response and the magnitude of the FFR. King et al. (2002) demonstrated that wave A of the onset response was at least 1 SD delayed in 20 of the 54 listeners with LLD they studied, and that these listeners also had delayed waves C and F. Wible et al. (2004) further studied the differences in brainstem encoding of speech between normal learning and children with LLD. They concluded that children with LLD had markedly shallower slopes of the transition between onset waves V and A, suggesting a more sluggish response in these children. They also showed that the amplitude of the FFR was significantly reduced among LLD children in the frequency region corresponding to the first formant (F1) of the /da/ stimulus used. Similarly, Cunningham et al. (2001) demonstrated that the magnitude of the FFR in response to a stimulus presented in background noise was reduced in a group of LLD children in the F1 frequency range. The magnitude of the response in the fundamental frequency (F0) range on the other hand was found to be normal in both quiet (Wible et al., 2004) and noise (Cunningham et al., 2001). Recently, Banai et al. (2005) estimated, in the largest sample yet studied with speech-ABR, that 30% of children with LLD show onset responses that are abnormal at the 2 SD level when a unifying onset score was created based on the latencies of onset waves V and A, as well as the duration and slope of the transition between them.

A similar phenomenon was recently shown with more simple stimuli. Marler and Champlin (2005) studied ABR elicited by tone bursts in a group of children with LLD (specifically diagnosed with SLI). They reported that even though wave V latencies did not differ between children with normal learning and children with LLD when tone bursts were presented alone, wave V of the LLD group was significantly delayed when the same tone was presented immediately followed by a noise burst (backward masking condition). It may be that a similar mechanism underlies abnormal onset responses to speech sounds (which are potentially masked by the steady state portion of the stimulus) and masked nonspeech sounds. Supporting this notion, children with LLD and elevated backward masking detection thresholds also have abnormal brainstem encoding of speech sounds (Johnson, Nicol, Zecker, Wright,& Kraus, 2004).

Neurons in the auditory system, including the auditory brainstem, show a high degree of sensitivity to oxygen shortage during development. A recent study of rats who suffered from experimentally induced anoxia at birth showed that one consequence of this oxygen shortage was a degraded click-ABR (Strata et al., 2005). It may be that a similar process contributes to abnormal ABRs measured to complex sounds in children with LLD. Although click ABR in these children are typically within clinical norms, they tend to be delayed (Song et al., 2006). It is therefore possible that scalp-measured ABR in humans are not sensitive enough to document this minute effect and that deficits are therefore observed only in response to more complex stimuli.

Taken together with the perceptual deficits present among individuals with LLD, this combined body of research suggests that processing of rapidly changing spectrally complex information at the level of the brainstem is one

likely source of APD. It is anticipated that the brainstem response to speech sounds will be incorporated into the clinical evaluation of APD (e.g., see BioMAP™—Biological Marker of Auditory Processing, Bio-logic Systems Corp, Mundelein, IL). Furthermore, as explained in detail in the relevant sections below, brainstem timing was found to correlate with the robustness of the cortical response in noise (Wible, Nicol, & Kraus, 2005), and the majority of individuals with abnormal cortical detection of rare acoustic events also have delayed speech-evoked ABRs (Banai et al., 2005). Thus, deficient brainstem timing may affect the cortical response to sound.

The timing of the N1 evoked response is sometimes considered an index of temporal processing at the cortical level. However, as it is optimally evoked with a stimulation rate slower than 2 Hz (Hall, 1992), and as the response is probably less affected by the physical characteristics of the stimulus, but rather by its functional significance (Kraus & McGee, 1992), it may be more useful to consider it as representing the initial cortical processing of the auditory signal. Its manifestations in individuals with LLD are discussed further below under Representation of Acoustic Features.

Encoding of Stimulus Temporal Envelope

Another measure of auditory encoding of stimulus structure can be obtained by recording the amplitude modulation following response (AMFR). This response encodes the frequency of the fluctuations in the amplitude envelope of an amplitude-modulated (AM) sound. The magnitude of this response has been found to be reduced in individuals with dyslexia, meaning they need deeper (larger) signal modulation to detect its presence compared to controls. This physiologic finding corresponds with behavioral findings of higher AM detection thresholds (McAnally & Stein, 1997; Menell, McAnally, & Stein, 1999), and suggests that auditory encoding of signal modulation difficulties may lead to perceptual difficulties in following such temporal modulations in speech. For a discussion of the role of temporal information in speech see Rosen (1992). The AMFR has multiple thalamic and cortical generators (Herdman et al., 2002; Kuwada, Batra, & Maher, 1986), with subcortical generators probably contributing to the processing of fast modulations (>80 Hz) and cortical ones to the processing of slower (<40 Hz) rates. However, behavioral evidence suggests that individuals with dyslexia have similar deficits across all modulation rates (Lorenzi, Dumont, & Fullgrabe, 2000; Menell et al., 1999), and the magnitudes of their AMFR were similarly reduced across the range from 10 to 320 Hz rates (Menell et al., 1999).

Temporal Order/Sequencing of Rapid Acoustic Events

Perceptual organization of sound, such as determining temporal order, is typically thought of as a function of the auditory cortex (see Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001 for review). Nagarajan et al. (1999) presented poor readers with pairs of brief tones, asking them to determine the order in which the tones were presented (high-low; low-high; high-high; low-low, a task originally used by Tallal with a language-impaired population) and recorded their

evoked magnetic responses to the tone pairs. Poor readers had a normal response to the first tone, but had a significantly reduced response to the second one when interstimulus interval (ISI) within the pair was short (100 or 200 ms), but not when it was longer (i.e., 500 ms). These neurophysiologic findings were consistent with better behavioral performance in the long ISI condition. These data suggest that while the basic cortical response in poor readers may be intact, representation of successive signals is impaired. Bishop and McArthur (2004) reported similar results in the population diagnosed with SLI. They reported enhanced correlations between the cortical response to a single tone and the response to tone pairs in individuals with SLI, indicating a less reliable processing of tone sequences. Bishop and McArthur suggested that these findings reflect immature auditory processing among some individuals with SLI. Similarly, Temple et al. (2000) using nonverbal analogues of a formant transition found a disruption of the neural response to the transient stimulus in subjects with dyslexia. They showed that an area in the left prefrontal cortex that became activated among normal readers in response to a rapidly transient stimulus, but not in response to a slower transition, did not show this increased activation in dyslexics in response to rapidly changing stimuli. Moreover, Poldrack et al. (2001) reported that an area within the left inferior frontal cortex (pars triangularis), that is specifically involved in phonologic processing, also showed changes in activation that were related to the degree of compression of a speech signal (i.e., temporal processing). These findings suggest that areas that are not typically considered auditory areas have an important role in auditory processing. Yet, since these areas are not sensitive to specific acoustic characteristics, some other functional property must be shared between "simple auditory" and phonological processing.

To summarize, populations diagnosed with LLD such as dyslexia and SLI are characterized by abnormalities in several different aspects of temporal processing as measured by imaging and electrophysiologic techniques. Importantly, these populations also manifest difficulties in the perception of temporal information. Some individuals with LLD have difficulties in tasks requiring temporal order judgments (Cacace, McFarland, Ouimet, Schrieber, & Marro, 2000; Farmer & Klein, 1995; Heath, Hogben, & Clark, 1999; Nagarajan et al., 1999; Tallal, 1980; Tallal & Piercy, 1973), detection of amplitude and frequency modulations in sound (Lorenzi et al., 2000; Menell et al., 1999; Rocheron, Lorenzi, Fullgrabe, & Dumont, 2002; Talcott et al., 2003; Witton, Stein, Stoodley, Rosner, & Talcott, 2002) and detection of backward masked tones (Griffiths, Hill, Bailey, & Snowling, 2003; Marler, Champlin, & Gillam, 2002; Wright et al., 1997). Overall, it is estimated that 30 to 50% of individuals diagnosed with dyslexia also manifest an auditory perceptual deficit characteristic of APD (Amitay, Ahissar, & Nelken, 2002; King, Lombardino, Crandell, & Leonard, 2003; Ramus, 2003). It has been suggested, most notably by Tallal and her colleagues, that such a pattern of deficits should lead to difficulties in the representation and discrimination of consonants characterized by brief formant transitions and consequently to difficulties in phonologic processing and reading which are the hallmarks of dyslexia (Tallal, 1980; Tallal, Miller, & Fitch, 1993). Subsequent studies

have indeed shown that many individuals with language-based learning problems, have poorer phonemic discrimination (Adlard & Hazan, 1998; Breier, Fletcher, Denton, & Gray, 2004; Breier et al., 2001; Cornelissen, Hansen, Bradley, & Stein, 1996; Joanisse, Manis, Keating, & Seidenberg, 2000; Reed, 1989; Rosen & Manganari, 2001; Ziegler, Pech-Georgel, George, Alario, & Lorenzi, 2005) in addition to their reading and phonologic deficits suggesting a possible link between temporal processing and literacy. Poor discrimination is not, however, restricted only to rapidly changing consonants, but found also for vowels (e.g. Putter-Katz et al., 2005; Rosen & Manganari, 2001). Also, it should be noted that speech perception deficits are probably mostly characteristic of children with a history of SLI (Joanisse et al., 2000).

Neurophysiology of Perception in Noise

A hallmark of APD is unusual difficulties in speech understanding in noisy environments (Chermak, Hall, & Musiek, 1999; Chermak, Tucker, & Seikel, 2002). Individuals with LLD show abnormal physiologic responses to sound at the cortical level when it occurs in background noise. Cunningham et al. (2001) investigated cortical and brainstem responses in normal learning children and children with LLD in response to speech stimuli in quiet and in noise. Physiologic responses at both the cortical and brainstem level did not differ between groups in ideal listening conditions (i.e., quiet). On the other hand, both cortical and brainstem responses of children with LLD were significantly reduced when the same /da/ stimulus was presented in noise. This pattern of neurophysiologic findings matched the observed pattern of perceptual deficits whereby children with LLD had normal discrimination thresholds in quiet, but significantly elevated thresholds in noise. Both perception and cortical responses significantly improved, however, when the stimuli were presented in a cue-enhanced "clear speech" mode. At the brainstem level, cue enhancement improved the timing of the onset response, but had no effect on response magnitude. Wible, Nicol and Kraus (2002) showed that repeated presentations of a stimulus in noise resulted in less reliable P1/N1/P2/N2 cortical responses (i.e., lower correlations between responses to repeated stimuli) in a subset of children with LLD, but not in normal learning children, suggesting that the LLD system is more sensitive to the stresses of a noisy listening situation. Warrier, Johnson, Hayes, Nicol and Kraus (2004) found that the correlation between cortical responses in quiet and noise (i.e., the degree of response degradation by noise), which serves to test the reliability of the cortical response in noise, also was severely reduced in about 20% of LD participants tested. Further studies showed a strong correlation between the brainstem onset response and the degree of degradation of cortical correlation in noise (Wible et al., 2005) and that only the subset of children with LLD with abnormal brainstem timing are likely to show severely abnormal cortical responses in noise (King et al., 2002). Furthermore, only in this group did listening training (i.e., Earobics) result in significant enhancement of the reliability of cortical function in noise (Hayes, Warrier, Nicol, Zecker, & Kraus, 2003; King et al., 2002). This abnormal physiology

coincides with poor perception of speech in noise (Cunningham et al., 2001). Furthermore, while children with LLD with both normal and abnormal brainstem timing alike also show poor discrimination of speech in quiet listening conditions, only among those children with LLD with abnormal brainstem timing did speech discrimination improve following listening training (King et al., 2002). *Taken together, these findings imply that among children with LLD, physiologic processing of speech in noise is abnormal at both the brainstem and cortical levels, and that encoding of speech in noise can be improved with either training or the use of cue enhanced stimuli.*

Taking a somewhat different approach, based on evidence linking the medial olivocochlear bundle (MOCB) of the lower brainstem to hearing in noise, Muchnik et al. (2004) objectively tested the function of the MOCB system in children diagnosed with APD using otoacoustic emissions (OAE) with and without acoustic stimulation of the contralateral ear. In the normal population, contalateral stimulation suppresses the OAE (e.g. Collet et al., 1990), probably reflecting the inhibitory control of the MOCB on the outer hair cells. Muchnik et al. (2004) reported that the suppression effect was significantly reduced in the APD group compared to normal controls, characterizing 11 of 15 children in the APD group. Furthermore, 80% of the children with APD in this study exhibited severely impaired speech perception in noise. These findings provide evidence for abnormal function of the descending auditory pathway in APD, and taken together with the cortical and higher brainstem findings summarized above, likely suggest an important top-down effect in APD.

Representation and Discrimination of Acoustic Features

Information about representation of sound at the level of the auditory cortex can be obtained by recording the obligatory cortical response to sound (P1/N1/P2/N2), whereas information on deficits in acoustic discrimination is most commonly obtained from the mismatch negativity response (MMN) (Näätänen, 1992). The MMN is generated in response to a change in a repetitive sequence of stimuli, that is, when rare acoustic stimuli are presented amidst common (standard) stimuli in an oddball paradigm. Under such presentation conditions, the brain generates a negative potential in response to the rare element, even when the difference between the standard and rare stimuli is barely perceptible. The MMN probably has several generators including the thalamocortical pathway, the auditory cortex, and frontal brain regions (Kraus et al., 1994; Rinne, Alho, Ilmoniemi, Virtanen, & Naatanen, 2000; Sams, Kaukoranta, Hamalainen, & Naatanen, 1991).

Representation of Acoustic Features

The ability of the cortex to adequately represent the acoustic stimulus is critical to our ability to further process the stimulus in functionally significant ways (e.g., discriminate, categorize, identify). In the dyslexic population, several studies have shown abnormal N1 responses to nonspeech and speech sounds (i.e., pseudowords and vowels) (Helenius, Salmelin, Richardson, Leinonen, & Lyytinen, 2002);

nonspeech sounds with temporal or spectral deviance, and syllables differing in voice onset time (VOT) or second formant (Moisescu-Yiflach & Pratt, 2005); 2000-Hz tone bursts (Pinkerton, Watson, & McClelland, 1989); and consonants and vowels (Putter-Katz et al., 2005). Less left-lateralized responses also have been reported (Heim, Eulitz, & Elbert, 2003), as well as abnormal cerebral asymmetry to speech sounds (Duara et al., 1991; Gross-Glenn et al., 1991; Leonard et al., 2001). Furthermore, it has been suggested that the generating sources of these potentials within the auditory system may vary between typically developing children and children with dyslexia (Heim et al., 2003; Heim et al., 2000). At birth, N1 responses to consonant-vowel syllables (/ga/, /ba/, /da/) of children with familial risk for dyslexia and SLI are different from those of not-at-risk newborns (Guttorm et al., 2001). Furthermore, N1 responses to syllables at birth are predictive of later development of language and literacy skills (Espy, Molfese, Molfese, & Modglin, 2004; Molfese, 2000). Later components of the auditory evoked response to speech-sounds at birth also have been linked to risk for dyslexia and to language and memory development (Guttorm et al., 2005; Guttorm et al., 2001; Molfese & Molfese, 1985, 1997); however, those components may not represent uniquely auditory processing and, therefore are not discussed further here.

Other studies failed to documents differences in the basic auditory cortical representation between typically developing individuals and individuals with LLD. Thus, in optimal listening conditions, the cortical representation of basic acoustic features (N1/P2/N2) in many individuals with learning problems may be intact, even though it is typically degraded in nonideal situations such as those involving noisy environment or rapid stimulus rate (Cunningham, Nicol, Zecker, & Kraus, 2000; Nagarajan et al., 1999; Wible et al., 2002).

In the SLI population, evidence suggests that the obligatory cortical response may be abnormal, at least in some diagnosed individuals. Neville, Coffey, Holcomb, and Tallal (1993) reported that N1 amplitudes to a pure tone were reduced and N1 latencies delayed only among language-impaired children with abnormal auditory temporal processing and poor reading. McArthur and Bishop (2004) reported that individuals with SLI had age inappropriate N1/P2/N2 responses to tonal stimuli. In a subsequent study, a subgroup of individuals with SLI had abnormal N1-P2 responses to both nonverbal tonally complex stimuli and to vowels (McArthur & Bishop, 2005). Taken together, these findings suggest that at least among some individuals with SLI the language deficit may be related to a more general auditory processing disorder.

To summarize, in subgroups of individuals with LLD the basic cortical representation of sound, manifested in the N1/P2 evoked response may be abnormal in response to both speech and nonspeech sounds.

Fine-Grained Auditory Discrimination

One hallmark of adequate perception is our ability to discriminate fine acoustic differences between similar stimuli. Such fine grained auditory discrimination of both speech and nonspeech elements is known to be impaired among many individuals with LLD (Adlard & Hazan, 1998; Ahissar, Protopapas, Reid, & Merzenich,

2000; Amitay et al., 2002; Banai & Ahissar, 2004; Ben-Yehudah, Banai, & Ahissar, 2004; Cacace et al., 2000; De Weirdt, 1988; Fischer & Hartnegg, 2004; France et al., 2002; McAnally & Stein, 1996; Mengler, Hogben, Michie, & Bishop, 2005; Walker, Shinn, Cranford, Givens, & Holbert, 2002). Physiologically, the MMN has been used to characterize discrimination at the preattentive level. MMN responses arise to a rare acoustic event occurring amidst frequent ones and index a detection of change in either acoustic feature (e.g., frequency) or complex sound pattern (e.g., order of sounds in a sequence). MMNs often are also conceptualized as indices of sensory or perceptual memory (see Näätänen et al., 2001 for review). Corresponding to perceptual deficits present in various clinical populations, MMNs are also attenuated in these groups, as discussed below. Yet, it should be noted that, because MMN responses currently can only be reliably quantified at the group level (Dalebout & Fox, 2001; McGee, Kraus, & Nicol, 1997), and thus are a useful tool for the study of auditory processing in predefined groups, they are ill-suited for use as a diagnostic tool at the individual level.

Discrimination of Speech Sounds

Children with learning and reading problems often exhibit difficulties behaviorally discriminating minimal pairs of speech sounds (e.g., /da/ vs. /ga/). Reduced or absent MMN responses to these contrasts also often have been documented in individuals with various learning problems, suggesting that impaired physiologic processing at a preattentive, preconscious level may account for poor perception. Kraus et al. (1996) showed that children with LLD and children with attention problems had reduced MMNs, especially when they had difficulties disciminating the /da/-/ga/ contrast used. In contrast, the same children had no difficulties perceiving a /ba/-/wa/ pair, and correspondingly had normal MMNs to this contrast. Similar findings were reported by Schulte-Korne, Deimel, Bartling, and Remschmidt (1998; 2001). Maurer, Bucher, Brem, and Brandeis (2003) studied the MMN response in children with familial risk for dyslexia compared to those of control children using a standard /ba/ and two deviants—/ta/ and /da/. They found that early positive mismatch responses (MMR) and late MMN responses were attenuated for the at-risk group. Children at risk had enhanced MMRs and reduced MMNs. Similar findings were obtained in a group of 6-month-old babies at risk for dyslexia (Leppanen et al., 2002).

More recently, researchers have looked at MMN in predefined subgroups of individuals with language-learning problems. Banai et al. (2005) compared MMNs in response to a deviant /da/ syllable in individuals with LD and normal and abnormal brainstem timing to the same speech syllable. MMN onsets were delayed in the latter group. Furthermore, individuals with abnormal brainstem timing were more likely to exhibit reduced MMN magnitude than individuals with normal brainstem timing. Lachmann, Berti, Kujala, and Schroger (2005) compared MMNs between diagnostic subgroups of dyslexia comparing subjects with deficits in nonword reading to those with deficits in common (frequent) word reading. They found that abnormal MMNs were characteristic of dyslexics with difficulties in reading frequent words, but not in those with difficulties specific to nonword reading. This was true for both a speech

(/ba/ vs. /da/) and a nonspeech (700 vs. 770 Hz) contrast. On the other hand, both dyslexic groups in this study had reduced N2 responses for both stimulus conditions. Similarly, in the population diagnosed with SLI, MMNs were absent in response to vowel deviants (/a/ standard, /i/ deviant) (Shafer, Morr, Datta, Kurtzberg, & Schwartz, 2005), yet when individual data were examined, no relationship was found between MMN and behavioral discrimination of the same speech contrast.

Discrimination of Acoustic Features (Frequency, Duration)

Because APD is associated with nonlinguistic deficits, and because a variety of nonverbal discrimination deficits have been observed in the LLD population, a review of the physiology of nonverbal discrimination deficits is relevant. Baldeweg, Richardson, Watkins, Foale, and Gruzelier (1999) recorded abnormal MMN responses to changes in frequency, but not to changes in the duration of a standard tone, a finding that coincides with the many reports of abnormal frequency discrimination in dyslexia (e.g., Ahissar et al., 2000; Baldeweg et al., 1999; Ben-Yehudah et al., 2004; McAnally & Stein, 1996). Similar findings were reported for at-risk 6-month-old infants and kindergarten children (Leppanen et al., 2002; Maurer et al., 2003, respectively) and for a subgroup of dyslexics with difficulties in frequent word reading (Lachmann et al., 2005). In contrast, other groups have reported that MMNs to frequency deviants did not differ between dyslexic and control subjects (Kujala, Belitz, Tervaniemi, & Naatanen, 2003; Schulte-Korne et al., 1998). Because the frequency difference in Kujala et al.'s (2003) study was 250 Hz, as opposed to 50 to 70 Hz in studies that did report a group difference, it is possible that group differences emerge only when stimulus differences are smaller.

Abnormal MMNs typically are attributed to abnormal function of the auditory cortex; however, observed behavioral deficits likely involve an interaction between the physical characteristics of the stimulus and the required cognitive operation. Thus, Johnsrude, Penhune, and Zatorre, (2000) reported that patients with surgical excision of either the left or the right Heschl's gyrus (auditory cortex) could still adequately discriminate pitch, but patients with right hemisphere excisions could no longer discriminate the direction of pitch change (up or down) even though they could readily discriminate the two sounds as different. Similar findings were observed in the dyslexic population where the degree of deficit in frequency discrimination also depends on the type of discrimination required (Banai & Ahissar, 2006; France et al., 2002).

Backward Masking

One manifestation of abnormal temporal acuity in children with language problems is increased detection thresholds for backward masked signals (Wright et al., 1997). It has been suggested that for some children with LLD, difficulties in discrimination of consonant-vowel syllables arise from a masking effect of the steady-state vowel and the brief initial consonant (Tallal, Merzenich, Miller, & Jenkins, 1998). As explained above (see Temporal Processing), this perceptual deficit may be related to abnormal processing of backward masked signals at the level of the brainstem (Marler & Champlin, 2005). Another physiologic

correlate of elevated backward masking thresholds is found, however, at the cortical level. Children with SLI exhibit delayed and smaller MMNs to backward masked signals (Marler et al., 2002). Similarly, in a group of participants with dyslexia, Kujala et al. (2003) found abnormal MMNs in response to sound order reversal within a tone pair when the pair was followed (i.e., backward masked) by an additional tone, but not when the pair was preceded by one (i.e., forward masked). In this study, no differences in MMN amplitude were observed to a simple frequency deviant or to an order reversal in a nonmasked condition as mentioned above.

The relationships between the MMN and brainstem abnormalities are not clear. Although in many cases deficits co-occur at both levels (Banai et al., 2005; Marler & Champlin, 2005), the causal direction is still not known. If one assumes that basic sensation is intact among children with LLD as evident from their basically normal responses to click-evoked ABR, their elevated backward masking thresholds may be attributed to an impairment of sensory memory (i.e., impaired cortical discrimination of sensory traces) (Kujala et al., 2003; Marler et al., 2002) or to other top-down influences.

Discrimination of Tonal Patterns

MMN responses can be elicited not only in response to a single-feature deviant, but also in response to deviations in tonal pattern or order. Several studies found abnormal MMNs in individuals with dyslexia in response to pattern deviations (Kujala et al., 2000; Kujala & Naatanen, 2001; Schulte-Korne, Deimel, Bartling, & Remschmidt, 1999). Schulte-Korne et al. (1999) reported reduced MMN among individuals with dyslexia in response to a violation of a sound pattern (i.e., the relative duration of two of the components in the pattern). Similarly, Kujala et al. (2000) reported reduced MMNs in a dyslexic group in response to rare tone sequences, but normal MMNs in response to rare tone pairs.

Summary

Available data imply that fine discrimination of small differences in acoustic features characterizes a subgroup of individuals diagnosed with LLD. Because MMNs are abnormal in response to both speech and nonspeech stimuli, these findings suggest that, when present, auditory discrimination deficits maybe of a general nature and probably not restricted to one type of stimulus. Future work will reveal if there are specific acoustic aspects, common to both speech and nonspeech signals that are deficiently perceived. For recent reviews of studies linking these auditory event related potentials (ERPs) to language-based learning problems see Lyytinen et al. (2005) and Heim and Keil (2004).

Binaural Processing

Binaural interaction is considered especially relevant to the diagnosis of APD, as binaural processing is thought to underlie deficits in both sound localization and listening in noise. Indeed, administration of behavioral tasks requiring the presence of binaural interaction is recommended in the report of the Consensus Conference on the Diagnosis of Auditory Processing Disorders (Jerger

& Musiek, 2000). A physiologic measure of binaural interaction can be obtained from the binaural interaction component (BIC) of the brainstem evoked response. The BIC is computed as the difference between the sum of the responses to monaural stimulation and the response to binaural stimulation (Dobie & Berlin, 1979). The BIC may serve as an objective measure of binaural processing. See Chapter 11 in volume 1 of this Handbook for discussion of clinical measures of binaural interaction.

Children suspected of or diagnosed with APD showed a different BIC pattern compared to normal children (Delb, Strauss, Hohenberg, & Plinkert, 2003; Gopal & Pierel, 1999). However, because the amplitude and latency of the BIC is rather variable in the normal population and highly variable in the APD population, Delb et al. (2003) concluded that the BIC is of limited diagnostic value, especially given the time commitment to obtain the three sets of measurements required for its calculation.

Consistent with the presence of deficit in binaural processing, deficits in accurate perception that require integration of information from both ears such as sound localization and dichotic listening (Amitay et al., 2002; Ben-Artzi, Fostick, & Babkoff, 2005; Edwards et al., 2004) have been found, but little is known about the biological correlates of these deficits in the LLD population. The role of the auditory brainstem in binaural processing has been demonstrated in a rare case of a patient with a unilateral lesion of the inferior colliculus. In this patient, sound localization was impaired behaviorally and wave V of the ABR was delayed when evoked by stimulation of the contralateral ear (Litovsky, Fligor, & Tramo, 2002).

(How) Can Training Help Individuals with Auditory Processing Deficits?

Research on the outcomes of training aimed specifically at groups diagnosed with APD is limited, yet available data indicate that difficulties in speech perception in noise can be alleviated by training. Putter-Katz et al. (2002) studied a group of 20 children diagnosed with APD. All trained children had normal audiometric thresholds, good word recognition in ideal listening conditions, and normal click-ABR. Their most common complaint was difficulty understanding speech in noisy environments (e.g., the classroom). The children participated in 13 to 15 weekly remediation sessions over a period of 4 months. At the same time, classroom modifications were recommended and implemented. The goal of the remediation sessions was to improve auditory processing abilities in noisy environments. The sessions included listening comprehension activities in the presence of noise and competing stimuli and tasks of selective and divided attention. Noise levels or degree of stimulus competition increased progressively throughout the course of the program. In addition, children were coached in the use of compensatory strategies such as speech-reading and metacognitive awareness. In addition, the use of FM devices was demonstrated and tried by the participants. At the end of the program, significant improvements in processing speech in noise and understanding competing sentences (dichotic listening) were documented. Furthermore, parents and teachers reported improved listening behavior at home and in the classroom following training.

Another approach to training is based on commercially available computer-based listening training programs such as Fast ForWord® (FFW) (Merzenich et al., 1996; Tallal et al., 1996) and Earobics® (Diehl, 1999). These programs have gained increasing popularity in the years following the reports of improved speech perception, language comprehension, and phonologic processing (Habib et al., 2002; Merzenich et al., 1996; Tallal et al., 1996). Despite differences between the programs, both emphasize improving speech perception and phonologic processing through the use of acoustically modified speech and an adaptive training regimen. The rationale behind this approach is that in cases of severe temporal processing deficits, children (most notably with SLI) are not able to distinguish naturally produced speech sounds, but may be able to tell apart larger, artificially enhanced temporal differences (Tallal et al., 1996). Following improvement, these enhancements are reduced, with the expectation that by the end of training the child will learn to adequately discriminate natural speech. In addition, these programs include modules with specific training on phonologic awareness, following oral instructions, and other tasks aimed at increasing the ability of the trainee to process language.

Although the benefits of such programs, compared with "traditional classroom instruction," seem obvious, independent assessments of their success have been rare. Several recent studies question training-related gains in reading and reading related skills (Agnew, Dorn, & Eden, 2004; Hook, Macaruso, & Jones, 2001), despite gains in nonverbal auditory discrimination (Agnew et al., 2004). In a randomized controlled trial, Cohen et al. (2005) compared outcome measures in children with severe SLI, all of whom continued their regular speech and language therapy in school, who participated either in home-based therapy with FFW or received home-based intervention using computer–based activities that did not employ modified speech. A third group received no additional intervention and served as the control. They found that each group made gains in language scores; however, FFW training resulted in gains in language skills that were no greater than that of the other computer intervention or the regular, school-based speech and language therapy.

In contrast to the disappointing gains in reading and reading-related skills reported in the Cohen et al. study, several studies have shown that commercial listening training may result in normalization of cortical function in children with LLD. Hayes Warrier, Nicol, Zecker, and Kraus (2003) have shown that cortical responses in quiet of LLD children trained with Earobics exhibited an accelerated pattern of maturation following training and that their cortical responses in noise were enhanced and became more resilient to the degrading effects of background noise. Warrier et al. (2004) found that the correlation between cortical responses in noise and in quiet increased following training, again suggesting increased reliability of cortical processing in noise following training. Moreover, Russo, Nicol, Zecker, Hayes, and Kraus (2005) showed that the FFR portion of the brainstem response to speech became more resilient to noise following training and that the magnitude of change was highly correlated with the degree of cortical change. The transient component of the speech-ABR appears to be unaffected by training

(Hayes et al., 2003; Russo, Nicol, Zecker, Hayes, & Kraus, 2005). Following FFW training, Temple et al. (2003) found increased activation in the left temporal parietal cortex and most notably in prefrontal cortex. *Taken together, these studies suggest that training serves to normalize brain function in trained children, although it does not necessarily result in immediate literacy-related changes. Yet, it is reasonable to hypothesize that normalized physiologic function may be a precondition to behavioral changes.*

Both Earobics and FFW have been criticized for the modest improvements in literacy related skills, which are typically stated as the reason for undertaking training. Remediation of LLD and APD remain, to date, an enormous challenge. Conventional phonologic-based intervention to reading problems does not always result in improved reading (Rivers & Lombardino, 1988), and in many cases reading remains abnormally slow (Wise, Ring, & Olson, 1999, 2000). Available data suggest that no single remediation is successful in all children with a variety of auditory-language disorders.

Another type of training that may enhance phonologic processing in normal learning children is training on the discrimination of a wide array of phonemic contrasts (Moore, Rosenberg, & Coleman, 2005). An intriguing outcome of the Moore et al. study is that the literacy-related improvements were observed in the face of little or no improvement on the trained task. Although this type of training may be effective in the LLD population as well, it should be noted that the pattern of training-related gains (i.e., nonspecific generalization) likely reflect plasticity of higher order mechanisms (auditory attention, auditory memory) rather than low-level sensory mechanisms (see Ahissar, 2001).

Moreover, because APD is associated with an auditory deficit that is not necessarily language-specific, it may be worthwhile referring to studies of nonverbal auditory training. In the general population, discrimination of many acoustic cues (e.g., pitch, duration) substantially improves with practice (Amitay, Hawkey, & Moore, 2005; Ari-Even Roth, Amir, Alaluf, Buchsenspanner, & Kishon-Rabin, 2003; Delhommeau, Micheyl, & Jouvent, 2005; Delhommeau, Micheyl, Jouvent, & Collet, 2002; Demany, 1985; Demany & Semal, 2002; Goldstone, 1998; Irvine, Martin, Klimkeit, & Smith, 2000; Wright, 2001; Wright et al., 1997) and training is accompanied by plastic neural changes in both humans (Atienza, Cantero, & Dominguez-Marin, 2002; Gottselig, Brandeis, Hofer-Tinguely, Borbely, & Achermann, 2004; Jancke, Gaab, Wustenberg, Scheich, & Heinze, 2001; Menning, Roberts, & Pantev, 2000) and other primates (E. Ahissar et al., 1992; Bao, Chang, Davis, Gobeske, & Merzenich, 2003; Beitel, Schreiner, Cheung, Wang, & Merzenich, 2003; Recanzone, Schreiner, & Merzenich, 1993), attesting to the plasticity of central auditory processing even in adulthood.

Studies of learning-impaired populations have been less common, but findings point to the potential of nonverbal auditory training. Kujala et al. (2001) trained 7-year-old children with reading impairment on an auditory-visual pattern matching task. Children heard a series of nonverbal sound patterns varying in pitch, duration, and intensity and were asked to match them to corresponding visual patterns. This training resulted in significant improvements in reading

accuracy and speed and in a significant increase in the MMN response to tone-order reversals. Schaffler, Sonntag, Hartnegg, and Fischer (2004) trained a large group of dyslexic listeners on an array of five auditory tasks (i.e., intensity and frequency discrimination, gap detection, temporal order judgments, and lateralization). Up to 80% of trained individuals improved on any given task, reaching age-matched control levels. These perceptual gains were accompanied by significant improvements in phonemic discrimination and spelling. Preliminary evidence suggests that similar training on a wide array of auditory discrimination tasks in a group of teenagers with severe dyslexia accompanied by additional learning problems also resulted in improved speech perception and verbal working memory (Banai & Ahissar, 2003).

Finally, preliminary findings regarding the positive outcomes of music training are worth mentioning. Overy (2003) studied the effects of musical training in eight children with dyslexia. Children trained on a series of musical games designed to emphasize timing and rhythm skills for 20 minutes per session, three times a week for 15 weeks in small groups improved significantly on rapid auditory processing, rhythm copying, phonologic processing, and spelling tests (although not on reading) compared to a 15-week pretraining waiting period.

Taken together with Moore et al.'s (2005) findings and with recent studies on the effects of prolonged musical experience on cognition (see Schellenberg, 2005) and verbal memory in both adults (Chan, Ho, & Cheung, 1998) and children (Ho, Cheung, & Chan, 2003), it seems that auditory training affects clusters of processes rather than the encoding of specific types of stimuli. *Importantly, these studies seem to suggest that effects of intensive training are not limited solely to the specific stimuli practiced, but rather extend to affect wider systems of the brain*, based on functional relationships with the trained processes, as would be suggested by theories regarding the hierarchy of perceptual processing (Hochstein & Ahissar, 2002). (See Chapter 4 in Volume II of this Handbook for additional review of the literature on auditory training and its use as treatment for APD.)

Summary

The findings reviewed in this chapter link different perceptual and cognitive manifestations of APD in the LLD population to different physiologic processes, as briefly summarized here. (1) Difficulties in *temporal processing* are linked to delays in neural timing at both the auditory brainstem and cortex, in response to speech and nonspeech sounds. (2) Abnormal *perception and cortical representation of speech in noise* similarly are linked with potential sources of deficit, as low as the brainstem. Furthermore, in individuals with LLD, cortical processing is more susceptible to the degrading effects of background noise compared to the normal population. (3) *Discrimination deficits* for both speech and nonspeech sounds are linked with abnormal cortical processing of fine stimulus differences (MMN). Furthermore, *auditory cortical processing* in infancy is predictive of later development of language and cognitive skills. (4) Little is known about the biological basis of abnormal *binaural*

processing in LLD, although reduced binaural components, probably originating at the brainstem have been recorded in children with APD. (5) Listening training (with modified speech stimuli) has been shown to be effective in normalizing cortical function in children with LLD. Furthermore, training was found to improve the resilience of auditory pathway activity to noise at both brainstem and cortical levels. Additional research is required to create training regimens with sizeable effects on language and literacy and to determine who are the subgroups of LDs that are most aided by training.

APD is heterogeneous in nature. Different types of APD are present among subgroups of populations diagnosed with language-based learning problems, manifesting deficits spanning a wide range of stimuli (pure tones to speech syllables), and processing time frames (fractions of milliseconds to seconds). Although the causal relationships between the presence of an APD and the linguistic and cognitive deficits which form the crux of learning disabilities are still poorly understood, it is clear that in many cases (estimates range from 30 to 50% of diagnosed individuals) the presence of APD may serve as a marker of a language or learning problem. On the other hand, data on cases of APD without accompanying language or cognitive deficits are rare, possibly because individuals with an isolated deficit in one auditory process are not likely to detect it unless tested. Indeed, available perceptual data indicate that in the general population different auditory abilities are not correlated, whereas in the LLD population significant correlations exist (Banai & Ahissar, 2004). This suggests that, although sporadic symptoms of APD are in some cases present in the normal population, they are unlikely to be diagnosed without the presence of additional pathology in the language or cognitive domain.

In addition to the variability in perceptual processing in the LLD population, the varied evoked response findings indicate that even among individuals with LLD with APD symptoms it is impossible to point to a single abnormal physiologic process. Thus, LLD subgroups exhibit abnormal processing at different levels of the auditory system, spanning the brainstem, the auditory cortex, or both. Additionally, individuals with LLD exhibit abnormal processing in areas outside what are considered classic auditory areas, such as prefrontal regions. In addition to the common bottom-up explanation for the role of auditory processing in literacy, a top-down account is thus also likely. Thus, it is possible that a deficient high-level process (e.g., attention, working memory) is manifested in literacy and language problems and in auditory processing deficits through feedback connections from higher to lower areas. It may be that these abnormalities, in turn, are accompanied by different behavioral manifestation of APD. Recent findings in animal models demonstrate how high-level influences shape auditory processing and plasticity (Fritz, Elhilali & Shamma, 2005; Polley, Steinberg & Merzenich, 2006). Thus, abnormal processing at the level of the lower and upper brainstem may be linked to difficulties in perception in noise, whereas cortical deficits may be more indicative of subtle discrimination deficits. Further research in well-defined groups is required to lend further support for this assertion.

In terms of etiology, numerous environmental and genetic mechanisms, as well as the interaction between genetics and environment, likely account for this

large spectra of behavioral and physiologic findings. For example, following both a short period of anoxia and induced cortical microgyria (small cortical lesions), rats show evidence of abnormal auditory processing as well as deficient sound-evoked brainstem timing (Clark, Rosen, Tallal, & Fitch, 2000; Fitch, Tallal, Brown, Galaburda, & Rosen, 1994; Strata et al., 2005), reminiscent of temporal-processing deficits in persons with LLD. Although the functional significance of APD to the development of language and cognitive abilities and ultimately to success in school is still poorly understood, data from developmental studies certainly suggest a predictive link between auditory processing and later cognitive development.

Early diagnosis and treatment of auditory processing deficits is of potential importance in easing future learning problems and improving language development among children with LLD with APD-related symptoms. In recent years, several biological markers of auditory processing, literacy, and language have been proposed. These markers include delayed brainstem timing in response to speech syllables (see Johnson et al., 2005, for review) and a differential pattern of the cortical evoked response to speech syllables in newborns (see Lyytinen et al., 2005, for review). In the clinic, using these markers in addition to available test batteries can help inform the diagnosis and treatment recommendations of APD. Further studies are required to elucidate the relationships between these markers and behavioral diagnostic measures of APD, as well as their applicability to different subgroups and in different developmental stages. In addition, future research should look at possible separate markers, corresponding to the various APD observed, rather than a single universal marker. This biologically based approach may ultimately lead to improved understanding of a variety of clinical conditions that are still insufficiently understood.

Finally, because the preconscious encoding of sound at the cortical and subcortical levels and the perception of many acoustic features can be enhanced with training, auditory training regimens are promising tools for the amelioration of APD. However, in order for training to fulfill an important role in remediation, further research is required to create optimal training regimens for children and clinical populations; better understand the relationships between the behavioral outcomes of training and neural plasticity; and develop training procedures that will optimize the outcome in terms of generalization and transfer of learning.

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