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CHAPTER 15

The Dynamic Brainstem: Implications for Auditory Processing Disorder

KAREN BANAI AND NINA KRAUS

From the cochlea to the auditory cortex, sound is encoded in multiple locations along the ascending auditory pathway, eventually leading to our conscious perception. Although there is no doubt that the cortex plays a major role in perception of speech, music, and other meaningful auditory signals, recent studies, reviewed in this chapter, suggest that subcortical encoding of sound is not merely a series of bottom-up processes successively transforming the acoustic signal to more complex neural code. Rather, subcortical processing dynamically interacts with cortical processing to reflect important nonsensory factors such as musical expertise (Musacchia, Sams, Skoe, & Kraus, 2007; Wong, Skoe, Russo, Dees, & Kraus, 2007), linguistic experience (Krishnan, Xu, Gandour, & Cariani, 2005), and attention (Galbraith, Bhuta, Choate, Kitahara, & Mullen, 1998; Galbraith, Olfman, & Huffman, 2003).

In this chapter, we focus on the encoding of speech-sounds at the upper brainstem/midbrain (the speech-ABR) in humans, emphasizing the fidelity of encoding within an individual, how encoding is affected by expertise, and how it is disrupted in clinical populations intersecting auditory processing disorder (APD). Because current electrophysiologic techniques provide reliable means to test subcortical, but not cortical encoding of sound at the individual listener level, we propose that these properties of subcortical auditory processing carry special relevance to the study and understanding of APD. Namely, these properties allow us to define an individual as having an APD if specific elements of their response are significantly disrupted. We can then ask whether individuals manifesting a certain physiological pattern also share similar perceptual, literacy-related, and cognitive profiles, and whether current definitions of APD, language disorders or learning problems can account for the observed profiles, or whether these physiological deficits and accompanying profiles "cut across" diagnoses.

Fidelity of Subcortical Encoding of Sound: Characteristics of Normal Subcortical Encoding of Speech Sounds

Synchronized neural activity in response to sounds can be measured noninvasively in humans by means of auditory evoked potentials. Simple (brief nonspeech) stimuli evoke an orderly pattern of responses from the auditory nuclei in low brainstem (waves I–III) and rostal (waves V–Vn, the FFR) brainstem nuclei, clinically known as the click-evoked ABR (Boston & Møller, 1985; Møller, 1999; Møller & Jannetta, 1985; Sohmer, Pratt, & Kinarti, 1977; Worden & Marsh, 1968). Slight deviations from the timing of the normal pattern are associated with hearing loss and other pathologies (Hall, 1992; Hood, 1998). Synchronized neural activity can also be measured in response to more complex sounds like synthetic vowels or consonant-vowel syllables. At low levels of the brainstem, the evoked responses to simple and complex sounds appear similar (Song, Banai, & Kraus, 2008). Here, we review work on auditory evoked responses originating at rostal brainstem/midbrain nuclei that reflect the temporal and spectral characteristics of complex stimuli with remarkable precision (Galbraith, Arbagey, Branski, Comerci, & Rector, 1995; Johnson, Nicol, & Kraus, 2005; Krishnan, 2002; Russo, Nicol, Musacchia, & Kraus, 2004; Akhoun et al, 2008).

Speech is a signal whose temporal and spectral properties change continuously. Studies in animal models indicate that many of its complex properties (formant structure, pitch, voicing, etc.) can be encoded through the firing patterns of auditory neurons (Delgutte & Kiang, 1984a, 1984b; Sachs & Young, 1979; Young & Sachs, 1979). In humans, two main classes of evoked responses (reflecting activity of large neural populations) are likely candidates to reflect these complex properties: the late waves of the auditory brainstem response (ABR), which are essentially onset responses, and the frequency following response (FFR), which reflects phase-locked activity of neural populations in the rostal brainstem, tracking the fundamental frequency of the sound and its harmonics.

Our approach to study the parallels between the acoustic properties of the speech signal and the brain evoked response is based on the source/filter model of speech production (Fant, 1970; and see Kraus & Nicol, 2005 for a detailed review of the application of the source/filter model to speech-evoked brainstem responses) and is demonstrated in Figure 15–1. In this view, the acoustic properties of the signal can be classified into one of two broad classes of responses: the source class and the filter class. The source class contains all parameters used to describe the properties of the sound source (the vocal folds in the case of speech, the strings in case of string instruments). The sound wave produced by the source is modified by the filter, that is, the shape of the vocal tract and the articulators in the case of speech or the shape of the musical instrument, and this modification produces the final acoustic structure. In the case of speech, the vocal folds produce a harmonic sound at a period determined by the rate of vibration. The filter then attenuates certain harmonics and enhances others harmonics to produce the formant structure of speech sounds.

In analyzing the physiologic response, we hypothesize that the onset and offset transient peaks of the speech-ABR reflect

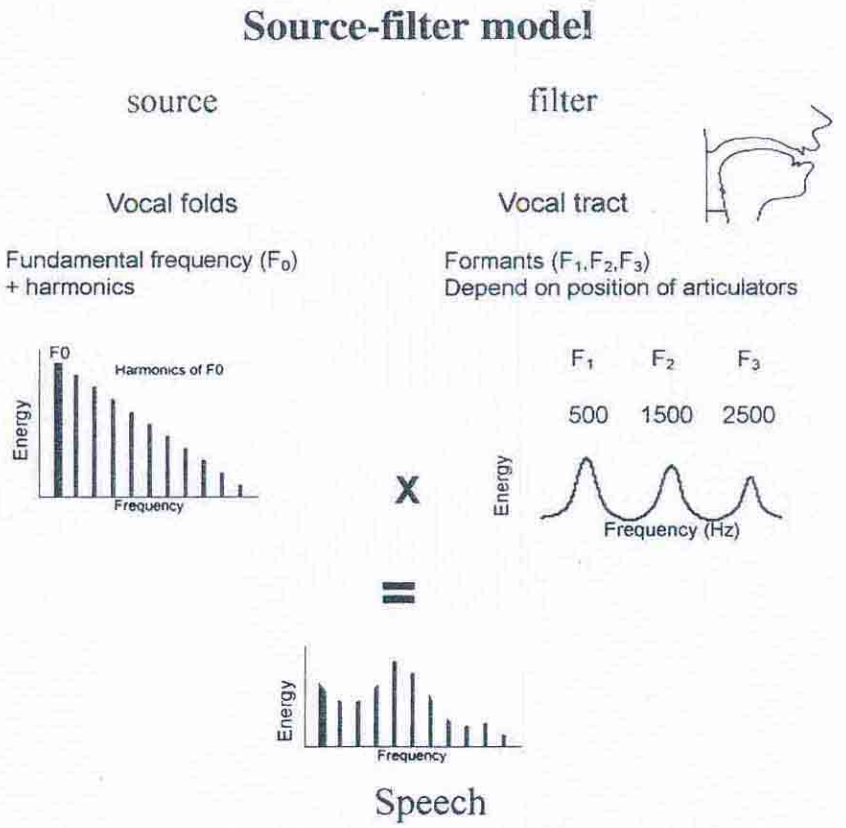

Figure 15–1. The source-filter model

mainly filter information, whereas the FFR probably reflects both source and filter properties of spectro-temporal elements and steady-state vowel-like stimuli (Kraus & Nicol, 2005; Johnson et al, in press), because the neural response shows phase-locking to the fundamental frequency of the stimulus (a source property) as well as to higher frequency formants (a filter characteristic). An examination of the evoked response to synthetic, steady-state vowels reveals a series of peaks, repeating at a rate corresponding to the fundamental frequency (F0) of the vowel—a source property. Furthermore, the spectral content of the response appears to reflect the first two formants of the vowel (Krishnan, 2002). Thus, frequency domain analyses of FFRs obtained to the synthetic vowels /u/, /ɔ/ and /a/ show that spectral peaks corresponding to the first and second formants, are increased in comparison to spectral peaks corresponding to the harmonics falling between F1 and F2 (Krishnan, 2002), thus reflecting filter properties as well.

We have been studying the brainstem response to the consonant-vowel syllable /da/ (Johnson et al., 2005; Russo et al., 2004). The brainstem response to /da/ (da-ABR) has both an onset portion occurring 6.7 ms (sd = 0.25 ms) after the stimulus onset and an FFR portion corresponding to the proper-

ties of the periodic formant transition and steady-state portion of the vowel /a/, as shown in Figure 15-2. Together, the onset and the FFR components of the da-ABR roughly reflect the acoustic parameters of the syllable /da/. The onset is a filter class response and likely repre-sents the initiation of the consonant, as it appears to be absent when a vowel is used on its own.

The speech stimulus /da/ and the response it evokes from a representative child are shown in Figure 15-2. It can be seen that the physiologic response to /da/, first reported by Cunningham, Nicol, Zecker and Kraus (2000) and described in the general population by Russo et al. (2004), includes an orderly series of peaks and troughs (peaks I through O). The initial peaks (I to A) are similar to those evoked by brief click stimuli. Waves I and III probably originate in the low brainstem, whereas peaks V and A originate in the rostal brainstem (the lateral lemniscus or inferior colliculus). Supporting the similarity between waves V and A in response to speech and clicks, Song, Banai, Russo and Kraus (2006) have reported significant correlations between the corresponding peak latencies in response to the two types of stimuli. Peak C possibly reflects the onset of voicing, whereas the later peaks (D, E, and F), comprising the FFR, occur at a rate equivalent to the fundamental frequency (F0) of the sound source and correspond to the format transition of the stimulus. Finally, peak O is likely an offset response, reflecting the end (stopping) of the sound. Figure 15-2C shows the spectra of the stimulus and the response, demonstrating how the major spectral peaks in the stimulus that fall within the phase-locking capabilities of the brainstem (F0 and F1) are represented in the response.

The feature of the speech-ABR that makes it useful in a wide array of studies and clinical applications is the high replicability of the response both within and across individuals. Thus, not only are the major morphologic features of the response stable over time within an individual (Russo, Nicol, Zecker, Hayes, & Kraus, 2005), the major peaks are also highly replicable between individuals (Russo et al., 2004; Akhoun et al, 2008), making deviations from the normal range easily identifiable and informative (Banai, Abrams, & Kraus, 2007; Banai & Kraus, 2006).

Supporting the separation between filter class and source class responses, significant correlations exist between latencies of the onset peaks V and A, which are considered filter class peaks. On the other hand, the latencies of the onset peaks are not correlated with the latencies of the FFR peaks or the response magnitude at the F0 (Kraus and Nicol 2005)—a source class response (Russo et al., 2004). For detailed discussions of the da-ABR, and how it is elicited and measured see Russo et al. (2004) and Johnson et al. (2005).

Because waves V and A of the speech-ABR appear to be similar to waves V and Vn of the click-evoked-ABR, it may be claimed that both reflect similar types of processing. Yet, it should be noted that whereas in the general population the latencies of wave V to click and speech are significantly correlated, this correlation breaks down in a subgroup of individuals with learning problems whose speech-ABRs are abnormal (Song et al., 2006, see below). Furthermore, different maturational patterns characterize click- and speech-evoked responses. Whereas the brainstem response to clicks is mature by 2 years of age (e.g., Salamy, 1984), the speech-evoked response only reaches adult like timing and morphology by the age of 5 (Johnson, Nicol, & Kraus, 2008). Taken together, these two lines of evidence support the idea that brainstem structures respond differently to speech- and click-sounds.

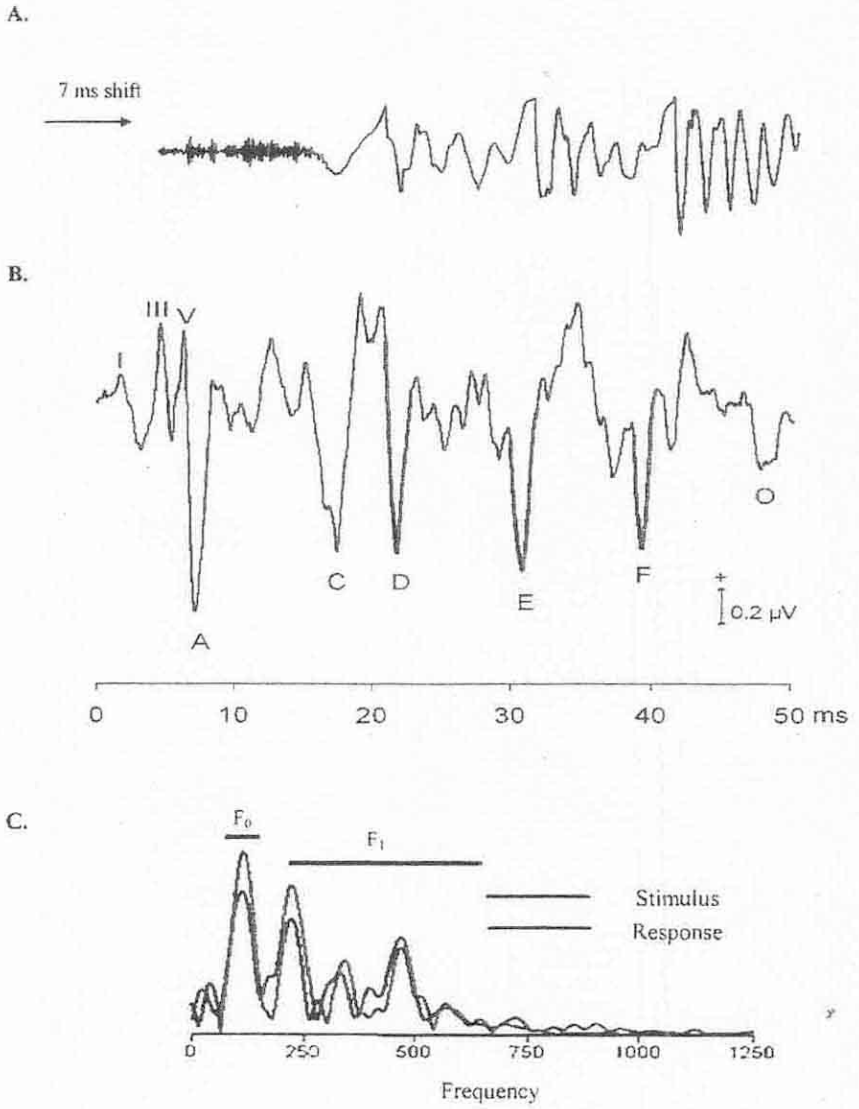

Figure 15–2. Subcortical encoding of the syllable /da/. **A.** The time/amplitude wave form of the speech syllable /da/. **B.** The time/amplitude waveform of the brainstem response from a typical child. Labels I-O denote the characteristic peaks of the response. Waves I and III originate at the low brainstem; waves V and A represent the onset of the response at the rostral brainstem. Waves D, E, and F are locked to the fundamental frequency of the /da/ stimulus. **C.** The spectra of the stimulus and the response from a typically developing child averaged over the entire stimulus and the last 40 ms of the response. Spectral peaks in the response correspond to F0 (103–125 Hz), and some of the higher harmonics comprising F1 (220–720 Hz). The stimulus has been filtered to mimic the phase-locking properties of the brainstem.

Malleability of Subcortical Encoding of Sound

The remarkable fidelity of subcortical encoding of speech, as measured using auditory evoked potentials, could suggest that encoding in these stations is based on automatic detection of the acoustic features of sound with no regard to higher level factors that are known to play a crucial role in perception such as expertise, attention, or context. Recent studies suggest that this is not the case, and that subcortical encoding is affected by expertise, input from other sensory modalities, and attention. Whether these influences are mediated in a top-down fashion, as predicted by the Reverse Hierarchy Theory (Hochstein & Ahissar, 2002) through the efferent, corticofugal system linking the auditory brainstem and cortex (Winer, 2006), through local mechanisms of adaptation to the acoustic properties of the input (Dean, Harper, & McAlpine, 2005), or through an interaction of afferent and efferent mechanisms is unknown.

Expertise and Subcortical Encoding of Speech

Brainstem responses to speech reflect differences in linguistic experience. The phase locking of neural activity to the pitch contour (that is the changes in F0 over time also known as pitch tracking) of Mandarin words (in which pitch provides an important cue to meaning) is stronger in native Mandarin compared to native English speakers, suggesting that the brainstems of Mandarin speakers encode Mandarin words more precisely than do the brains of English speakers (Swaminathan et al., 2008; Krishnan et al., 2005). These findings suggest that pitch encoding mechanisms in the human brainstem are sensitive to language experience; however, they can not resolve whether this plasticity is more consistent with corticofugal modulation of the subcortical structures by language experience or with statistical learning based on the input statistics of Mandarin speech sounds.

Indeed, several recent studies on the effects of experience on subcortical encoding reached opposing conclusions. On the one hand, Xu, Krishnan, and Gandour (2006) have shown that the subcortical encoding advantage of Mandarin speakers disappears following slight manipulations to the acoustic properties of the Mandarin tokens, while still preserving their meaning and allowing Mandarin speakers to perceive them as good quality Mandarin sounds. This is more consistent with a statistical learning argument than with corticofugal modulation because it suggests that the brains of Mandarin speakers are fine tuned only to the exact contours they hear in everyday speech. In this case, knowledge of Mandarin was not sufficient to confer a brainstem encoding advantage. On the other hand, Wong et al. (2007) have shown that musical experience results in more robust encoding of linguistic pitch-patterns in the brainstem (Figure 15-3 presents more details of this study). Because the musicians in this study were native English speakers, with no prior exposure to Mandarin, it is unlikely that their more robust encoding of Mandarin sounds was the result of statistical learning of Mandarin sounds, but of a more general influence of music training on multipurpose pitch encoding mechanisms (though it could still be some other local general pitch extracting mechanism that is driven by music training but not by speaking Mandarin). The findings from the Wong et al. (2007) study suggest

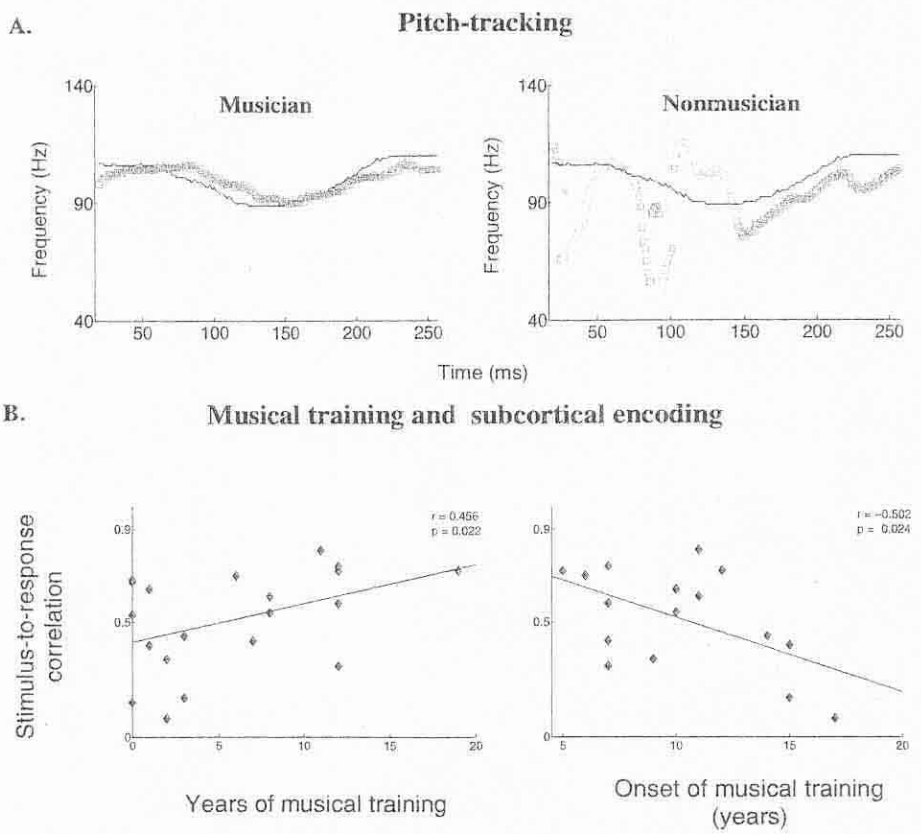

Figure 15–3. The effects of musical experience on speech encoding at the brainstem. **A.** Linguistic pitch encoding. The typical musician's brain (*left*) encodes the pitch content of Mandarin speech sounds more precisely than does the brain of the typical nonmusician (*right*). The thin line denotes the pitch contour of the stimulus, the thick line is the pitch contour extracted from the brainstem response. **B.** Musical experience and the fidelity of brainstem encoding. With increasing duration of musical training, the brainstem response more closely mimics the stimulus (indicated by increased stimulus-to-response correlation, *left*). Similarly, the age of onset of musical training is inversely correlated with the fidelity of brainstem encoding (*right*). Based on Wong, Skoe, Russo and Kraus (2007); Musacchia, Sams, Skoe and Kraus (2007).

common subcortical mechanisms for pitch processing in linguistic and nonlinguistic contexts. These findings are consistent with behavioral findings showing that Mandarin speakers use pitch information differently from native English speakers even in a nonlinguistic context when they are required to identify (but not discriminate) pitch contours (Bent, Bradlow, & Wright, 2006). Similar to the Wong et al. (2007) findings, musicians also show more robust brainstem encoding of the English syllable /da/, in particular when the auditory syllable was presented together with a visual counterpart in a lip-reading condition (Musacchia et al., 2007; Musacchia, Strait, and Kraus, 2008).

Taken together, the Wong et al. (2007) and the Musacchia et al. (2007 & 2008) studies suggest that the consequences of musical experience extend across domains (e.g. language) and levels of processing in the auditory pathway (see Kraus & Banai, 2007 for further discussion of this point). Moreover, despite the well-known cortical segregation of speech and music function (Zatorre, Belin, & Penhune, 2002), a common subcortical network for speech and music is implied.

Visual Influences on Subcortical Encoding of Speech

The addition of visual input to the auditory speech stimulus, changes the way the brainstem encodes acoustic information as early as 11 ms after the onset of the acoustic stimulus (Musacchia, Sams, Nicol, & Kraus, 2006). When a visual stimulus—a face uttering a syllable or a musical instrument being played—is presented along with the acoustic stimulus (a syllable or a musical note, respectively), the brainstem response to the speech syllable is modified by the presence of the visual stimulus, and this form of auditory-visual interaction is significantly enhanced in musicians compared to non-musicians (Musacchia et al., 2007; Musacchia et al., 2008). These findings suggest sub-cortical involvement in multi-sensory integration in addition to multi-modal cortical regions typically thought to engage in this function.

Effects of Attention on Subcortical Encoding

Like visual input, attending to sound influences brainstem encoding of speech and nonspeech sounds, in addition to, and earlier than the more widely documented cortical effects. Two types of attentional effects on the human FFR have been suggested. A spatial-attention (ear-related) effect and a modality effect. 'A spatial attention effect was observed in a dichotic listening paradigm; when two different syllables were presented simultaneously, one to each ear, and listeners were required to switch their attention between the two ears, the encoding of the fundamental frequency of the attended syllable was selectively enhanced (Galbraith et al., 1998). A small but significant effect on the FFR latency (with no effect on amplitude) was also reported with a different attentional paradigm in which listeners were required to respond to targets that occurred in the same ear as a cue ("attended") or in the contralateral ear ("unattended") (Hoormann, Falkenstein, & Hohnsbein, 2004). Frequency following response amplitudes were also found to increase when attention was directed to the auditory modality (listeners were asked to count auditory targets) compared to when attention was directed to the visual modality (listeners were asked to count visual targets while ignoring the sounds) (Galbraith et al., 2003). These findings suggest the existence of crude attentional mechanisms at the level of the auditory brainstem. These mechanisms could serve to enhance auditory encoding by direct-ing processing resources to the appropriate modality, or within the auditory modality to the appropriate ear. It is still not clear if more refined attentional, related to specific auditory features, occurs at the brainstem.

Taken together, the findings that language and musical experience, as well as inputs from the visual modality and attention affect auditory encoding of sound at subcortical levels of the auditory pathway suggest that these areas are more plastic and dynamic than was typically assumed by sensory neuroscientists, and that at least

some of these influences are mediated by top-down mechanisms.

Subcortical Encoding of Speech in Noise Can Be Improved with Training

Further evidence for the dynamic nature of subcortical auditory encoding comes from the effects of training on the speech-ABR. Russo et al. (2005) have shown that in a group of children with language-based learning disorders undergoing auditory training, the resilience of the brainstem to the degrading effects of background noise improved following training. Because the training was not specific to the syllable used to elicit the brainstem response, or to perception in noise, it is not likely that training affected local low-level mechanisms at the brainstem. This outcome therefore raises the possibility that the influences of training on the brainstem were mediated in a top-down fashion.

In addition to enhancing the brainstem response in noise, short-term training may improve pitch encoding in the brainstem in a way similar to that of long-term musical experience. Thus, when native English speakers were trained to use lexical pitch patterns to identify Mandarin words, tracking of some Mandarin pitch patterns in their brainstems became more precise (Song, Skoe, Wong, & Kraus, 2008).

Vulnerability of Subcortical Encoding of Sound

Our focus has been on children with language-based learning problems (LD). Previous work concentrated on cortical processing in this clinical group and revealed that various forms of auditory cortical processing are abnormal in a substantial subgroup of this population (e.g., Baldeweg, Richardson, Watkins, Foale, & Gruzelier, 1999; Bishop & McArthur, 2004; Hari & Renvall, 2001; Heim et al., 2000; Helenius, Salmelin, Richardson, Leinonen, & Lyytinen, 2002; Kraus et al., 1996; Kujala et al., 2000; Lachmann, Berti, Kujala, & Schroger, 2005; Moisescu-Yiflach & Pratt, 2005; Nagarajan et al., 1999; Wible, Nicol, & Kraus, 2002). Our studies reveal that, in addition to cortical processing deficits, brainstem responses to speech are abnormal in about a third of children diagnosed with language-based learning problems (Banai, Nicol, Zecker, & Kraus, 2005). Compar-ed to typically developing children, in this subgroup of the LD population, waves A, C, and F were found to be delayed (King, Warrier, Hayes, & Kraus, 2002), the onset response at the upper brainstem (waves V, A) is prolonged and less synchronized (Figure 15–4), and the spectral representation of F1 (but not F0) is reduced (Wible, Nicol, & Kraus, 2004). On the other hand, the brainstem responses to click in this group are normal (Song et al., 2006) suggesting that the timing deficit in response to speech sounds does not reflect a universal deficit. A similar dissociation was reported in a group of children with specific language impairment (SLI) in which brainstem responses to pure tones were of normal latency, but responses to backward masked ones were delayed (Marler & Champlin, 2005). Finally, children on the autism spectrum have been found to have abnormal subcortical pitch-tracking, consistent with known deficits in prosody perception in this population (Russo, Bradlow, Skoe, Trommer, Nicol, Zecker and Kraus, 2008).

For a more complete discussion of our approach for determining whether speech-ABR is abnormal, as well as for normative data see Banai, Abrams, and Kraus (2007). It is of interest however to note here that the proportion and degree of speech-ABR

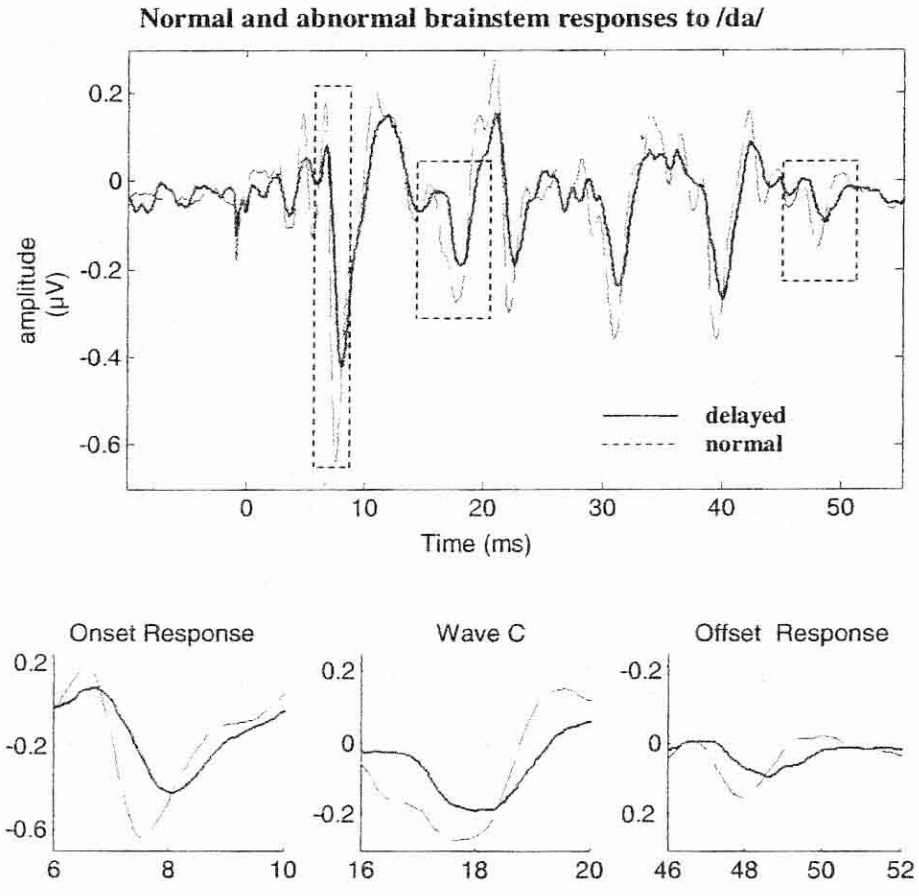

Figure 15–4. Abnormal speech ABR. *Top:* Grand averages of the time domain response in children with learning problems and abnormal responses (in *dark gray lines*) versus typically developing children (*light gray dashed line*). Dashed boxes mark the regions of the response that significantly differ between individuals with normal and abnormal responses. *Bottom*: Focus on the onset (*left*), the transition period (*middle*) and the offset (*right*) portions of the response.

deficits in all of our previous studies was unrelated to the specific diagnosis (APD, SLI, ADHD, or LD), with the exception of poor readers where the incidence is higher, suggesting that perhaps similar underlying physiological bases can cut across existing diagnostic categories. It should also be noted that, although these findings suggest an association between learning problems and abnormal processing at the level of the brainstem, they cannot be taken to indicate causality. Nonetheless, the reliability of the response within an individual makes the speech-ABR a useful marker of auditory function in the assessment of listening and learning disorders, and has led to the translation of the research to a clinically available tool—BioMAP (Biological Marker of Auditory Processing, Bio-logic Systems Corp, a Natus Company, Mundelein, IL).

The Relationships Between Cortical and Subcortical Auditory Processing

Because abnormal cortical processing of both nonspeech (Baldeweg et al., 1999; Corbera, Escera, & Artigas, 2006; Stoodley, Hill, Stein, & Bishop, 2006) and speech (Kraus et al., 1996; Schulte-Korne, Deimel, Bartling, & Remschmidt, 1998) sounds has been implicated in many cases of LD, whereas responses to acoustic clicks from structures up to the rostal brainstem were typically found to be normal in LDs (Grontved, Walter, & Gronborg, 1988; Jerger, Martin, & Jerger, 1987; Lauter & Wood, 1993; Mason & Mellor, 1984; McAnally & Stein, 1997; Purdy, Kelly, & Davies, 2002), the extent of auditory pathway deficit characterized using responses evoked by the same stimulus in the subgroup of LDs with abnormal speech-ABRs is of interest. We have examined auditory pathway encoding to the speech syllable /da/ across multiple levels of the auditory pathway.

At the lowest levels of the pathway, timing of peaks I and III in LDs with abnormal later peaks appears normal (Song, Banai et al., 2008), placing the rostal brainstem as the lowest possible source of deficit. On the other hand, when speech-ABR is abnormal, several aspects of auditory cortical processing appear abnormal as well. First, a strong correlation between brainstem timing and the resilience of the cortical response to the presence of background noise was found (Wible, Nicol, & Kraus, 2005). As shown in Figure 15-5A, noise had more detrimental effects on the cortical responses of individuals with delayed brainstem timing, compared to those with earlier timing, and this was true in both typically developing children and those with language based learning problems. Second, abnormal brainstem timing is associated with reduced cortical discrimination of fine acoustic differences (MMNs, Banai et al., 2005b). As shown in Figure 15-5B, as a group, individuals with abnormal speech-ABRs failed to show an MMN at all, suggesting that delayed timing in the brainstem and cortical discrimination are related. Third, the degree of brainstem deficit is associated with the degree of laterality of cortical processing of speech sounds (Abrams, Nicol, Zecker, & Kraus, 2006). As shown in Figure 15-5C, the normal pattern of leftward cortical asymmetry in response to speech sound is disrupted when brainstem timing is delayed. Finally, effects of musical experience are expressed in brainstem-cortical relationships (Musacchia et al., 2008).

Taken together these studies suggest strong relationships between auditory processing at the brainstem and the cortex. Because the brainstem and the cortex are linked by both ascending and descending pathways (see Winer, 2006 for review), these studies cannot resolve the direction of causality, namely, whether a subtle timing deficit at the brainstem adversely affects cortical processing or whether abnormal cortical processing exercises abnormal feedback on the brainstem, manifested by the pattern of timing deficits observed in individuals with abnormal speech-ABR. Recent studies in animal models are consistent with the top-down direction though (Ma & Suga, 2001; Palmer et al., 2006; Popelar, Nwabueze-Ogbo, & Syka, 2003). One possible route through which the descending pathway could exert its influence is by influencing selective attention, which in turn aids in gating of sensory information to the cortex. If processing in the cortex is not robust enough, it may not be able to properly "tune" the subcortical structures to relevant acoustic features.

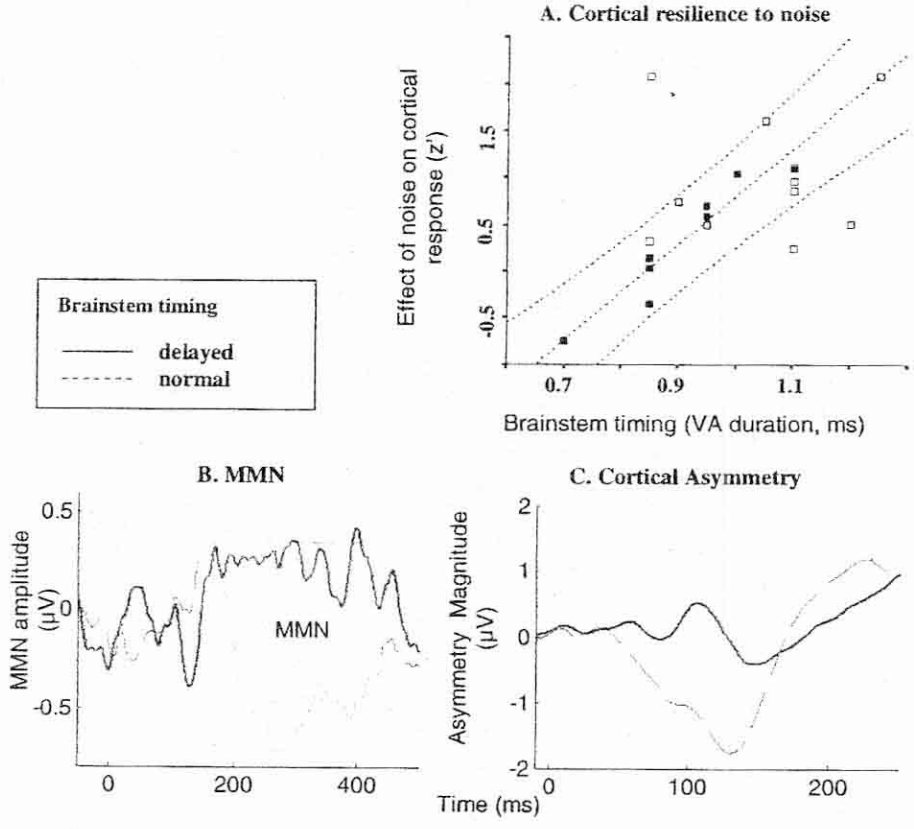

Figure 15–5. Cortical processing as a function of brainstem timing. **A.** The relationship between brainstem timing (VA duration) and the cortical susceptibility to noise. Filled symbols denote typically developing children; empty symbols denote children with LD showing a similar trend across both groups. z' was computed by subtracting cortical response correlations in noise from those in quiet. The larger z', the more pronounced effect noise had on response reliability. Based on Wible et al. (2004). **B.** Normally (and among individuals with early brainstem timing denoted in *light gray dashed line*) the cortical detection of rare acoustic evens among frequent ones is indexed by a negative deflection starting about 150 ms after stimulus onset (Mismatch negativity, MMN). This negative deflection is not present when brainstem timing is delayed (*solid line*). Based on Banai et al. (2005). **C.** Normally, cortical processing of speech sounds is stronger in the left hemisphere of the brain, as denoted by the left asymmetry of the cortical response of individuals with early brainstem timing (*dashed line*). This pattern is disrupted when brainstem timing is delayed (*solid line*). Based on Abrams et al. (2006).

Functional Correlates of Subcortical Encoding of Sound

How subcortical encoding of sound contributes to perception, language, and other cognitive functions is still not clear, but studies point to relationships between brainstem encoding of speech sounds and some perceptual and literacy related measures. It has been observed that more than 80% of individuals with abnormal brainstem timing are poor readers (Banai et al., 2005; Figure 15-6). This figure is higher than the proportion of poor readers typically observed in the highly heterogeneous group of individuals with LD that comprised the majority of our studies.

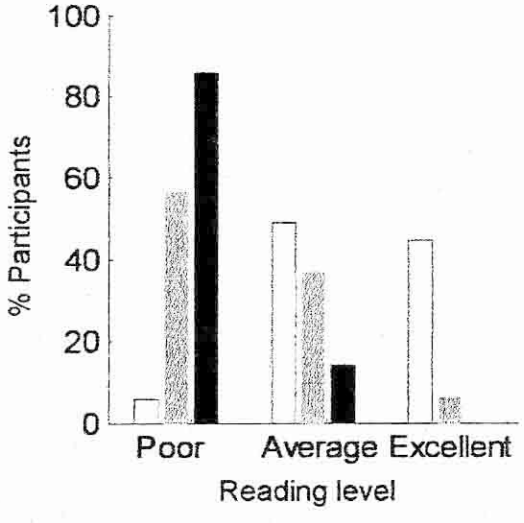

Figure 15–6. Brainstem processing and literacy. Histogram showing the distribution of reading abilities among typically developing 8- to 12-year-old children (*unfilled bars*), children with learning disabilities and normal speech-evoked ABRs (*gray bars*) and children with learning problems and abnormal speech-evoked ABRs (*black bars*). The majority of children with abnormal ABRs are poor readers. Based on Banai et al. (2005).

Regarding speech-perception, the picture is more complicated and tentative. Based on a review of unpublished data (Banai, Abrams, & Kraus, 2007), it appears that many individuals with LD and abnormal speech-ABR can have normal speech discrimination JNDs when tested behaviorally. It therefore seems that abnormal brainstem timing does not necessarily result in impaired perception of single syllables in laboratory conditions. This observation is surprising and unintuitive if one assumes that a physiologic deficit at the brainstem, with cortical correlates should have an influence on perception. However, it suggests that the link between brainstem encoding and higher level literacy related skills is not a direct outcome of abnormal speech perception at the syllable level but rather may refect a more general language deficit. Noteworthy is that in the cases where impaired perception of syllables was observed, it appears that training improves perception for individuals with abnormal brainstem timing but not for those with normal timing (C. King et al., 2002). In ongoing work, we are studying the perception of sentences presented in challenging listening conditions in individuals with abnormal speech-ABRs to investigate further the relationship between abnormal brainstem encoding and speech perception.

Poor temporal resolution, determined by elevated thresholds for the detection of backward masked tones, is characteristic of many individuals with language and learning problems (e.g., Wright et al., 1997). Although it is typically assumed that cortical processing is critical for backward masking, two studies suggest that subcortical areas of the auditory pathway may also be implicated in abnormal backward masking thresholds. In the first study, Marler and Champlin (2005) found that the auditory brainstem responses of individuals with SLI were normal when elicited with pure tones,

but abnormal when the same tones were backward masked with noise. In the second study, Johnson et al. (2007) looked specifically in children with LD and poor temporal resolution (defined by performance on a backward masking task), in comparison to children with LD and normal temporal resolution. They found that as a group, children with poor temporal resolution exhibited abnormal encoding of speech at the brainstem and, furthermore, that the encoding deficit was specific to the onset and offset portion of the brainstem response, with the FFR being normal, thus linking abnormal temporal resolution with speech encoding.

Evidence for the involvement of IC (the putative neural generator of waves V and A of the speech-ABR and of the FFR) in auditory processing under challenging listening conditions, as well as in sound localization come from the few available case studies of individuals who suffered a localized lesion to the IC unilaterally or bilaterally. Whereas a bilateral lesion involving IC seems to result in auditory agnosia (Johkura, Matsumoto, Hasegawa, & Kuroiwa, 1998) or central deafness (Musiek, Charette, Morse, & Baran, 2004), unilateral lesions may result in more subtle deficits in sound localization (Champoux et al., 2007; Litovsky, Fligor, & Tramo, 2002), and in recognition of duration patterns and speech in the presence of a competing signal (Champoux et al., 2007) when the ear contralateral to the lesion is stimulated.

Implications for APD

ABRs Are Reliable in Individuals

The ABR can be recorded reliably in individuals, making it a prominent tool in the clinic (Hood, 1998). Speech-ABR is no exception (Russo et al., 2004; Akhoun et al., 2008). The relationships among speech-ABR, literacy, and temporal resolution discussed above indicate that speech-ABRs may aid in the diagnosis and assessment of APD. Furthermore, because abnormal speech-ABRs are not characteristic of a specific type of learning disorder, but rather are found among 30% of LD individuals, irrespective of their specific diagnosis and to a greater extent in poor readers, and because APD and LD often co-occur (W. M. King, Lombardino, Crandell, & Leonard, 2003; Sharma et al., 2006), it is also likely that they characterize at least a subgroup of the individuals currently being diagnosed with APD. It could be that these individuals have a different type of disorder than those with behavioral manifestations of APD but normal speech-ABRs. Further research is required to establish the relationships between the behavioral symptoms of APD and brainstem encoding of speech.

ABRs May Be Used to Predict the Effects of Auditory Training

Auditory training is often used in remediation of both learning problems and APD, but outcomes are variable and clinicians currently do not have a way of deciding if a child is a good candidate for auditory training or not. The resilience of the speech-ABR to noise can improve with training (Russo et al., 2005). Furthermore, children with abnormal brainstem timing to speech have been shown to be more likely than those with normal brainstem timing to improve their speech perception and the resilience of their cortical responses in noise following auditory training (Hayes, Warrier, Nicol, Zecker, & Kraus, 2003; C. King et al., 2002). These findings, together with the malleability of brainstem function with long and short-term training, suggest that, in addition to objectively assessing

training outcomes, clinical measurements of speech-ABRs can be used to aid in deciding on a course of therapy.

APD Research and Diagnosis Could Benefit from the Use of Objective Measures

Current diagnosis of APD is based on a battery of auditory tests, but it is often not clear how these tests relate to underlying physiologic processes that may be impaired in APD. Furthermore, it is likely that APD is not a uniform phenomenon and that individuals that are impaired on some aspects of auditory function are unimpaired on others. Subcortical encoding can be used to define subgroups that are homogeneous on a particular biological indicator (e.g. onset timing, phase-locking, noise susceptibility). Then it can be determined whether individuals within these subgroups share a similar perceptual profile. In addition to the speech-ABR discussed in detail in this chapter, another subcortical measure that has been used in research and that is sensitive to the presence of clinically diagnosed APD is the binaural interaction component (BIC) (Delb, Strauss, Hohenberg, & Plinkert, 2003; Gopal & Pierel, 1999). The BIC is a putative index of binaural processing. It is therefore possible to hypothesize that the BIC and the speech-ABRs may reveal two distinct subtypes of APD, with distinct perceptual profiles. Alternatively, they may both be impaired in the same population.

The Nature of APD

An influential current definition of APD (ASHA, 2005) suggests that the neural deficits in the central nervous system that give rise to APD may be reflected by difficulties in one or more of a long list of auditory skills including sound localization and lateralization, auditory discrimination, auditory pattern recognition, multiple aspects of temporal processing, processing of competing acoustic signals, and processing of degraded acoustic signals. It also requires that these auditory deficits are not due to primarily high-order factors such as attention or memory. This heterogeneity of symptoms suggests the potential existence of distinct subtypes of APD. Attempts to define subprofiles of APD were made by Bellis and Ferre (1999) who suggested, based on case studies and clinical observations, several subtypes of APD, based on the putative underlying neurophysiology of each subtype.

1. A left hemisphere subtype characterized by deficits in auditory decoding, including deficits on auditory closure tasks, poor temporal resolution and poor performance on dichotic speech tasks (bilateral or right ear). Furthermore, individuals may have difficulties in other high-level language skills associated with left hemisphere function.
2. A right hemisphere subtype characterized by prosodic deficits including a left ear deficit on dichotic speech tasks, poor temporal patterning and poor frequency, intensity and duration discrimination. In addition, individuals may have difficulties in other high-level skills associated with the right hemisphere such as prosody perception, sight word reading, and pragmatic skills.
3. An integration deficit subtype characterized by deficits in tasks that indicate inefficient hemispheric transfer. Deficits include poor temporal patterning and left-ear deficit on dichotic speech tasks. Higher level deficits may include speech in noise and localization defi-

cits and poor performance with multimodal cues.

This model illustrates two problems inherent in the ASHA definition of APD (ASHA, 2005). First, it suggests that a unimodal deficit confined to the auditory system alone is unlikely. Second, because individuals in each of the subgroups may have higher level deficits, the idea that the auditory deficits can not be a consequence of high-order deficits seems unlikely.

It Is Not Reasonable to Expect an Auditory-Only Disorder

The central role of the auditory modality in APD led to the suggestion that modality specificity should be incorporated into the definition and differential diagnosis of APD (Cacace & McFarland, 2005). For several reasons outlined here, we would like to claim that it is unlikely that APD is a modality specific condition. First, there is little evidence to link the general listening difficulties experienced by individuals with APD in challenging listening conditions with a *specific*, single underlying auditory physiologic deficit. In fact, the evidence from localized IC lesions discussed above are not consistent with the APD phenotype because they result in more specific deficits than those typically present in individuals diagnosed with APD. As discussed in this chapter, a specific (and subtle) timing deficit at the brainstem may be related to a general form of learning disability rather than to a specific perceptual deficit. Furthermore, the brainstem deficit is strongly linked with cortical processing abnormalities (Abrams et al., 2006; K. Banai, T. Nicol, S. Zecker, & N. Kraus, 2005a; Banai et al., 2005b; Wible et al., 2005). Second, multisensory processing is carried out in structures such as IC and the auditory cortex, probably influencing the subcortical auditory processes reviewed in this chapter. In addition, these processes are influenced by higher level factors such as attention and memory. These influences are not likely to be modality specific either. Indeed, in individuals with conditions overlapping APD such as developmental dyslexia, auditory perceptual deficits often co-occur with visual (Amitay, Ben-Yehudah, Banai, & Ahissar, 2002; Ramus et al., 2003) and haptic deficits (Laasonen, Service, & Virsu, 2001). Furthermore, recent studies in animal models and in humans (e.g., Alain, 2007; Brechmann et al., 2007; Moore, Palmer, Hall, & Sumner, 2007; Näätänen, Tervaniemi, Sussman, Paavilainen, & Winkler, 2001; Nelken, 2004; Scheich, Brechmann, Brosch, Budinger, & Ohl, 2007) document both high-level influence on auditory function, and the presence of multiple "cognitive" processes in the auditory cortex itself, making the idea that even performance on simple auditory tasks can be dissociated from "cognitive processes" impossible. For example, auditory processing deficits may be more dependent on cognitive factors such as working memory than on auditory encoding per se (Banai & Ahissar, 2006). It is likely that similar processes operate in individuals with APD, though to our knowledge, such a study has not been published.

Summary

Subcortical auditory processes are more dynamic than typically thought. As discussed in this chapter, they interact with other modalities and factors such as attention, visual influence, and experience. The role of subcortical auditory processes in perception and cognition is far from under-

stood, but available data suggest that they relate to cognitive processes involved in language and music, rather than to specific aspects of fine-grained auditory perception. Taken together, the evidence challenge some of the assumptions embedded in current conceptualization of APD.

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References

Abrams, D. A., Nicol, T., Zecker, S. G., & Kraus, N. (2006). Auditory brainstem timing predicts cerebral asymmetry for speech. *Journal of Neuroscience, 26*, 11131-11137.

Akhoun, I., Gallégo, S., Moulin, A., Ménard, M., Veuillet, E., Berger-Vachon, C., Collet, L., Thai-Van, H. (2008). The temporal relationship between speech auditory brainstem responses and the acoustic pattern of the phoneme /ba/ in normal-hearing adults. *Clincal Neurophysiology, 119*, 922-933.

Alain, C. (2007). Breaking the wave: effects of attention and learning on concurrent sound perception. *Hearing Research, 229*, 225-236.

Amitay, S., Ben-Yehudah, G., Banai, K., & Ahissar, M. (2002). Disabled readers suffer from visual and auditory impairments but not from a specific magnocellular deficit. *Brain, 125*(Pt. 10), 2272-2285.

ASHA. (2005). *(Central)' Auditory Processing Disorders* American Speech-Language-Hearing Association. http://www.asha.org/members/deskref-journals/deskref/default.

Baldeweg, T., Richardson, A., Watkins, S., Foale, C., & Gruzelier, J. (1999). Impaired auditory frequency discrimination in dyslexia detected with mismatch evoked potentials. *Annals of Neurolology, 45*, 495-503.

Banai, K., Abrams, D., & Kraus, N. (2007). Sensory-based learning disability: Insights from brainstem processing of speech sounds. *International Journal of Audioliology 46*, 524-532.

Banai, K., & Ahissar, M. (2006). Auditory processing deficits in dyslexia: Task or stimulus related? *Cerebral Cortex, 16*, 1718-1728.

Banai, K., & Kraus, N. (2006). Neurobiology of (central) auditory processing disorder and language-based learning disability. In: *Handbook of Central Auditory Processing Disorder: Volume I: Auditory Neuroscience and Diagnosis*, G. D. Chermak, F. E. Musiek (eds), San Diego: Plural Publishing, pp. 89-116.

Banai, K., Nicol, T., Zecker, S. G., & Kraus, N. (2005). Brainstem timing: implications for cortical processing and literacy. *Journal of Neuroscience, 25*, 9850-9857.

Bellis, T. J., & Ferre, J. M. (1999). Multidimensional approach to the differential diagnosis of central auditory processing disorders in children. *Journal of the American Academy of Audiology, 10*, 319-328.

Bent, T., Bradlow, A. R., & Wright, B. A. (2006). The influence of linguistic experience on the cognitive processing of pitch in speech and nonspeech sounds. *Journal of Experimental Psychology and Human Perceptual Performance, 32*, 97-103.

Bishop, D. V., & McArthur, G. M. (2004). Immature cortical responses to auditory stimuli in specific language impairment: Evidence from ERPs to rapid tone sequences. *Developmental Science, 7*, F11-F18.

Boston, J. R., & Møller, A. R. (1985). Brainstem auditory-evoked potentials. *Critical Review of Biomedical Engineering, 13*, 97-123.

Brechmann, A., Gaschler-Markefski, B., Sohr, M., Yoneda, K., Kaulisch, T., & Scheich, H. (2007). Working memory-specific activity in auditory cortex: Potential correlates of sequential processing and maintenance. *Cerebral Cortex, 17*, 2544-2545.

Cacace, A. T., & McFarland, D. J. (2005). The importance of modality specificity in diagnosing central auditory processing disorder.

American Journal of Audiology, 14, 112-123.

Champoux, F., Paiement, P., Mercier, C., Lepore, F., Lassonde, M., & Gagne, J. P. (2007). Auditory processing in a patient with a unilateral lesion of the inferior colliculus. *European Journal of Neuroscience, 25*, 291-297.

Corbera, S., Escera, C., & Artigas, J. (2006). Impaired duration mismatch negativity in developmental dyslexia. *NeuroReport, 17*, 1051-1055.

Cunningham, J., Nicol, T., Zecker, S., & Kraus, N. (2000). Speech-evoked neurophysiologic responses in children with learning problems: development and behavioral correlates of perception. *Ear and Hearing, 21*, 554-568.

Dean, I., Harper, N. S., & McAlpine, D. (2005). Neural population coding of sound level adapts to stimulus statistics. *Nature Neuroscience, 8*, 1684-1689.

Delb, W., Strauss, D. J., Hohenberg, G., & Plinkert, P. K. (2003). The binaural interaction component (BIC) in children with central auditory processing disorders (CAPD). *International Journal of Audiology, 42*, 401-412.

Delgutte, B., & Kiang, N. Y. (1984a). Speech coding in the auditory nerve: I. Vowel-like sounds. *Journal of the Acoustical Society of America, 75*, 866-878.

Delgutte, B., & Kiang, N. Y. (1984b). Speech coding in the auditory nerve: IV. Sounds with consonant-like dynamic characteristics. *Journal of the Acoustical Society of America, 75*, 897-907.

Fant, G. (1970). *Acoustic theory of speech production*. The Hague: Mouton.

Galbraith, G. C., Arbagey, P. W., Branski, R., Comerci, N., & Rector, P. M. (1995). Intelligible speech encoded in the human brain stem frequency-following response. *NeuroReport, 6*, 2363-2367.

Galbraith, G. C., Bhuta, S. M., Choate, A. K., Kitahara, J. M., & Mullen, T. A., Jr. (1998). Brain stem frequency-following response to dichotic vowels during attention. *NeuroReport, 9*, 1889-1893.

Galbraith, G. C., Olfman, D. M., & Huffman, T. M. (2003). Selective attention affects human brain stem frequency-following response. *NeuroReport, 14*, 735-738.

Gopal, K. V., & Pierel, K. (1999). Binaural interaction component in children at risk for central auditory processing disorders. *Scandinavian Audiology, 28*, 77-84.

Grontved, A., Walter, B., & Gronborg, A. (1988). Auditory brain stem responses in dyslexic and normal children. A prospective clinical investigation. *Scandinavian Audiology, 17*, 53-54.

Hall, J. W. (1992). *Handbook of auditory evoked responses*. Needham Heights, MA: Allyn & Bacon.

Hari, R., & Renvall, H. (2001). Impaired processing of rapid stimulus sequences in dyslexia. *Trends in Cognitive Sciences, 5*, 525-532.

Hayes, E. A., Warrier, C. M., Nicol, T. G., Zecker, S. G., & Kraus, N. (2003). Neural plasticity following auditory training in children with learning problems. *Clinical Neurophysiology, 114*, 673-684.

Heim, S., Eulitz, C., Kaufmann, J., Fuchter, I., Pantev, C., Lamprecht-Dinnesen, A., et al. (2000). Atypical organisation of the auditory cortex in dyslexia as revealed by MEG. *Neuropsychologia, 38*, 1749-1759.

Helenius, P., Salmelin, R., Richardson, U., Leinonen, S., & Lyytinen, H. (2002). Abnormal auditory cortical activation in dyslexia 100 msec after speech onset. *Journal of Cognitive Neuroscience, 14*, 603-617.

Hochstein, S., & Ahissar, M. (2002). View from the top: hierarchies and reverse hierarchies in the visual system. *Neuron, 36*, 791-804.

Hood, L. J. (1998). *Clinical applications of the auditory brainstem response*. San Diego, CA: Singular.

Hoormann, J., Falkenstein, M., & Hohnsbein, J. (2004). Effects of spatial attention on the brain stem frequency-following potential. *NeuroReport, 15*, 1539-1542.

Jerger, S., Martin, R. C., & Jerger, J. (1987). Specific auditory perceptual dysfunction in a learning disabled child. *Ear and Hearing, 8*, 78-86.

Johkura, K., Matsumoto, S., Hasegawa, O., & Kuroiwa, Y. (1998). Defective auditory recognition after small hemorrhage in the inferior colliculi. *Journal of the Neurological Sciences, 161*, 91-96.

Johnson, K. L., Nicol, T. G., & Kraus, N. (2005). Brain stem response to speech: A biological marker of auditory processing. *Ear and Hearing, 26*, 424-434.

Johnson, K. L., Nicol T., Kraus, N. (2008). Developmental plasticity in the human auditory brainstem. *Journal of Neuroscience,* 4000-4007.

Johnson, K. L., Nicol, T. G., Zecker, S. G., & Kraus, N. (2007). Auditory brainstem correlates of perceptual timing deficits. *Journal of Cognitive Neuroscience, 19*, 376-385.

Johnson, K. L., Nicol, T. G., Zecker, S. G., Bradlow, A., Skoe, E., Kraus, N. (2008). Brainstem encoding of voiced consonant-vowel stop syllables. *Clinical Neurophysiology*, in press.

King, C., Warrier, C. M., Hayes, E., & Kraus, N. (2002). Deficits in auditory brainstem pathway encoding of speech sounds in children with learning problems. *Neuroscience Letters, 319*, 111-115.

King, W. M., Lombardino, L. J., Crandell, C. C., & Leonard, C. M. (2003). Comorbid auditory processing disorder in developmental dyslexia. *Ear and Hearing, 24*, 448-456.

Kraus, N., & Banai, K. (2007). Auditory-processing malleability: Focus on language and music. *Current Directions in Psychological Science, 16*, 105-110.

Kraus, N., McGee, T. J., Carrell, T. D., Zecker, S. G., Nicol, T. G., & Koch, D. B. (1996). Auditory neurophysiologic responses and discrimination deficits in children with learning problems. *Science, 273*, 971-973.

Kraus, N., & Nicol, T. (2005). Brainstem origins for cortical 'what' and 'where' pathways in the auditory system. *Trends in Neuroscience, 28*, 176-181.

Krishnan, A. (2002). Human frequency-following responses: Representation of steady-state synthetic vowels. *Hearing Research, 166*, 192-201.

Krishnan, A., Xu, Y., Gandour, J., & Cariani, P. (2005). Encoding of pitch in the human brainstem is sensitive to language experience. *Brain Research and Cognitive Brain Research, 25*, 161-168.

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

Laasonen, M., Service, E., & Virsu, V. (2001). Temporal order and processing acuity of visual, auditory, and tactile perception in developmentally dyslexic young adults. *Cognitive Af-fect and Behavioral Neuroscience, 1*, 394-410.

Lachmann, T., Berti, S., Kujala, T., & Schroger, E. (2005). Diagnostic subgroups of developmental dyslexia have different deficits in neural processing of tones and phonemes. *International Journal of Psychophysiology, 56*, 105-120.

Lauter, J. L., & Wood, S. B. (1993). Auditory brainstem synchronicity in dyslexia measured using the REPs/ABR protocol. *Annals of the New York Academy of Sciences, 682*, 377-379.

Litovsky, R. Y., Fligor, B. J., & Tramo, M. J. (2002). Functional role of the human inferior colliculus in binaural hearing. *Hearing Research, 165*, 177-188.

Ma, X., & Suga, N. (2001). Plasticity of bat's central auditory system evoked by focal electric stimulation of auditory and/or somatosensory cortices. *Journal of Neurophysiology, 85*, 1078-1087.

Marler, J. A., & Champlin, C. A. (2005). Sensory processing of backward-masking signals in children with language-learning impairment as assessed with the auditory brainstem response. *Journal of Speech Language and Hearing Research, 48*, 189-203.

Mason, S. M., & Mellor, D. H. (1984). Brain-stem, middle latency and late cortical evoked potentials in children with speech and language disorders. *Electroencephalography and Clinical Neurophysiology, 59*, 297-309.

McAnally, K. I., & Stein, J. F. (1997). Scalp potentials evoked by amplitude-modulated tones in dyslexia. *Journal of Speech Language and Hearing Research, 40*, 939-945.

Moisescu-Yiflach, T., & Pratt, H. (2005). Auditory event related potentials and source current density estimation in phonologic/auditory dyslexics. *Clinical Neurophysiology, 116*, 2632-2647.

Møller, A. R. (1999). Neural mechanisms of BAEP. *Electroencephalography and Clinical Neurophysiology Suppl, 49*, 27-35.

Møller, A. R., & Jannetta, P. (1985). Neural generators of the auditory brainstem response. In J. T. Jacobson (Ed.), *The auditory brainstem response* (pp. 13-32). San Diego, CA: College-Hill Press.

Moore, D., Palmer, A., Hall, D., & Sumner, C. (2007). Hearing research special issue "Auditory cortex 2006—The listening brain." *Hearing Research, 239*,1-2.

Musacchia, G., Sams, M., Nicol, T., & Kraus, N. (2006). Seeing speech affects acoustic information processing in the human brainstem. *Experimental Brain Research, 168*, 1-10.

Musacchia, G., Sams, M., Skoe, E., & Kraus, N. (2007). Musicians have enhanced subcortical auditory and audiovisual processing of speech and music. *Proceedings of the National Academy of Science USA, 104*, 15894-15898.

Musacchia, G., Strait, D., Kraus, N. (2008). Relationships between behavior, brainstem and cortical encoding of seen and heard speech in musicians and nonmusicians. *Hearing Research, 241*, 34-42.

Musiek, F. E., Charette, L., Morse, D., & Baran, J. A. (2004). Central deafness associated with a midbrain lesion. *Journal of the American Academy of Audiology, 15*, 133-151; quiz 172-133.

Näätänen, R., Tervaniemi, M., Sussman, E., Paavilainen, P., & Winkler, I. (2001). "Primitive intelligence" in the auditory cortex. *Trends in Neuroscience, 24*, 283-288.

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

Nelken, I. (2004). Processing of complex stimuli and natural scenes in the auditory cortex. *Current Opinion in Neurobiology, 14*, 474-480.

Palmer, A. R., Hall, D. A., Sumner, C., Barrett, D. J., Jones, S., Nakamoto, K., et al. (2006). Some investigations into non-passive listening. *Hearing Research, 229*, 148-157.

Popelar, J., Nwabueze-Ogbo, F. C., & Syka, J. (2003). Changes in neuronal activity of the inferior colliculus in rat after temporal inactivation of the auditory cortex. *Physiological Research, 52*, 615-628.

Purdy, S. C., Kelly, A. S., & Davies, M. G. (2002). Auditory brainstem response, middle latency response, and late cortical evoked potentials in children with learning disabilities. *Journal of the American Academy of Audiology, 13*, 367-382.

Ramus, F., Rosen, S., Dakin, S. C., Day, B. L., Castellote, J. M., White, S., et al. (2003). Theories of developmental dyslexia: insights from a multiple case study of dyslexic adults. *Brain, 126*(Pt 4), 841-865.

Russo, N., Nicol, T., Musacchia, G., & Kraus, N. (2004). Brainstem responses to speech syllables. *Clinical Neurophysiology, 115*, 2021-2030.

Russo, N., Nicol, T. G., Zecker, S. G., Hayes, E. A., & Kraus, N. (2005). Auditory training improves neural timing in the human brainstem. *Behavioural Brain Research, 156*, 95-103.

Russo, N. M., Bradlow, A. R., Skoe, E., Trommer, B. L., Nicol, T., Zecker, S., Kraus, N., (2008). Deficient brainstem encoding of pitch in children with autism spectrum disorders. *Clinical Neurophysiology, 119*,1720-1731.

Sachs, M. B., & Young, E. D. (1979). Encoding of steady-state vowels in the auditory nerve: representation in terms of discharge rate. *Journal of the Acoustical Society of America, 66*, 470-479.

Salamy, A. (1984). Maturation of the auditory brainstem response from birth through early childhood. *Journal of Clinical Neurophysiology, 1*, 293-329.

Scheich, H., Brechmann, A., Brosch, M., Budinger, E., & Ohl, F. W. (2007). The cognitive auditory cortex: Task-specificity of stimulus representations. *Hearing Research, 229*, 213-214.

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

Sharma, M., Purdy, S. C., Newall, P., Wheldall, K., Beaman, R., & Dillon, H. (2006). Electrophysiological and behavioral evidence of auditory processing deficits in children with reading disorder. *Clinical Neurophysiology, 117*, 1130–1144.

Sohmer, H., Pratt, H., & Kinarti, R. (1977). Sources of frequency following responses (FFR) in man. *Electroencephalography and Clinical Neurophysiology, 42*, 656–664.

Song, J. H., Banai, K., & Kraus, N. (2008). Brainstem timing deficits in children with learning impairment may result from corticofugal origins. *Audiology and Neurootology, 13*, 335–344.

Song, J. H., Banai, K., Russo, N. M., & Kraus, N. (2006). On the relationship between speech- and nonspeech-evoked auditory brainstem responses. *Audiology and Neurootology, 11*, 233–241.

Song, J. H., Skoe, E., Wong, P. C., & Kraus, N. (2008). Plasticity in the adult human auditory brainstem following short-term linguistic training. *Journal of Cognitive Neuroscience*. DOI: 10.1162/jocn.2008. 20131.

Stoodley, C. J., Hill, P. R., Stein, J. F., & Bishop, D. V. (2006). Auditory event-related potentials differ in dyslexics even when auditory psychophysical performance is normal. *Brain Research, 1121*, 190–199.

Swaminathan, J., Krishnan, A., Grandour, J. T. (2008). Pitch encoding in speech and nonspeech contexts in the human auditory brainstem. *Neuroreport, 19*, 1163–1167.

Wible, B., Nicol, T., & Kraus, N. (2002). Abnormal neural encoding of repeated speech stimuli in noise in children with learning problems. *Clinical Neurophysiology, 113*, 485–494.

Wible, B., Nicol, T., & Kraus, N. (2004). Atypical brainstem representation of onset and formant structure of speech sounds in children with language-based learning problems. *Biological Psychology, 67*, 299–317.

Wible, B., Nicol, T., & Kraus, N. (2005). Correlation between brainstem and cortical auditory processes in normal and language-impaired children. *Brain, 128*(Pt. 2), 417–423.

Winer, J. A. (2006). Decoding the auditory corticofugal systems. *Hearing Research, 212*(1–2), 1–8.

Wong, P. C., Skoe, E., Russo, N. M., Dees, T., & Kraus, N. (2007). Musical experience shapes human brainstem encoding of linguistic pitch patterns. *Nature Neuroscience, 10*, 420–422.

Worden, F. G., & Marsh, J. T. (1968). Frequency-following (microphonic-like) neural responses evoked by sound. *Electroencephalography and Clinical Neurophysiology, 25*, 42–52.

Wright, B. A., Lombardino, L. J., King, W. M., Puranik, C. S., Leonard, C. M., & Merzenich, M. M. (1997). Deficits in auditory temporal and spectral resolution in language-impaired children. *Nature, 387*, 176–178.

Xu, Y., Krishnan, A., & Gandour, J. T. (2006). Specificity of experience-dependent pitch representation in the brainstem. *NeuroReport, 17*, 1601–1605.

Young, E. D., & Sachs, M. B. (1979). Representation of steady-state vowels in the temporal aspects of the discharge patterns of populations of auditory-nerve fibers. *Journal of the Acoustical Society of America, 66*, 1381–1403.

Zatorre, R. J., Belin, P., & Penhune, V. B. (2002). Structure and function of auditory cortex: Music and speech. *Trends in Cognitive Science, 6*, 37–46.