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Brainstem Timing Deficits in Children with Learning Impairment May Result from Corticofugal Origins

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Key Words
Auditory processing · Auditory brainstem response · Speech encoding · Learning disability · Brainstem timing deficits · Corticofugal modulation

Abstract
A substantial proportion of children with language-based learning problems [learning disabilities (LD)] display abnormal encoding of speech at rostral levels of the auditory brainstem (i.e. midbrain) as measured by the auditory brainstem response (ABR). Of interest here is whether these timing deficits originate at the rostral brainstem or whether they reflect deficient sensory encoding at lower levels of the auditory pathway. We describe the early brainstem response to speech (waves I and III) in typically developing 8- to 12-year-old children and children with LD. We then focus on the early brainstem responses in children with LD found to show abnormal components of the rostral speech-evoked ABR (waves V and A). We found that wave I was not reliably evoked using our speech stimulus and recording parameters in either typically developing children or those with LD. Wave III was reliably evoked in the large majority of subjects in both groups and its timing did not differ between them. These data are consistent with the view that the auditory deficits in the majority of LD children with abnormal speech-evoked ABR originate from corticofugal modulation of subcortical activity.

Introduction

It has long been recognized that language-based learning problems [learning disabilities (LD)], typically manifested in poor reading and phonological processing [Snow et al., 1998], are associated with abnormal cortical processing of sound. Cortical evoked responses to both speech [e.g., Kraus et al., 1996; Lachmann et al., 2005; Paul et al., 2006] and nonspeech [e.g., Baldeweg et al., 1999; Kujala et al., 2006; Nagarajan et al., 1999] sounds differ between typically developing normal-learning (NL) individuals and those diagnosed with LD. Generalizing across studies is complicated by the heterogeneity of the LD population and the many methods used to evoke and collect the physiological responses [Bishop, 2007], but taken together the evidence suggests that cortical processing of sound differs between NL and some LD children.

Much less is known about the involvement of subcortical structures in developmental learning and language disorders, but recent studies suggest that subcortical structures are much more affected by high-level factors such as language and musical experience and context than traditionally assumed [Krishnan et al., 2005; Musacchia et al., 2007; Palmer et al., 2007; Russo et al., 2005; Song et al., 2008; Wong et al., 2007] making it likely that

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they could also be affected by LD. These studies indicate that brainstem function is modulated by lifelong language and music experience as well as short-term training. As to whether these effects are modulated through the corticofugal system or through local mechanisms is at present unknown, and recent data suggest that both are at play [Chandrasekaran et al., 2007; Dean et al., 2005; Perez-Gonzalez et al., 2005; Perrot et al., 2006].

The auditory brainstem response (ABR) is commonly used to study the encoding of sound in normal and clinical populations and is a convenient and reliable measure of subcortical auditory function. The ABR, as far-field recording with electrodes placed on the head, represents the summation of neuronal discharge synchronized to the rate of presentation of an acoustic stimulus. A click-evoked ABR typically consists of 7 waves which occur within 10 ms after the onset of the acoustic stimulus. Of these, waves I, III, and V are most clinically useful as they are the most robust and appear within expected latency ranges [Hood, 1998]. Individuals with LD are typically found to exhibit normal wave I, III, and V latencies in response to clicks [Grøntved et al., 1988; Jerger et al., 1987; Mason and Mellor, 1984; Song et al., 2006; Tait et al., 1983], leading to the view that subcortical structures in the ascending auditory pathway are not involved in LD.

ABRs can also be evoked using other acoustic signals that are relatively brief in duration and presented repetitively. A growing number of studies have used speech sounds (syllables) to assess auditory processing to linguistic elements [Akhoun et al., 2008; Galbraith et al., 2004; Krishnan, 2002; Russo et al., 2004]. Similar to the click-evoked ABR, the onset response of the speech-evoked ABR is transient with wave durations lasting tenths of milliseconds and can be analyzed conventionally in terms of the latency of its major components [Johnson et al., 2005; Russo et al., 2004]. Unlike the click-evoked ABRs, ABRs evoked by speech stimuli can differ between NL subjects and a subset of LD patients [Banai et al., 2005; Cunningham et al., 2001; Johnson et al., 2007; King et al., 2002; Wible et al., 2004, 2005].

Following the first characterization of the speech-evoked ABR in typically developing children [Russo et al., 2004], these studies focused on the onset portion of the speech-evoked ABR, starting at wave V. A subgroup of LD children demonstrated abnormal transcription of both temporal and spectral dimensions of speech sounds. Relevant to the present investigation, reading-impaired children demonstrate delays in the latencies of waves V and A and/or prolonged and desynchronized transition between the two peaks (determined by VA duration and slope) [Banai et al., 2005]. Abnormal wave V and A latencies have been found to reflect neural timing deficits in structures that are rostrally situated in the brainstem [Lynn and Verma, 1985].

Interestingly, the group of children with abnormal speech ABRs manifests a dissociation between the processing of speech- and click-evoked stimuli [Song et al., 2006]. A further dissociation is seen in the development of click- and speech-evoked responses [Johnson et al., 2008]. Possible reasons for this dissociation may be related to the stimulus differences between the two conditions. For example, the vowel portion of the speech syllable may backward mask the brief consonant, hence inducing a delay on the onset of the speech-evoked ABR, consistent with the presence of elevated backward-masking thresholds [Wright et al., 1997] and prolonged wave V latencies in response to backward-masked, but not unmasked sounds [Marler and Champlin, 2005] in children with LD. Moreover, speech stimuli have a more gradual onset compared to clicks. Thus, if a neural system is more sensitive to the effects of desynchronization, this susceptibility will become more apparent in response to the speech stimulus. Finally, the differences may relate to the greater familiarity of humans with speech sounds compared to clicks. By this account, context-related enhancement of brainstem encoding, reported recently in animal models [Dean et al., 2005; Escabi et al., 2003] and in humans [Krishnan et al., 2005; Musacchia et al., 2007; Russo et al., 2005; Song et al., 2008; Wong et al., 2007], is disrupted in individuals whose brainstem encoding of speech sounds is abnormal perhaps due to the abnormal operation of statistical language learning mechanisms [Maye et al., 2002; Saffran, 2001]. Taken together, the dissociation between processing of different types of stimuli among individuals with LD at the level of wave V leaves open the possibility that more peripheral deficits will be observed if ABRs are elicited by speech sounds.

This question is of interest because it appears that when speech-evoked ABR is abnormal at the midbrain level, auditory cortical deficits often ensue [Abrams et al., 2006; Banai et al., 2005; Wible et al., 2004]. Yet, it is not known whether they can be associated with a more peripheral source of deficit because earlier waves of the speech-evoked ABR have not been systematically studied in either the normal or the LD population. Thus, it is not known if neural timing deficits reflected in later portions of the ABR onset response to speech may be occurring even earlier in the auditory pathway. While a one-to-one correlation between the neuroanatomical structures of the brainstem and ABR waves cannot be made, animal

studies have revealed that waves I and II are generated by the auditory nerve and waves III, IV, and V are generated by more centrally positioned brainstem structures, i.e. cochlear nucleus, superior olivary complex, lateral lemniscus, and inferior colliculus. Specifically, wave III is thought to be largely generated by axons emerging from the cochlear nuclei in the ventral acoustic stria and waves IV, V and Vn (referred to as wave A here) are generated higher in the brainstem [Møller and Jannetta, 1985].

The first goal of the current study was to characterize the early waves of the speech-evoked ABR in the typically developing NL population. A second goal was to investigate the possible existence of differences in earlier components (waves I and III) of the speech-evoked onset ABR recorded between typically developing children and those clinically diagnosed with language-based LD. In particular, we were interested in determining whether disruption of later waves was systematically related to that of earlier waves. Differences in wave I and/or III latencies between these groups to a speech stimulus would signal disruption in the encoding of sound more peripherally in the auditory pathway. We reasoned that comparable waves I and III between groups would indicate intact processing of speech signals at the eighth nerve and caudal brainstem in LD children, whereas delayed or missing waves I or III would indicate abnormal processing at these levels of the auditory pathway.

Methods

Participants

One hundred and eighty-three native English-speaking children (8–12 years old) participated in the study. All participants had normal hearing (<20 dB hearing level for octaves from 500 to 4000 Hz), click-evoked ABRs within clinical norms, and normal intelligence (standard score >85) as measured by the Brief Cognitive Scale [Woodcock and Johnson, 1989] or the Test of Nonverbal Intelligence [Brown et al., 1997]. Ninety participants were NL children with no prior history of learning problems at school. Ninety-three participants had been diagnosed with an LD by independent clinicians before acceptance into the study. The LD children were divided into two groups based on their brainstem responses, as described below.

Supplementing the independent diagnosis, study-internal psychoeducational tests were performed to measure reading and reading-related abilities. The tests consisted of the word attack from the Woodcock-Johnson Psychoeducational Battery – Revised [Woodcock and Johnson, 1989], subtests from the Wide Range Achievement Test 3 [Wilkinson, 1993] to assess reading and spelling skills and subtests taken from the Comprehensive Test of Phonological Processing to assess phonological skills [Wagner et al., 1999]. These subtests were elision, phoneme reversal, and segmenting nonwords. These measures were used to verify the presence of reading-related deficits in the LD group and confirm the absence of any deficits among the children in the NL group. Verification was necessary to ascertain that all LD children in the current study were below average readers and that NL participants read within normal levels. To be included in the LD group, the participants had to have ≤100 on a combined literacy score (the average of scores in reading, spelling and word attack). NL subjects had to show ≥90 on the combined literacy score and ≥25th percentile of the published norms on the rest of the study-internal measures. The overlap of reading scores between NL subjects and LD children was allowed to reflect the clinical and educational reality in the school districts attended by study participants.

Table 1. Average scores (±1 SD) on literacy-related and cognitive tests

	NL	LD
Reading and spelling		
Word attack[1]	118 (14)	89 (10)
Reading[2]	115 (11)	88 (12)
Spelling[2]	115 (14)	86 (10)
Literacy score[4]	116 (13)	87 (11)
Phonological processing		
Elision[3]	12 (2)	8 (3)
Phoneme reversal[3]	11 (3)	8 (2)
Segmenting nonwords[3]	11 (2)	9 (2)
Cognitive test		
Brief Cognitive Scale[1]	123 (12)	100 (14)

[1] Woodcock-Johnson Psychoeducational Battery Test of cognitive abilities [Woodcock and Johnson, 1989].
[2] Wide Range Achievement Test 3 [Wilkinson, 1993].
[3] Comprehensive Test of Phonological Processing.
[4] Average of word attack, reading and spelling.

Participants in the current study were a subgroup of participants (n = 165) from a previous study [Song et al., 2006] and an additional 18 participants whose data had not previously been reported. Of the 234 participants in the study by Song et al. [2006], 39 NL and 30 LD participants were removed from the data to meet the more stringent inclusion criteria of the current study with respect to literacy scores. Average scores of NL and LD subjects on the literacy-related and cognitive tests are shown in table 1. As can be seen, children with LD scored significantly below NL participants on all literacy-related measures.

Among the LD group, 22 had a concomitant diagnosis of LD and attention deficit disorder. As these children did not differ from the rest of the LD group on any study-internal measures, and because we were interested in the relationship between auditory processing and literacy-related skills rather than attention, they were categorized as LD.

Participants were recruited through advertisements in newspapers and flyers posted on the Northwestern University campus. All participants and their guardians provided their informed consent before taking part in this study in accordance with the Northwestern Institutional Review Board guidelines.

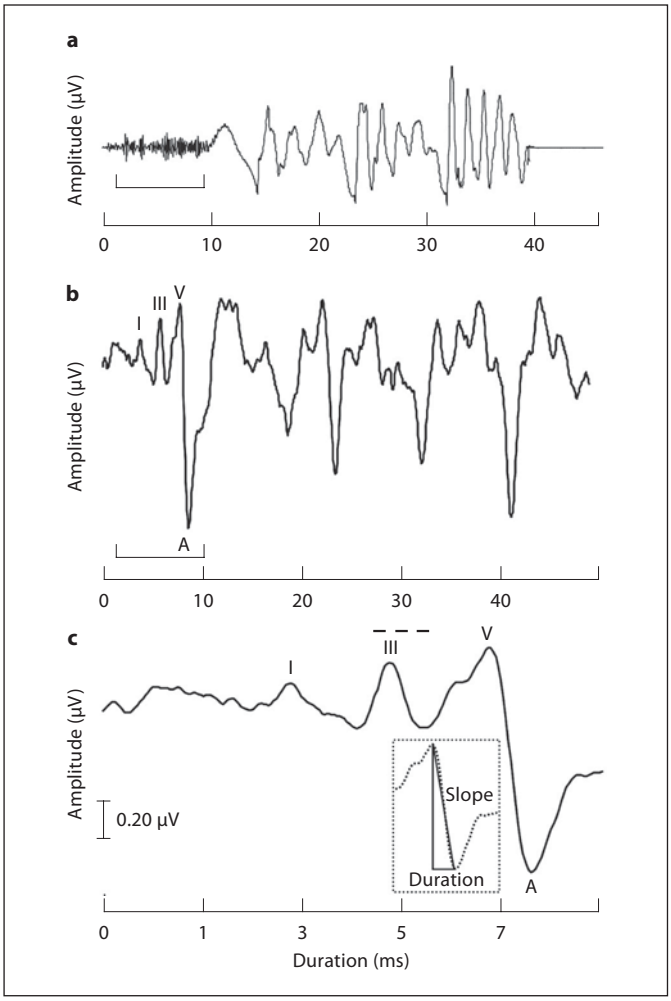

Fig. 1. a Stimulus waveform for the /da/ stimuli. The /da/ stimulus is a synthesized speech-like sound that contains the onset burst frication of the third to fifth formant frequencies during the initial 10 ms, followed by 30 ms of the first and second formant transitions which stop promptly before the sustained vowel portion (see Johnson et al. [2005] for further stimulus details). **b** The onset of the speech-evoked ABR includes three prominent positive peaks (i.e., waves I, III and V) followed immediately by its negative trough (wave A). The onset portion of the /da/ stimulus and response is bracketed from the entire waveform and reflects its transient quality. The sustained activity beginning at approximately 18 ms is the frequency following response to the periodic formant transition into the vowel. **c** The onset portion of the speech-evoked ABR of a typical NL subject. The dashed line above wave III represents the ±2 SD range in the NL group. The inset shows where VA slope and VA duration were measured.

Physiological Recording and Stimuli

A detailed description of the stimuli and recording procedures can be found in previous publications [Banai et al., 2005; Russo et al., 2004]. Stimuli were presented monaurally to the right ear via insert earphones (ER-3; Etymotic Research, Elk Grove Village, Ill., USA). During physiological recording, participants watched a videotape with the sound level at <40 dB SPL to their left ear to facilitate cooperation. Responses were recorded using Ag-AgCl scalp electrodes.

Speech-evoked ABRs were elicited using a five-formant speech syllable /da/ (fig. 1a), generated with a digital speech synthesizer (SenSyn, Somerville, Mass., USA). For more details regarding speech synthesis parameters, refer to King et al. [2002]. The syllable /da/ was 40 ms in duration and contained an initial 10-ms burst with frequencies centered around the beginning frequencies of formants 3–5 in the range of 2580 to 4500 Hz. It was presented at 80 dB SPL in alternating polarities with an interstimulus interval of 51 ms and interonset interval of 91 ms. Responses were differentially recorded at a sampling rate of 20000 Hz from Cz (active) to the right earlobe (reference), with the forehead as ground. Responses were bandpass filtered online from 100 to 2000 Hz, 6 dB per octave. Three blocks of 2000 repetitions were recorded. Responses were averaged online (Neuroscan; Compumedics, El Paso, Tex., USA) with a 70-ms recording window starting 10 ms before stimulus onset. Trials with eyeblinks >35 μV were artifact rejected online. Responses of alternating polarities were summed to minimize contributions from the cochlear microphonic response, a receptor potential produced by the cochlear hair cells [Gorga et al., 1985] (see fig. 1b for the typical response obtained through this procedure).

Brainstem Response Data Analysis

The focus of this study was the early portion of the onset timing of the brainstem response to the syllable /da/, specifically the positive waves I and III (fig. 1c). Using Neuroscan software, two experienced peak pickers manually marked the peaks of waves I and III, as well as waves V and A, in the averaged response blinded to the subjects' identities and group membership. In cases where the two peak pickers were not in agreement regarding the latency of a particular peak, a third experienced peak picker was consulted. This task was accomplished by selecting the peak with the largest positive amplitude for waves I, III and V and with the largest negative amplitude for wave A within an estimated time range they were predicted to occur (i.e., 1.50–3.50 ms, 4.00–6.00 ms, 6.00–8.00 ms, and 7.00–9.00 ms, respectively) for each subject if it was visibly above the noise floor provided by the prestimulus period. The latencies of these peaks were measured for each subject. Waves I and III were marked absent when peaks in the averaged response were undetectable within their predicted time ranges, however waves V and A were present for all subjects in the current study.

Subgrouping LD Participants Based on Rostral Brainstem Function

Our goal here was to determine if abnormal properties of the rostral portion of the speech-evoked ABR, found in approximately 30% of LD individuals, reflect a more peripheral source of deficit. To that end, the LD group was divided into two subgroups based on the rostral portion of the response. Four parameters of the rostral brainstem response, all characterizing the VA complex, proved useful in our previous studies [Banai et al., 2005; King et al., 2002; Wible et al., 2004, 2005]. These were the latencies of waves V and A, as well as the duration and the slope of the transition between these two peaks which index the degree of neural synchrony during this time period (fig. 1c). To account for

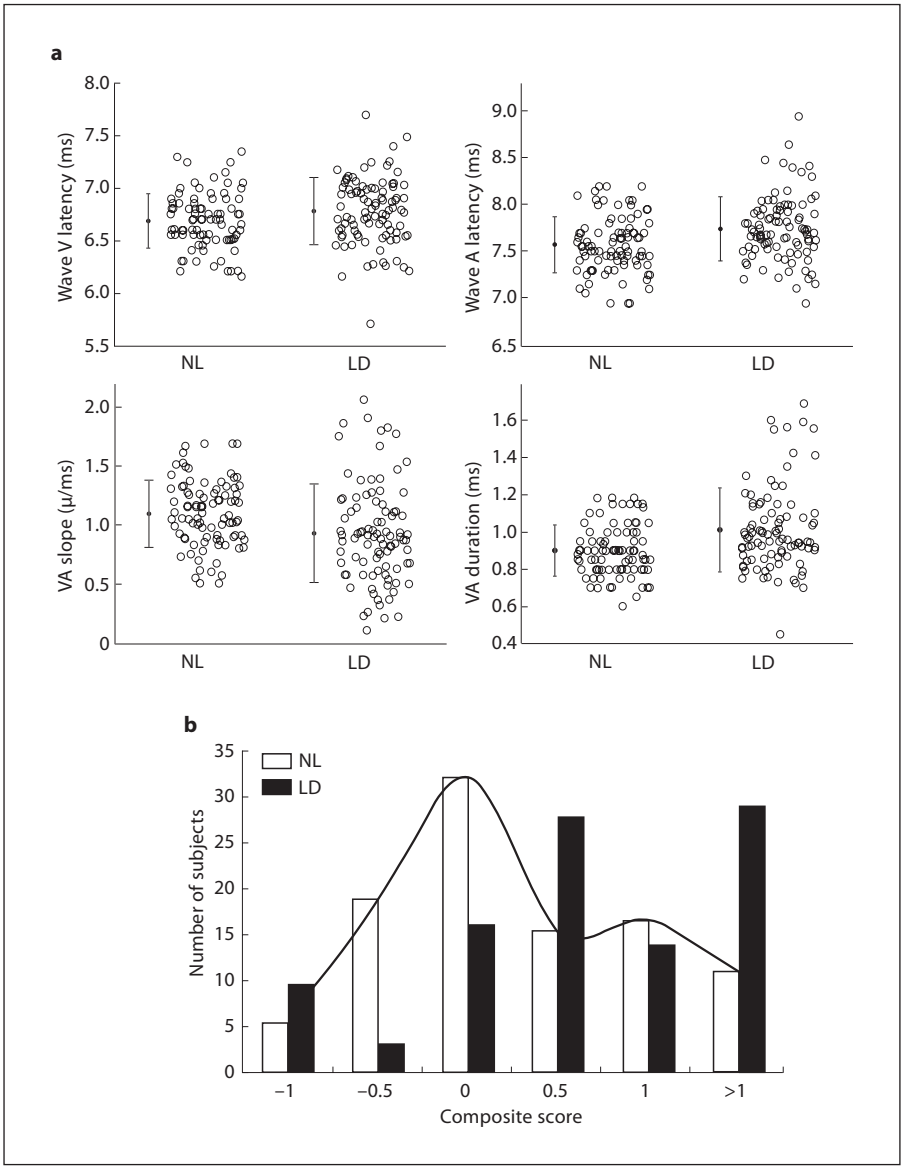

Fig. 2. a Distribution of individual subject data of speech-evoked brainstem timing parameters (i.e., wave V and A latencies, VA complex slope and duration). **b** The distribution of the composite scores among NL and LD participants.

the significant correlations between these two measures, a composite rostral brainstem score was calculated for each participant (see the Results section below). If the combined score exceeded 1, the rostral response was deemed abnormal.

Results

Rostral Brainstem Timing Measures

Individual subject scores on brainstem timing measures are shown in figure 2a. Many of the LD children's scores overlapped with those of NL subjects. However, a large subgroup had abnormally delayed latencies of waves V and A, or extremely imprecise responses as reflected by reduced VA slopes and prolonged duration of the VA transition. To further characterize the extent of this abnormality, we first examined the characteristics of these four measures in the NL group. Because the latencies of waves V and A were highly correlated, whereas the correlations among the latencies of these waves, VA duration and VA slope were lower (see table 2 for correlation values), we based further analyses on these three measures only: wave A latency, VA duration and VA slope.

For each participant, a rostral brainstem composite score was calculated in the following way. An individual Z score was calculated for each subject and each measure, relative to the means and standard deviations of the

Table 2. Correlation values of the speech-evoked brainstem timing measures (i.e., wave V and A latencies, VA duration and VA slope) among NL participants

	A latency	VA duration	VA slope
V latency	0.820**	–0.088	–0.199*
A latency		0.498**	–0.418**
VA duration			–0.427**

* p = 0.007; ** p < 0.0001.

Table 3. Incidence of NL, LD+ and LD– children with normal, abnormal or absent (NR) wave III responses

	Wave III		
	normal	abnormal	NR
NL (normal VA measures)	73	2	5
NL (abnormal VA measures)	9	1	0
LD+	58	3	5
LD–	21	2	4

Table 4. Average wave III latencies (±1 SD) for NL, LD+ and LD– groups

	NL	LD+	LD–
Wave III latencies, ms	4.83 (0.27)	4.85 (0.30)	4.89 (0.42)
Number of subjects	85	61	23

NL group. These three scores were then averaged to achieve the combined score. The distribution of the composite scores among NL and LD participants is shown in figure 2b. It can be seen that a high proportion of LD children (29%) had abnormally high scores (>1; corresponding to the 89th percentile in the NL group). This criterion was chosen as the cutoff point, beyond which scores were defined as abnormal (LD–, n = 27). Twenty-one of the LD– individuals had abnormal scores on at least two of the measures comprising the rostral brainstem composite score. The other 6 were abnormal on only one measure. From the 10 NL subjects whose composite scores fell outside the normal limit, 6 were abnormal on only one measure, while the other 4 were abnormal on at least two measures typically falling in the borderline-normal range. Neither the data nor the subject histories of these participants could account for this finding which underscores the need to develop classification procedures that will minimize the amount of overlap between normal and clinical populations. Waves I and III are compared among the two LD groups and NL participants below.

Wave I

Wave I was detected in 62.2% (56 out of 90) NL participants and in 47.3% (44 out of 93) LD participants. It should be noted that even when wave I appeared present, the agreement between the two original peak pickers regarding its latency was low in both subject groups (only in about half the cases) and the third picker had to be consulted. The low rate of detectability and interrater agreement of wave I even among NL participants indicates that the stimulus or the recording parameters (e.g. the electrode montage) were not efficient in eliciting wave I in many individuals whose later waves were clearly present. Therefore, the meaning of an absent response in the LD group could not be interpreted and wave I latencies were not further analyzed or compared between the groups. When more lenient criteria were chosen for wave I detection (that is, wave I was marked if a peak was observed during the expected time range, even if not visually above the prestimulus noise floor), wave I was present in >90% of the individuals in both groups with no significant latency differences between the groups. Because this method carries clear disadvantages and because it differs from that used for the rest of the peaks, it was not further pursued.

Taken together, the present data provide no evidence for meaningful group differences between NL and LD participants at the most peripheral level of the auditory brainstem.

Wave III of Typically Learning Children

Detectability. Wave III was detected in all but 5 NL participants (table 3).

Response Latency. The average normal latency of wave III, obtained from typically developing children with present responses (n = 85), was 4.83 ± 0.27 ms (table 4). Out of these children, 3 had responses outside the normal range (>2 SD) (fig. 3).

Wave III of Children with Learning Problems

Detectability. Based strictly on the detectability of wave III, 5 LD+ and 4 LD– children had absent wave III responses. Pearson χ^2 showed that detectability of wave III was not significantly different between NL, LD+ and LD– participants (p = 0.283).

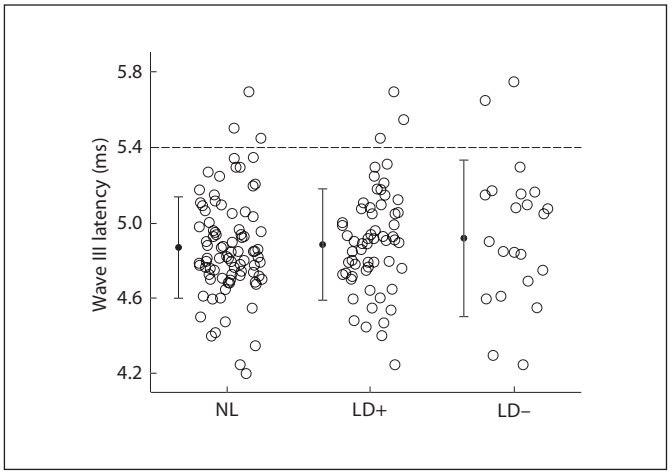

Fig. 3. Average latencies (±1 SD) and distribution of individual latencies for NL, LD+, and LD– participants for wave III. The average in the NL group includes all NL children. The dashed line indicates 2 SDs above the norm established for wave III latency.

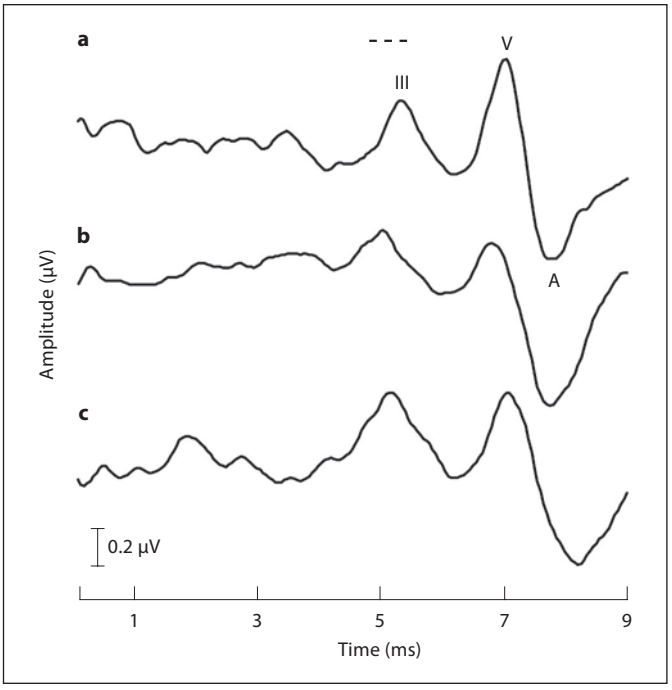

Fig. 4. Representative examples of speech-evoked ABRs of individual NL (**a**), LD+ (**b**) and LD– (**c**) (defined based on abnormal VA slope) participants. The dashed line indicates 2 SDs from the norm for wave III latency. No significant difference in wave III latency of speech-evoked ABRs was found between NL and LD children.

Response Latency. The average wave III latency for the LD+ group was 4.85 ± 0.30 ms and the average wave III latency for the LD– group was 4.89 ± 0.42 ms (table 4). One-way ANOVA showed no significant differences in wave III latencies between NL, LD+ and LD– children ($F = 0.286$, $p = 0.752$). Seventy-nine LD children, including LD+ and LD–, exhibited wave III latencies that were within the norm. Three LD+ and 2 LD– children exhibited wave III latencies that were outside the norm. The majority of LD participants from both groups (LD+: 58 out of 61 children, LD–: 21 out of 23) who had responses also had normal wave III latencies. In summary, neither wave III detectability, nor its latency differed significantly among the three groups of participants (fig. 3). Figure 4 shows representative examples of speech-evoked ABRs of individual NL, LD+ and LD– participants.

The Relationships between Wave III and Rostral Brainstem Measures

Among NL subjects, wave III significantly correlated with the rostral brainstem Z score ($r = 0.53$, $p < 0.001$). This correlation is similar in magnitude to that observed among the rostral measures themselves. On the other hand, among LD children, no significant correlation was observed ($r = 0.11$, $p > 0.3$) providing further support to the claim that in this group, abnormal timing at the rostral brainstem was not related to the timing of more peripheral components.

Discussion

Unlike with click stimuli, the speech stimuli used here did not evoke ABR wave I in a large proportion of typically developing children and children with learning problems, while wave III was present in the vast majority of these children. When the latency of wave III in response to speech is compared to normative latencies for click-evoked responses [Hood, 1998], the responses to speech measured in the current study (table 4) appear to be approximately 1.2 ms delayed. This difference in latencies between click- and speech-evoked responses for wave III likely reflects aforementioned differences in acoustic features of the stimuli, such as the longer rise time and greater acoustic complexity of the speech sounds.

Several stimulus and recording factors could account for the poor detectability of wave I in the current study, consistent with the difficulties in characterizing wave I in the click-evoked ABR [Hall, 1992]. One likely factor relates to the electrode montage used here, which was designed to enhance the rostral components of the ABR

[Hall, 1992], perhaps at the expense of wave I. Therefore, it may be that as for clicks, the use of a horizontal montage would have yielded higher rates of detectability. Moreover, the speech stimulus we used may not have been effective in eliciting wave I due to its more gradual rise time compared to a click stimulus.

In addition to the finding that wave I is considerably undetectable for both NL and LD groups, both the detectability and the latency of wave III of the speech-evoked ABR were shown to be comparable among typically developing children and the two groups of children with LD. This finding is consistent with previous reports that waves I and III of click-evoked ABR are normal among LD children [Grøntved et al., 1988; Jerger et al., 1987; Mason and Mellor, 1984; Song et al., 2006; Tait et al., 1983]. Furthermore, LD children with abnormal rostral brainstem responses were not more likely to have a missing or delayed wave III, consistent with the hypothesis that abnormal speech-evoked ABR likely originates central to the cochlear nucleus (e.g. lateral lemniscus, inferior colliculus) with more peripheral processing intact. In other words, for the most part, abnormal responses of rostrally located components of the speech-evoked ABR, such as those observed in previous investigations [Banai et al., 2005; Cunningham et al., 2001; Johnson et al., 2007; King et al., 2002; Wible et al., 2004, 2005], are not apparent earlier in the speech-evoked ABR processing stream.

A caveat to these assertions is that the ABR is a summation of contributions from specific regions of the cochlea such that wave V has contributions from regions extending from mid to low frequencies whereas wave III has more basal weighting [Hyde, 1985]. Abnormal peripheral encoding of low to mid frequencies, which are the major components of speech sounds, could thus contribute to abnormal V and A measures even if wave III latency is normal. Further research is needed to determine the exact contributions of the frequency composition of the speech sound on different components of the speech-evoked ABRs.

Interestingly, the normal pattern of relationships between rostral brainstem and lower brainstem timing was not observed in the LD group. This pattern of findings, taken together with the observation that abnormalities in speech-evoked ABRs co-occur with auditory cortical processing abnormalities [Abrams et al., 2006; Banai et al., 2005; Wible et al., 2005], suggests that abnormal speech-evoked ABR at the rostral brainstem may reflect abnormal corticofugal modulation in the auditory system of LD– individuals, rather than a bottom-up deficit. One of the postulated roles of the corticofugal system is in selective attention, which is required in numerous tasks, such as language, and may shape the development of sensory circuitry (e.g. brainstem). By this account, input from the cortex serves to fine-tune sensory processing in subcortical structures by enhancing relevant signals and suppressing unwanted ones [He, 2003; Winer, 2006]. If cortical function is disrupted, as is the case in the majority of LD– individuals, subcortical encoding would be disrupted too.

Support for the idea of corticofugal modulation in humans comes from the finding that electrical stimulation of the auditory cortex can result in a reduction in the amplitude of evoked otoacoustic emissions measured from the contralateral ear [Perrot et al., 2006]. While there are no parallel findings associating corticofugal modulation with rostral brainstem function in humans, findings in animal models suggest that neural processing in the thalamus [He, 2003] and in the inferior colliculus [Palmer et al., 2007; Popelar et al., 2002, 2003; Sun et al., 2007; Yan and Ehret, 2002] are directly influenced by corticofugal modulation. Also, long-term experience with language [Krishnan et al., 2005] and music [Musacchia et al., 2007; Wong et al., 2007], short-term training [Russo et al., 2005; Song et al., 2008] and development [Johnson et al., 2008] have been shown to shape subcortical auditory responses, consistent with the idea that corticofugal-driven modification of brainstem circuitry occurs as a result of auditory learning. Interestingly, evidence of experience-driven malleability is observed even under the passive listening conditions used to record the speech-evoked ABR. By this account, abnormal corticofugal modulation during development in LD– individuals leads, in the long term, to functional or even anatomical changes resulting in abnormal rostral brainstem timing.

Alternatively, the abnormal rostral brainstem timing may result locally from abnormal function of the neural generators of waves V and A, putatively the inferior colliculus. Indeed, neurons in the inferior colliculus have been shown to be sensitive to the statistical properties of acoustic stimulation [Dean et al., 2005; Perez-Gonzalez et al., 2005], and deficiencies in these local processes, especially during critical developmental periods, could lead to changes in subcortical structures that then affect sensorineural coding and processing which may be independent of corticofugal influences [Ene et al., 2007; Leake et al., 2006; Seidl and Grothe, 2005]. Taken together, shaping of subcortical pathway function likely derives from reciprocal interaction between local and corticofugal mechanisms.

Corticofugal activity has been shown to modulate efferent suppression of otoacoustic emissions, which is a noninvasive measure of corticofugal modulation [Khalfa et al., 2001; Perrot et al., 2006]. Thus, the corticofugal hypothesis leads us to predict that because corticofugal modulation is not limited to midbrain structures, LD– individuals may also exhibit reduced suppression of otoacoustic emissions, similar to findings in children with learning impairment [Veuillet et al., 1999], central auditory processing disorder [Muchnik et al., 2004], and selective mutism [Bar-Haim et al., 2004]. On the other hand, if the locus of the deficit is peripheral to the generators of the rostral components of the ABR, our LD– individuals could exhibit a normal degree of otoacoustic emission suppression, similar to other findings in children with specific language impairment [Clarke et al., 2006]. Other possibilities are that speech-evoked ABR and otoacoustic emissions are sensitive to different aspects of lower brainstem function and are not informative about each other or that far-field response of the speech-evoked ABR does not reflect local cochlear activity to which otoacoustic emissions are sensitive. Moreover, a discrepancy between ABR and otoacoustic emission responses could be attributed to differences in stimuli or the paradigms used to elicit the responses.

Whether wave III appears normal because the generator is functioning normally or because it is not sensitive to an existing deficit, the fact remains that it reveals no deficit. Further studies employing both sets of measures (that is, speech-evoked ABR and otoacoustic emissions) are required to resolve this issue. In summary, we have demonstrated that at early stages of the auditory pathway, processing of a spectrally and temporally complex acoustic stimulus is similar in NL and LD participants. Disordered brainstem function only occurs in waves likely to predominantly reflect midbrain activity. Thus, the V and A measurements of the brainstem response to speech sounds are critical in the assessment of auditory processing deficits.

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