informa
healthcare

Original Article

International Journal of Audiology 2007; 46:524–532

Karen Banai[*,†]
Daniel Abrams[*]
Nina Kraus[*,§,†]

[*]Auditory Neuroscience Laboratory, Northwestern University, Evanston, USA
[§]Neurobiology and Physiology, Otolaryngology, Northwestern University, Evanston, USA
[†]Northwestern Institute of Neuroscience, Northwestern University, Evanston, USA

Key Words
AEP
ABR
Auditory processing
Dyslexia
Learning disability
Speech encoding

Abbreviations
AEP: Auditory-evoked potentials
ABR: Auditory brainstem response
FFR: Frequency following response
FFT: Fast Fourier transform
IC: Inferior colliculus
LD: Language-based learning disability

Sensory-based learning disability: Insights from brainstem processing of speech sounds

Abstract
Speech-evoked auditory brainstem responses (speech-ABR) provide a reliable marker of learning disability in a substantial subgroup of individuals with language-based learning problems (LDs). Here we review work describing the properties of the speech-ABR in typically developing children and in children with LD. We also review studies on the relationships between speech-ABR and the commonly used click-ABR, and between speech-ABR and auditory processing at the level of the cortex. In a critical examination of previously published data, we conclude that as many as 40% of LDs have abnormal speech-ABRs and that these individuals are also likely to exhibit abnormal cortical processing. Yet, the profile of learning problems these individuals exhibit is unspecific. Leaving open the question of causality, these data suggest that speech-ABR can be used to identify a large sub-population of LDs, those with abnormal auditory physiological function. Further studies are required to determine the functional relationships among abnormal speech-ABR, speech perception, and the pattern of literacy-related and cognitive deficits in LD.

Sumario
Las respuestas del tallo cerebral evocadas por lenguaje (ABR por lenguaje) aportan un marcador confiable de discapacidad para el aprendizaje en un subgrupo sustancial de individuos con problemas de aprendizaje dependientes del lenguaje (LD). Aquí revisamos trabajos que describen las propiedades de las ABR por lenguaje en niños con un desarrollo típico y en niños con LD. También revisamos estudios sobre la relación entre las ABR por lenguaje y las comúnmente utilizadas ABR inducidas por clicks, y entre las ABR inducidas por lenguaje y el procesamiento auditivo a nivel de la corteza. Luego de un examen crítico de datos previamente publicados, concluimos que hasta un 40% de los LD tienen ABR por lenguaje anormales, y que estos individuos son más propensos a exhibir un procesamiento cortical anormal. Sin embargo, el perfil de problemas de aprendizaje mostrado por estos individuos es inespecífico. Dejando de lado la pregunta sobre la causalidad, estos datos sugieren que las ABR por lenguaje pueden ser utilizadas para identificar un gran sub-población de sujetos con LD, aquellos con una función fisiológica auditiva anormal. Se requieren más estudios para determinar las relaciones funcionales entre la anormalidad de las ABR por lenguaje, la percepción del lenguaje y las patrones de LD relacionados con el nivel de educación y las deficiencias cognitivas.

The auditory system is extremely sensitive to the temporal characteristics of sound (see Frisina, 2001; Oertel, 1997 for reviews), and auditory-evoked potentials (AEPs) are commonly used to characterize these temporal properties in a non-invasive fashion. Furthermore, AEPs have long been recognized as a reliable vehicle for providing objective information about the structural and functional integrity of the central auditory system (Hall, 1992; Kraus & McGee, 1992). AEPs provide an important tool not only in auditory neuroscience laboratories but also in the audiologist's clinic (Hood, 1998), and the operating room (Martin & Mishler, 2002).

Brief and rapid acoustic events (i.e. clicks) result in a synchronized pattern of neural activity in nuclei along the auditory brainstem. When recorded from the scalp, this activity results in a series of voltage fluctuations known as the click-ABR. This response provides information about brainstem nuclei along the ascending auditory pathway (Hood, 1998; Jacobsen, 1985; Møller, 1999). Fractions of a millisecond deviations from the normal pattern are clinically important in the diagnosis of hearing loss (Hood, 1998), and pathologies such as brainstem tumors (Musiek & Gollegly, 1985) and multiple sclerosis (Keith & Jacobson, 1985).

Known temporal properties of brainstem neurons, which can phase lock up to ~1000 Hz, as well as the remarkable temporal precision of the scalp recorded response they evoke implies that the brainstem is likely to also faithfully encode many of the acoustic properties of speech and other complex auditory signals. Evidence that AEPs may be used to study various aspects of this complex speech/acoustical encoding in humans has been obtained in several laboratories (Galbraith et al, 1995; Krishnan, 2002; Russo et al, 2004). Here we review work on the normal subcortical encoding of one of the building blocks of speech—consonant vowel (CV) syllables—and the disruption of this normal process in the learning-impaired population.

The speech-evoked brainstem response

Speech is a complex signal whose acoustic properties change continuously over time and whose processing extends from the cochlea to the cortex. Work in animal models has shown that

ISSN 1499-2027 print/ISSN 1708-8186 online
DOI: 10.1080/14992020701383035

Received: March 12, 2007
Accepted: April 4, 2007

Karen Banai
Auditory Neuroscience Laboratory, Northwestern University, 2240 Campus Drive, Evanston, IL 60208, USA.
E-mail: k-banai@northwestern.edu

neurons in the auditory nerve and the cochlear nucleus are sensitive to various properties of speech-like stimuli such as formant structure (Delgutte, 1980; Delgutte & Kiang, 1984a), formant transitions (Delgutte & Kiang, 1984b), and voice onset time (Clarey et al, 2004). Relatively little is known about the encoding of speech or speech-like stimuli in higher areas of the brainstem, where the majority of animal studies focused on simpler stimuli such as amplitude-modulated noise bursts to study coding properties at both the single cell and multi-unit levels (e.g. Langner & Schreiner, 1988; Schreiner & Langner, 1988).

Nonetheless, clinical evidence indicates that higher brainstem nuclei such as the inferior colliculus (IC) play an important role in auditory processing in humans (Johkura et al, 1998; Musiek et al, 2004). For example, Johkura et al (1998) report the case of a patient with bilateral IC lesions who showed symptoms of auditory agnosia in the absence of a cortical temporal lobe lesion. Indeed, the response generators of both the late waves of the ABR (V and Vn, here called A) and the FFR (frequency following response) have been localized to the upper brainstem (lateral lemniscus, IC), (Boston & Møller, 1985; Møller, 1999). Corroborating evidence from animal models supports the idea that these regions of the brainstem are sensitive to complex spectral and temporal properties of complex stimuli (Eggermont & Ponton, 2002; Irvine, 1992; Langner & Schreiner, 1988; Schreiner & Langner, 1988; Sinex & Chen, 2000) and are therefore likely to have a role in speech processing in humans.

Encoding of speech and speech-like signals at the level of the brainstem (lateral lemniscus, IC) has been studied in humans using AEPs (Galbraith et al, 1995; Krishnan, 2002; Plyler & Ananthanarayan, 2001; Russo et al, 2004). In particular, studies focusing on the FFR demonstrated its role in encoding speech and speech-like sounds (Galbraith et al, 2004, 1995; Krishnan, 2002; Krishnan et al, 2004). Understanding how complex acoustic stimuli are encoded in the brainstem, and how this processing is related to processes taking place in lower (e.g. the auditory nerve) and higher (e.g. the auditory cortex) areas of the auditory pathway, should lead to a better understanding of processes underlying normal and abnormal human communication.

Description of the normal speech-ABR

Brainstem responses elicited by speech stimuli can provide clues about encoding of the sound structure of speech syllables by the CNS. In recent years it has been demonstrated that the neural code indeed reflects specific features of the acoustic signal (e.g. formants, VOT). Thus, the morphology of the brainstem response elicited by a speech syllable can be described in terms similar to those used to describe the physical stimulus itself. As shown in Figure 1, the brainstem response can be divided into two components: an onset response, and the frequency following response (FFR).

Together, the onset and the FFR components of the speech-ABR roughly reflect the acoustic parameters of the CV stimulus used to evoke the response. The onset component arises as a response to the onset of sound. In the case of a CV stimulus the onset represents the initiation of the consonant and contains aperiodic information. Its initial waves are similar to those observed in response to click stimuli (waves I, III and the VA complex), whereas wave C possibly reflects the onset of voicing. The FFR reflects phase locking to the fundamental frequency of the stimulus. It arises in response to the periodic information present in the vowel at the frequency of the sound source (i.e. the glottal pulse). Thus the period between peaks D, E, and F of the FFR corresponds to the fundamental frequency of the stimulus (F0), whereas the peaks between waves D, E, and F represent phase locking at the frequencies of the first formant (F1). The parallels between the morphology of the syllable /da/ and the ABR it evokes have been recently reviewed in detail by Johnson et al (2005), and by Russo et al (2004).

In the following paragraphs the characteristics of the speech-ABR evoked by the syllable /da/ will be described in some detail. The Kraus laboratory has been studying this response intensively in both typically developing children and children with learning problems 8–12 years of age. We will first describe the characteristics of the normal response and then examine the abnormal response as measured in a large group of children with language-based learning problems (LD). The stimulus and recording parameters have been described in detail in previous publications (Johnson et al, 2005; Russo et al, 2004; Song et al, 2006).

The speech-evoked brainstem response is a complex pattern of voltage fluctuations. As can be seen in Figure 1, the physiological

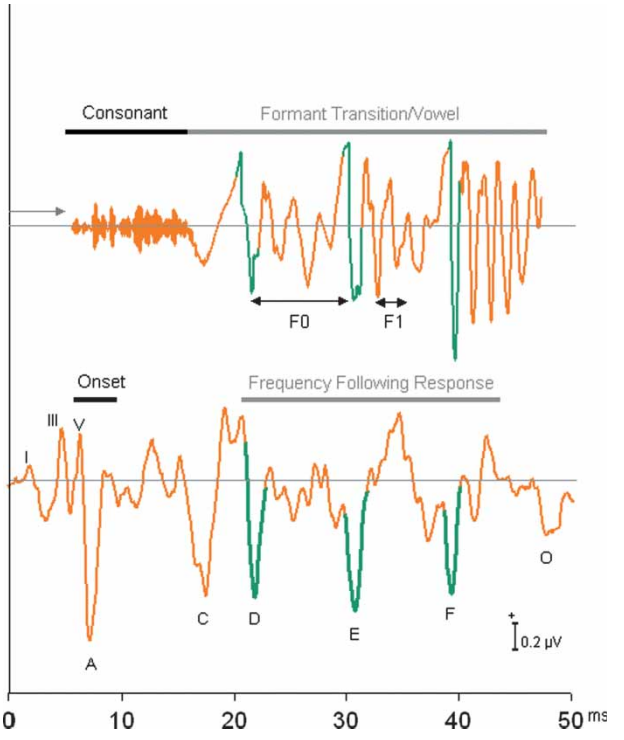

Figure 1. Top: Amplitude vs. time waveform of the syllable /da/. Bottom: Example of a typical speech-ABR waveform recorded to a 40 ms 80 dB /da/ (stimuli were presented at a rate of 11/s, response is the average of 6000 presentations) showing the onset and the FFR portion of the response. The stimulus has been shifted by ~7 ms (representing the delay in neural conduction at the brainstem) to demonstrate the similarities between the stimulus and the response over the FFR period. The thin horizontal lines intersecting the stimulus and response represent 0 μV.

response includes an orderly series of peaks and troughs. In analysing the response, both timing (peak latencies) and magnitude measures (peak amplitudes, RMS) are used. The first positive peaks (labeled I and III in Figure 1) are similar to waves I and III generated by click stimulation and likely originate at low levels of the auditory system (the 8th nerve and the low brainstem respectively) (Boston & Møller, 1985). Similarly, wave V represents the onset of the speech stimulus at the upper brainstem, followed by a large negative deflection (wave A). Characteristic latency and amplitude values are shown in Table 1 (top part). The brainstem response evoked by the /da/ syllable is reliable at the individual level. First, between different individuals the speech-evoked brainstem response is consistent, with the same morphological and spectral features identifiable for the large majority of individuals (see Table 1 for mean and standard deviation values in the normal population). Second, within an individual the evoked responses measured on different occasions are highly replicable (Russo et al, 2004).

In addition to the peak latency/amplitude analysis, yielding information about transient events within the response, sustained aspects of the response can be analysed as well. A sustained magnitude measure describing total response energy over different time windows is the RMS. Additional sustained measures can be obtained using an analysis in the frequency domain (Fast Fourier transform, FFT), providing information about the presence of specific frequencies in the response. As shown in Figure 2, an FFT over the periodic portion of the response (23–44 ms) reveals that the bulk of physiological energy is distributed in frequency ranges roughly corresponding to the F0 and F1 formants of the /da/ syllable. Characteristic magnitude values are shown in Table 1 (bottom). While the formants are prominent in the /da/ signal, by definition formant frequencies always correspond to harmonics of the fundamental. Thus while the spectral peaks observed in Figure 2 around 220 Hz and 450 Hz are larger than those roughly corresponding to the other harmonics, it could still be claimed that the response is encoding, at least in part, the harmonics and not F1. Also it should be noted that because both F0 and F1 change over time, the FFT, which is calculated over time, provides only an approximation for the spectral shape of the response in any given point in time.

Table 1. Normative speech-ABR values based on 88 typically developing 8–12 year old children. (A) Transient measures. (B) Sustained measures (12–47 ms). Mean ± s.d. values are shown.

Speech-ABR measures		
A. Transient	*Peak latencies (ms)*	*Peak amplitudes (μV)*
V	6.68 ± 0.25	0.31 ± 0.15
A	7.59 ± 0.31	−0.67 ± 0.17
C	17.86 ± 0.48	−0.32 ± 0.13
D	22.29 ± 0.43	−0.33 ± 0.17
E	30.99 ± 0.44	−0.39 ± 0.13
F	39.54 ± 0.44	−0.44 ± 0.19
O	47.95 ± 0.52	−0.19 ± 0.11
B. Sustained	Magnitude	
RMS	0.20 ± 0.03	
FFT F0 (μV)	0.081 ± 0.032	
FFT F1 (μV)	0.034 ± 0.009	

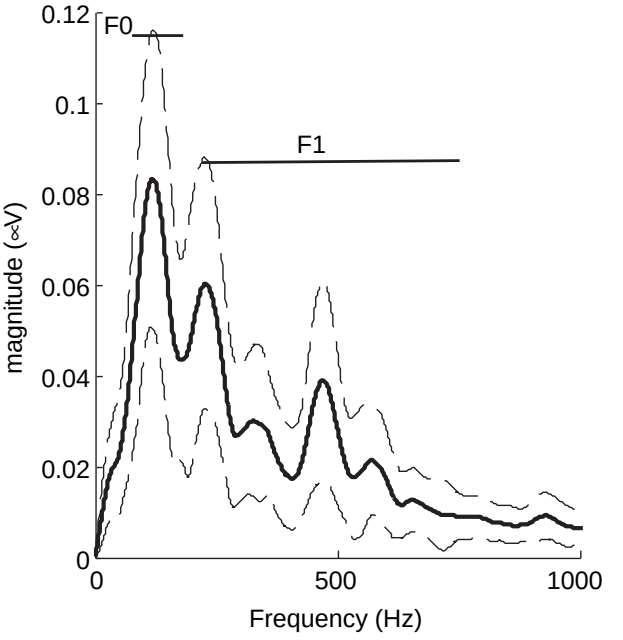

Figure 2. Mean FFT magnitude (average spectra from 23 to 44 ms) during the periodic portion of the response for 90 normal learning children. Spectral peaks are observed at regions corresponding to F0 and F1 in the /da/ stimulus (stimulus F0: 103–125 Hz; F1: 220–720 Hz), however, F0 is more strongly represented. The thick line denotes mean magnitude; thin dashed lines are ±1 s.d. of the mean.

In the normal population, significant correlations exist between the latencies of the onset measures, but not between the latencies of the onset and the FFR waves (see Russo et al, 2004 for details). Russo et al (2004) have further found that significant correlations also exist between the latencies of the onset measures and the spectral magnitude of F1, indicating a relationship between precision of temporal and spectral aspects of the response. It has been suggested that the pattern of correlation between the onset peaks, and the lack of correlation between the onset and the FFR peaks, reflects dissociation between these two classes of response—filter and source classes respectively, representing the building blocks of the message (i.e. the content) vs. talkers' identity (see Kraus & Nicol, 2005). Taken together with the pattern of brainstem abnormalities observed in children with LD (reviewed below), Kraus & Nicol (2005) proposed that the separate encoding of these response classes at the brainstem may be a precursor for the cortical 'what/where' pathways (Rauschecker & Tian, 2000; Romanski et al, 1999).

Finally, in the presence of background noise, brainstem encoding of speech is disrupted. In particular, noise interferes with the onset response. In the majority of normal subjects the onset response is severely degraded, while in 40% of subjects it is completely abolished. On the other hand, the FFR portion of the response is less susceptible to noise and the FFR peaks are identifiable in cases where the onset has disappeared (Russo et al, 2004).

Abnormal speech-ABR and learning disability

The focus here is on children with language-based learning problems. Previous work indicated that some children with LDs exhibit abnormal encoding of sound at the cortical level (see Heim & Keil, 2004; Lyytinen et al, 2005 for recent reviews), and our studies (Banai et al, 2005b; King et al, 2002; Wible et al, 2004, 2005) have also revealed abnormal encoding at the brainstem level. The first studies looking into brainstem encoding in the LD population compared learning-disabled children to typically developing ones at the group level. Thus, Cunningham et al (2001) found that wave V latency was delayed in a group of LDs in noise, but not in quiet. They further demonstrated that the magnitude of the spectral content of the response in children with LD during the FFR period was reduced in background noise, especially in the frequency range corresponding to F1. Using a slightly different version of the /da/ stimulus (described in Russo et al, 2004; Wible et al, 2004), subsequent studies found that LDs had delayed waves A, C, and F (King et al, 2002), a less synchronized onset of the speech-ABR as measured by the VA complex (Wible et al, 2004) and, consistent with the findings of Cunningham et al (2001), reduced spectral representation in the F1 range (Wible et al, 2004). Wible et al (2004) also established that the slope of the VA complex (i.e. the inter-peak amplitude divided by the inter-peak duration) provides a useful metric to describe the abnormal response by capturing both the duration of the V-to-A transition and its amplitude in a single number; and indeed this measure has been found useful in later studies with larger samples. These findings were in contrast to the normal click-evoked ABRs typically reported in earlier studies in individuals with LD (see 'The relationship between speech- and click-ABR', below).

A careful examination of the data however, reveals that, in the group with LD, responses are abnormal due to the contribution of a subgroup of the LD population, whereas many children with LD exhibit a normal response. For example, King et al (2002) have observed for wave A that 20/54 children with LD had responses deviating from the mean normal response latency by 1 standard deviation or more. Thus the question arises – how to define and characterize the abnormal response at the individual level?

Definition of the abnormal speech-ABR

Like most biological signals the speech-ABR is a continuous response. Consequently each parameter of the response may span a wide range of values, even in the normal population. Determining whether an individual response is abnormal presents a challenge. From a purely scientific standpoint it may be advantageous to look at the entire response continuum, but from a clinical perspective it is important to be able to easily distinguish a normal from an abnormal response based on some classification rule. In order for the definition of an abnormal response to be meaningful, the criteria chosen should be sensitive to the clinical population at hand, but also have a low rate of false positives. Yet, it should be noted that every criterion chosen will be arbitrary to some extent.

Indeed, King et al (2002) used a 1 SD criterion for wave A latency, whereas Banai et al (2005b) used 1.5–2 SD over a wider range of response parameters that included all onset measures. Based on these two criteria, 30–40% of LD responses were classified as abnormal, but each yielded a somewhat different grouping of LDs to those with 'normal' vs. 'abnormal' responses. In ongoing work, Abrams et al (work in progress) are looking at different classification criteria. Our goal is to optimize grouping by using a criterion that will be sensitive to the presence of LD while keeping the false positive rate (i.e. the number of typically developing children whose responses are classified as abnormal) under 10%. This effort is geared towards a sub-group within the LD population and is not necessarily related to the debate surrounding causal role of abnormal speech-ABR in LD. Indeed, several scenarios can account for the presence of abnormal speech-ABR (and other auditory functions) in some but not all persons with LD. First, abnormal brainstem function could be a cause of LD in some individuals, whereas LD is caused by other reasons in other individuals. Alternatively, abnormal brainstem function could be a risk factor that contributes to the learning problem only when present with other genetic and environmental risk factors (see Bishop, 2006). This scenario can explain both why there is a high incidence of auditory processing deficits among individuals with LD, and why some people have abnormal auditory processing but do not develop LD.

In order for the speech-ABR to be clinically useful, it is important to establish its test re-test reliability not only in the general population, but also among individuals with learning problems. Ten of the children with LD identified by Banai et al (2005b) as having abnormal speech-ABR were retested using a clinical system (BioMAP™, see below). Since the number of sampling points differs between the BioMAP™ and the original laboratory measurement, it was not possible to directly calculate a correlation score between the two measurements for each individual. However, using the norms collected for the clinical system and the same classification criteria used in the original study, all ten individuals were, again, classified as having an abnormal response, indicating that abnormal responses identified in the first measurement were not of transient nature.

The relationships between click- and speech-ABR

Numerous studies in the LD population have shown that individuals with LD have normal click-ABRs (Grontved et al, 1988a,b; Jerger et al, 1987; Lauter &Wood, 1993; Mason & Mellor, 1984; McAnally & Stein, 1997; Purdy et al, 2002). A prerequisite to participation in our speech-ABR studies is a clinically normal click-evoked wave V, to rule out peripheral hearing loss as a cause of abnormal speech-ABRs. In the general population, the early waves of the speech-ABR are similar to the waves evoked by click stimuli. Furthermore, in the normal population, significant correlations exist between the latency of wave V evoked by a click, and the latencies of waves V and A evoked by speech (Song et al, 2006), suggesting that processing of these two types of stimuli is (at least to some extent) shared. This pattern of correlation is maintained among children with LD. On the other hand, this normal pattern of correlation is disrupted when speech-ABR is delayed, such that in children with abnormal onset of speech-ABR the correlation between the latencies of the speech- and click-evoked measures is significantly reduced. These findings indicate that these two processes do not always overlap.

Song et al (2006) further noted that among children with abnormal speech-ABR, click-ABR latencies were delayed compared to children with normal speech-ABR, even if latencies were still within the normal range. This provides further support for the notion that speech and click stimuli are not independently encoded, even if deficits can not be observed using common clinical procedures.

Song et al (2006) suggested that while the encoding of speech and click stimuli shares some common characteristics, the ABRs they evoke differ, based on the acoustic characteristics of the evoking stimuli. Thus, the acoustic characteristics of the speech syllable /da/ used to measure the speech-ABR may be more challenging to the auditory system of persons with LD since the periodic portion of the vowel may mask the abrupt onset of the consonant (backward masking). This idea received support in a recent study by Marler and Champlin (2005) demonstrating, in a group of children with language disorder, a significant delay in wave V latency under backward masking conditions. Alternatively, the slower rise time of the speech-stimulus compared to the click could potentially enhance the effects of neural desynchronization in the population with LD.

The findings of slightly delayed (yet within normal) click-ABR is consistent with recent findings in an animal model. Strata et al (2005) have shown that experimentally induced perinatal anoxia in rats results in progressively delayed auditory processing from the brainstem to the auditory cortex. Taken together with our own findings regarding the relationships between click- and speech-ABR, these findings raise the possibility that abnormal speech-ABR may be a manifestation of a broader 'problem' in the central auditory system not detected by pure-tone audiometry or supra-threshold click-ABR. This hypothesis should be tested in further studies.

Early waves of the speech-ABR

Song et al (manuscript in preparation) are looking at the early waves (I, III) of the speech-ABR, aiming to characterize those waves, similarly to the work of Russo et al, (2004) for the later waves (wave V and later). Preliminary findings indicate the timing of the early waves appears normal in the majority of individuals with abnormal late waves (V and A) suggesting that, for the most part, the origins of the speech encoding deficits documented using the speech-ABR are retrocochlear.

The relationships between brainstem and cortical processing

Deficient brainstem timing has been linked to several manifestations of abnormal cortical processing.

First, in the normal population, the robustness of cortical speech-encoding in noise is correlated with brainstem timing. Wible et al (2005) showed that a strong correlation exists between brainstem timing and the effects of background noise on the cortical response, placing children with LD and delayed brainstem timing on the opposite end of this continuum with respect to those with normal timing and normal learning children.

Second, abnormal brainstem timing is associated with reduced cortical discrimination of fine acoustic differences (MMNs). Thus, as a group, individuals with delayed brainstem timing do not show a significant MMN response to an oddball stimulus, even though their basic cortical representation of the same sound (the P1/N1 complex) is normal. At the individual level, MMN was small or absent in more than 40% of individuals with LD and abnormal brainstem timing, as opposed to only 10–15% among typically developing children and children with LD and normal brainstem timing (Banai et al, 2005b).

Third, Abrams et al (2006) have shown a relationship between the degree of delay in brainstem timing and the degree of laterality in cortical auditory processing. Thus, individuals with delayed brainstem timing showed a smaller degree of left/right cortical asymmetry in response to the speech sound /da/.

Taken together, this series of studies suggests that abnormal processing at the auditory brainstem and cortex are intimately linked. While it is tempting to interpret the findings that a single deficit at the level of the brainstem is related to a wide array of abnormalities in cortical function to support a bottom-up causal relationship between the midbrain and the cortex, this is not necessarily the case. On the one hand, developmental studies indicate that the brainstem responses probably mature at an earlier age than cortical potentials (see Hood (1998), and Johnson et al (2006) for maturation of the click- and speech-ABRs respectively; and Sharma et al (1997), Cunningham et al (2000), and Ponton et al (2002) for maturation of cortical AEPs). Thus, a deficit in brainstem timing would result in degraded input to the still-developing cortex. On the other hand, similar genetic or environmental factors leading to abnormal brainstem timing could also cause abnormal cortical function. Indeed, Strata et al (2005) reported that in rats, anoxia results in deficits in both the auditory brainstem and cortex, and that the cortical abnormalities were more pronounced. A third possibility was suggested by Galaburda (1999) who claimed that cortical ectopias, emerging at a relatively early developmental stage actually affect lower brain regions (i.e. the thalamus) to which they are connected and thus are responsible for temporal processing deficits observed in ectopic mice (and humans with dyslexia). Recent studies (reviewed in Kraus & Banai, 2007) indicate that language experience affects encoding at the level of the brainstem. Krishnan et al (2005) have shown that brainstem encoding of Mandarin speech-sound differs between native speakers of Mandarin and English speakers. These findings suggest that encoding at the level of the brainstem could be malleable to top-down effects (e.g. experience and context). A potential explanation for top-down influences on sensory processing is provided by the reverse hierarchy theory (RHT), (Ahissar & Hochstein, 2004). The RHT suggests that conscious perception is typically based on the highest possible representation of the stimulus along the perceptual hierarchy. With repeated exposures, higher levels are thus likely not only to use input from lower levels, but also influence the ways the lower levels encode incoming stimuli in a context dependent manner. This is consistent with the effect of musical experience on brainstorm function (Wong et al, 2007). How top-down influences interact with developmental factors in accounting for the speech-ABR deficits in children with LD is at present unknown. Alternatively, the differences between Mandarin and English speakers could be accounted for by the former's greater exposure to the specific statistics of Mandarin pitch patterns. In support of this view Xu et al (2006) have

recently shown that the more robust pitch encoding in Mandarin speakers was specific to naturally occurring pitch contours, but not to slightly unnatural pitch contours that could still be heard as good quality Mandarin words.

The functional significance of abnormal speech-ABR

How abnormal speech encoding in the brainstem affects behavior is still poorly understood. In the two following sections we discuss speech perception, literacy-related and cognitive abilities in individuals with LD, and abnormal speech-ABR. The data were obtained by pooling together data from our previously published studies (Abrams et al, 2006; Banai et al, 2005a; King et al, 2002; Wible et al, 2004, 2005), and reclassifying participants with LD into normal and abnormal speech-ABR groups based on the norms presented in Table 1.

Speech-ABR and speech perception

We hypothesized that abnormal speech-ABR should manifest itself in difficulties in speech perception. To test this hypothesis, a speech discrimination task was administered to study participants in our laboratory. Discrimination thresholds were determined using an adaptive protocol and a four-interval two-alternative forced choice task. Stimuli were taken from the /da-ga/ continuum. On every trial, participants heard two pairs of 100 ms syllables (e.g. /da-da/ and /da-ga/) and were required to select the pair in which the two sounds differed from each other. Initially, the endpoints of the continuum were used and, following correct responses, the F3 frequency of the /ga/ token was made more similar to that of the /da/ token which served as an anchor. Just noticeable difference (JND) was determined for each subject at the 69% percent correct level. See Bradlow et al (1999) and King et al (2002) for further description, but note that the stimuli were slight modifications of the stimuli described in these two papers. JNDs were measured in quiet and in background noise.

At the group level, the two groups of children with LD (those with normal and abnormal speech-ABRs) had significantly higher JNDs compared to normal learning children, but did not differ significantly from each other in either quiet or in the presence of background noise as shown in Table 2 (means are for 43 normal learning children, 35 children with LD and normal speech-ABR, and 33 children with LD and abnormal speech-ABR). This finding is surprising, and suggests that abnormal speech-ABR is not necessary or sufficient for abnormal speech perception. However, if difficulties in phonological processing are related to abnormal phonological representations which may be the result of difficulty in the perception of fine acoustic differences, it makes sense that speech discrimination will be impaired in the majority of persons with LD, irrespective of their brainstem status.

Speech-ABR, literacy-related and other cognitive abilities

All study participants in our laboratory are routinely tested on a psychoeducational test battery that provides information on their current level of performance on literacy-related tasks, phonological awareness, and other cognitive abilities. Group means and standard deviations for 75–90 normal learning children, 34–44 children with learning disability and normal speech-ABR, and 30–49 children with learning disability and

Table 2. Speech, literacy related and cognitive abilities in normal learning (NL) and learning disabled groups (LD) with normal and abnormal speech-ABR. Mean ± s.d. values are shown. Values in bold type indicate that the highlighted group was significantly different ($p \leq 0.037$) from the other groups on a Scheffe post-hoc comparison.

	NL	*LD normal speech-ABR*	*LD abnormal speech-ABR*	*F (p)*
Speech perception (JNDs, Hz)				
Quiet	105 ± 49	149 ± 75	155 ± 69	6.99 (0.001)
Noise	232 ± 130	317 ± 110[&]	285 ± 141	4.46 (0.014)
*Phonological **a**bilities (CTOPP scores)*				
Elision	11.7 ± 2.1	7.9 ± 2.9	7.9 ± 2.8	41.02 (<0.001)
Phoneme Reversal	11.0 ± 2.5	7.7 ± 1.8	7.6 ± 1.9	39.84 (<0.001)
Segmenting **n**onwords	10.8 ± 1.9	9.4 ± 2.3	8.6 ± 2.4	13.17 (<0.001)
Literacy (standard scores)				
Reading	115 ± 11	89 ± 10	85 ± 13	140.4 (<0.001)
Spelling	115 ± 14	88 ± 8	85 ± 11	140.6 (<0.001)
Word **a**ttack	117 ± 14	90 ± 9	88 ± 11	114.0 (<0.001)
*Other **c**ognitive **a**bilities (standard scores)*				
Memory **f**or **w**ords	108 ± 16	94 ± 11	95 ± 12	21.2 (<0.001)
Listening **c**omprehension	120 ± 16	106 ± 19	105 ± 19	22.2 (<0.001)
Cross **o**ut	114 ± 13	100 ± 16	98 ± 19	15.4 (<0.001)
Brief **c**ognitive Scale	123 ± 12	100 ± 13	100 ± 15	72.8 (<0.001)
TONI-3[$]	117 ± 16	107 ± 16	101 ± 11	10.0 (<0.001)

[&]This group was significantly different from NLs, but not from the other group of LDs.
[$]This test was completed by 61 normal-learning children, 23 children with LD and normal speech-ABR, and 21 children with LD and abnormal speech-ABR.

abnormal speech-ABR are shown in Table 2. Literacy was measured using the reading and spelling subtests of the wide range achievement test (WRAT, Wilkinson, 1993), and the word attack subtest of the Woodcock Johnson revised (WJ-R, Woodcock and Johnson, 1989Woodcock and Johnson, 1990). Phonological processing was measured using three subtests taken from the comprehensive test of phonologicalp (CTOPP, Wagner et al, 1999); Elision, phoneme reversal and segmenting non-words; as well as the memory for words subtest from the WJR. Non-verbal cognitive ability was estimated using the test of non-verbal intelligence (TONI-3, Brown et al, 1997) and the brief cognitive scale (WJ). In addition, the listening comprehension and the cross out (a measure of visual speed of processing) subtests of the WJR were also administered. Children with LD scored lower than normal learning children on all of these measures, but children with LD and normal or abnormal speech-ABR did not differ from each other.

The analyses of the speech perception and psychoeducational data leads us to conclude, at-present, that on the one hand, the cognitive profiles of children with LDs with either normal or abnormal speech-ABRs are similar. On the other hand, available data suggest that more than 80% of LD individuals with abnormal brainstem timing are poor readers (Banai et al, 2005b). This figure is much higher than the proportion of poor readers in our larger sample (50–60% poor readers) of children with an LD diagnosis (not specifically selected for poor reading) and reflects the generally estimated proportion of poor readers from the total LD population in the US (Snow et al, 1998). The implication is that speech-ABRs can serve to help organize the highly heterogeneous population of LDs into more homogenous subgroups, at least with respect to the physiological correlates of their LD.

Furthermore, following auditory training programs for LDs, both auditory cortical processing and speech discrimination tend to significantly improve in LDs with abnormal brainstem processing, compared to LDs whose brainstem processing is normal, even though the degree of speech perception deficits is similar in these two groups before training (Hayes et al, 2003; King et al, 2002). These outcomes suggest that, at least for speech discrimination, the etiology of the deficit may differ between children with LD with normal and abnormal speech-ABR, hence the different effects of training. Enrolling in a demanding training program is resource intensive. If further studies support these findings, and perhaps extend them to other training programs and outcome measures, the speech-ABR may help to determine when to refer a child to training, and reduce the frustration of parents and educators from the uncertainty of outcomes.

Summary

Evidence accumulating during nearly a decade of research suggests that a substantial sub-population of LDs exhibit abnormal encoding of speech at the level of the brainstem. In particular, abnormal onset of the response and reduction of its magnitude over the FFR period distinguish normal from abnormal responses, suggesting less precisely timed neural response to complex sounds in a subgroup of children with LD. The abnormal speech-ABR, in turn, shows a relationship to cortical processing and literacy deficits. The importance of these relationships and the relative ease with which speech-ABR may be measured has recently led to its translation as a clinical tool: the BioMAP™ (Biological marker of auditory processing, Bio-Logic, Mundelein, IL), designed to provide knowledge about physiological encoding of sound during the course of LD diagnosis. Further research and clinical use of the speech-ABR should lead to a refinement of our understanding of the neural bases of auditory processing and improve clinical diagnosis and treatment. Further research comparing children with LD with normal versus abnormal speech-ABR on other perceptual, language, and cognitive measures, familiality of LD, and medical history is required to establish whether abnormal speech-ABR is associated with any specific phenotype among individuals with learning problems. Developmental cross-sectional or longitudinal studies are required to determine the relationships between abnormal brainstem function and the emergence of learning problems.

Acknowledgements

Supported by NIH/NIDCD RO1-01510, F32DC008052 and the Hugh Knowles Center for Clinical and Basic Science in Hearing and its Disorders. We would like to thank Nicole Russo, Judy Song, Trent Nicol, Gabriella Musacchia, Krista Johnson, and Erika Skoe for their help at various stages of this project.

Statement regarding conflict of interest: Nina Kraus is a co-inventor of the BioMAP™, but has no financial stake in the commercialization process. Northwestern University holds the patent and licensed it to Biologic for commercialization. Karen Banai and Daniel Abrams are not involved with BioMAP™, and declare no conflict of interest.

References

Abrams, D.A., Nicol, T., Zecker, S. & Kraus, N. 2006. Auditory brainstem timing predicts cerebral asymmetry for speech. *J Neurosci*, 26, 11131–11137.

Ahissar, M. & Hochstein, S. 2004. The reverse hierarchy theory of visual perceptual learning. *Trends Cogn Sci*, 8, 457–464.

Banai K., Nicol T., Zecker S. & Kraus N. 2005a. Cortical and cognitive consequences of brainstem timing deficits (abstract). *Association for Research in Otolaryngology Midwinter Meeting*. New Orleans: ARO.

Banai, K., Nicol, T., Zecker, S.G. & Kraus, N. 2005b. Brainstem timing: Implications for cortical processing and literacy. *J Neurosci*, 25, 9850–9857.

Bishop, D.V. 2006. Developmental cognitive genetics: How psychology can inform genetics and vice versa. *Q J Exp Psychol*, (Colchester) 59, 1153–1168.

Boston, J.R. & Møller, A.R. 1985. Brainstem auditory-evoked potentials. *Crit Rev Biomed Eng*, 13, 97–123.

Bradlow, A.R., Kraus, N., Nicol, T.G., McGee, T.J. & Cunningham, J., et al. 1999. Effects of lengthened formant transition duration on discrimination and neural representation of synthetic CV syllables by normal and learning-disabled children. *J Acoust Soc Am*, 106, 2086–2096.

Brown, L., Sherbenou, R.J. & Johnsen, S.K. 1997. *Test of nonverbal intelligence* (3rd edition). Austin, Tx: Pro-ed.

Clarey, J.C., Paolini, A.G., Grayden, D.B., Burkitt, A.N. & Clark, G.M. 2004. Ventral cochlear nucleus coding of voice onset time in naturally spoken syllables. *Hear Res*, 190, 37–59.

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 Hear*, 21, 554–568.

Cunningham, J., Nicol, T., Zecker, S.G., Bradlow, A. & Kraus, N. 2001. Neurobiologic responses to speech in noise in children with learning problems: Deficits and strategies for improvement. *Clin Neurophysiol*, 112, 758–767.

Delgutte, B. 1980. Representation of speech-like sounds in the discharge patterns of auditory-nerve fibers. *J Acoust Soc Am*, 68, 843–857.

Delgutte, B. & Kiang, N.Y. 1984a. Speech coding in the auditory nerve: I. Vowel-like sounds. *J Acoust Soc Am*, 75, 866–878.

Delgutte, B. & Kiang, N.Y. 1984b. Speech coding in the auditory nerve: IV. Sounds with consonant-like dynamic characteristics. *J Acoust Soc Am*, 75, 897–907.

Eggermont, J.J. & Ponton, C.W. 2002. The neurophysiology of auditory perception: From single units to evoked potentials. *Audiol Neurootol*, 7, 71–99.

Frisina, R.D. 2001. Subcortical neural coding mechanisms for auditory temporal processing. *Hear Res*, 158, 1–27.

Galaburda, A.M. 1999. Developmental dyslexia: A multilevel syndrome. *Dyslexia*, 5, 183–191.

Galbraith, G.C., Amaya, E.M., de Rivera, J.M., Donan, N.M., Duong, M.T., et al. 2004. Brainstem evoked response to forward and reversed speech in humans. *Neuroreport*, 15, 2057–2060.

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.

Grontved, A., Walter, B. & Gronborg, A. 1988a. Auditory brainstem responses in dyslexic and normal children. A prospective clinical investigation. *Scand Audiol*, 17, 53–54.

Grontved, A., Walter, B. & Gronborg, A. 1988b. Normal ABRs in dyslexic children. *Acta Otolaryngol Suppl*, 449, 171–173.

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

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. *Clin Neurophysiol*, 114, 673–684.

Heim, S. & Keil, A. 2004. Large-scale neural correlates of developmental dyslexia. *Eur Child Adolesc Psychiatry*, 13, 125–140.

Hood, L.J. 1998. *Clinical applications of the auditory brainstem response*. San Diego, CA: Singular Publishing Group, Inc.

Irvine, D.R. 1992. Physiology of the auditory brainstem. In A.N. Popper & R.R. Fay (eds.) *The mammalian auditory pathway: Neurophysiology*. New York: Springer-Verlag, pp. 153–231.

Jacobsen, J. 1985. *The auditory brainstem response*. San Diego: College-Hill Press.

Jerger, S., Martin, R.C. & Jerger, J. 1987. Specific auditory perceptual dysfunction in a learning disabled child. *Ear Hear*, 8, 78–86.

Johkura, K., Matsumoto, S., Hasegawa, O. & Kuroiwa, Y. 1998. Defective auditory recognition after small hemorrhage in the inferior colliculi. *J Neurol Sci*, 161, 91–96.

Johnson, K.L., Nicol, T.G. & Kraus, N. 2005. Brainstem response to speech: A biological marker of auditory processing. *Ear Hear*, 26, 424–434.

Johnson K.L., Nicol T.G. & Kraus N. 2006. Maturation of the Speech-Evoked Auditory Brainstem Response (abstract). American Auditory Society Meeting, March 5–7, Scottsdale, AZ.

Keith, R.W. & Jacobson, J.T. 1985. Physiological responses in multiple sclerosis and other demyelinating diseases. In J.T. Jacobson (ed.), *The auditory brainstem response*. San Diego: College-Hill 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. *Neurosci Lett*, 319, 111–115.

Kraus, N. & Banai, K. 2007. Auditory-processing malleability: Focus on language and music. *Corr Directions Psychol Sci*, 16, 105–110.

Kraus, N. & McGee, T. 1992. Electrophysiology of the human auditory system. In A. Popper & R. Fay (eds.) *The mammalian auditory system*. New-York: Springer Verlag, pp. 335–404.

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

Krishnan, A. 2002. Human frequency-following responses: Representation of steady-state synthetic vowels. *Hear Res*, 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 Res Cogn Brain Res*, 25, 161–168.

Krishnan, A., Xu, Y., Gandour, J.T. & Cariani, P.A. 2004. Human frequency-following response: Representation of pitch contours in Chinese tones. *Hear Res*, 189, 1–12.

Langner, G. & Schreiner, C.E. 1988. Periodicity coding in the inferior colliculus of the cat. I. Neuronal mechanisms. *J Neurophysiol*, 60, 1799–1822.

Lauter, J.L. & Wood, S.B. 1993. Auditory-brainstem synchronicity in dyslexia measured using the REPs/ABR protocol. *Ann N Y Acad Sci*, 682, 377–379.

Lyytinen, H., Guttorm, T.K., Huttunen, T., Hamalainen, J., Leppanen, P.H.T., et al. 2005. Psychophysiology of developmental dyslexia: A review of findings including studies of children at risk for dyslexia. *Journal of Neurolinguistics*, 18, 167–195.

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. *J Speech Lang Hear Res*, 48, 189–203.

Martin, W.H. & Mishler, E.T. 2002. Intraoperative monitoring of auditory evoked potentials and facial nerve electromyography. In J. Katz (ed.), *Handbook of clinical audiology*. Baltimore, MD: Williams & Wilkins Company, pp. 323–348.

Mason, S.M. & Mellor, D.H. 1984. Brainstem, middle latency, and late cortical evoked potentials in children with speech and language disorders. *Electroencephalogr Clin Neurophysiol*, 59, 297–309.

McAnally, K.I. & Stein, J.F. 1997. Scalp potentials evoked by amplitude-modulated tones in dyslexia. *J Speech Lang Hear Res*, 40, 939–945.

Møller, A.R. 1999. Neural mechanisms of BAEP. *Electroencephalogr Clin Neurophysiol,* Suppl, 49, 27–35.

Musiek F.E., Charette L., Morse D. & Baran J.A. (2004) Central deafness associated with a midbrain lesion. *J Am Acad Audiol*, 15, 133–151; quiz 172–133.

Musiek, F.E. & Gollegly, K.M 1985. ABR in eight nerve and low brainstem lesions. In J. T. Jacobson (ed.), *The auditory brainstem response*. San Diego: College-Hill Press.

Oertel, D. 1997. Encoding of timing in the brainstem auditory nuclei of vertebrates. *Neuron*, 19, 959–962.

Plyler, P.N. & Ananthanarayan, A.K. 2001. Human frequency-following responses: Representation of second formant transitions in normal-hearing and hearing-impaired listeners. *J Am Acad Audiol*, 12, 523–533.

Ponton, C., Eggermont, J.J., Khosla, D., Kwong, B. & Don, M. 2002. Maturation of human central auditory system activity: Separating auditory evoked potentials by dipole source modeling. *Clin Neurophysiol*, 113, 420.

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. *J Am Acad Audiol*, 13, 367–382.

Rauschecker JlPl & Tian B. 2000. Mechanisms and streams for processing of'what' and'where' in auditory cortex. *Proc Natl Acad Sci USA 97*, 11800–11806.

Romanski, L.M., Tian, B., Fritz, J., Mishkin, M., Goldman-Rakic, P.S., et al. 1999. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nat Neurosci*, 2, 1131–1136.

Russo, N., Nicol, T., Musacchia, G. & Kraus, N. 2004. Brainstem responses to speech syllables. *Clin Neurophysiol*, 115, 2021–2030.

Schreiner, C.E. & Langner, G. 1988. Periodicity coding in the inferior colliculus of the cat. II. Topographical organization. *J Neurophysiol*, 60, 1823–1840.

Sharma, A., Kraus, N., McGee, T.J. & Nicol, T.G. 1997. Developmental changes in P1 and N1 central auditory responses elicited by consonant-vowel syllables. *Electroencephalogr Clin Neurophysiol*, 104, 540–545.

Sinex, D.G. & Chen, G.D. 2000. Neural responses to the onset of voicing are unrelated to other measures of temporal resolution. *J Acoust Soc Am*, 107, 486–495.

Snow C.E., Burns M.S. & Griffin P. (eds.) 1998. *Preventing reading difficulties in young children*. Washington DC: National Academic Press.

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

Strata, F., Deipolyi, A.R., Bonham, B.H., Chang, E.F., Liu, R.C., et al. 2005. Perinatal anoxia degrades auditory system function in rats. *Proc Natl Acad Sci USA*, 102, 19156–19161.

Wagner R.K., Torgesen J.K. & Rachotte C.A. 1999. *Comprehensive test of phonological processing (CTOPP)*. Austin: Pro-Ed, Inc.

Wible, B., Nicol, T. & Kraus, N. 2004. A typical brainstem representation of onset and formant structure of speech sounds in children with language-based learning problems. *Biol Psychol*, 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, 417–423.

Wilkinson, G.S. 1993. *Wide range achievement test (WRAT3)*. Wilmington, DE: Wide Range, Inc.

Wong, P., Skoe, E., Russon, N., Dees, T. & Kraus, N. 2007. Musical experience shapes human brain stem encoding of linguistic pitch patterns. *Nat Neuro Sci*, 10, 420–422.

Woodcock R.W. & Johnson M.B. 1989, 1990. *Woodcock Johnson psychoeducational battery: Tests of cognitive ability (WJ-R)*. Allen, TX: DLM Teaching Resources.

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