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Biological Psychology 67 (2004) 299–317
BIOLOGICAL PSYCHOLOGY
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Atypical brainstem representation of onset and formant structure of speech sounds in children with language-based learning problems

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Received 26 June 2003; accepted 22 February 2004

Available online 24 April 2004

Abstract

This study investigated how the human auditory brainstem represents constituent elements of speech sounds differently in children with language-based learning problems (LP, $n = 11$) compared to normal children (NL, $n = 9$), especially under stress of rapid stimulation. Children were chosen for this study based on performance on measures of reading and spelling and measures of syllable discrimination. In response to the onset of the speech sound /da/, wave V–V_n of the auditory brainstem response (ABR) had a significantly shallower slope in LP children, suggesting longer duration and/or smaller amplitude. The amplitude of the frequency following response (FFR) was diminished in LP subjects over the 229–686 Hz range, which corresponds to the first formant of the/da/ stimulus, while activity at 114 Hz, representing the fundamental frequency of /da/, was no different between groups. Normal indicators of auditory peripheral integrity suggest a central, neural origin of these differences. These data suggest that poor representation of crucial components of speech sounds could contribute to difficulties with higher-level language processes.

Keywords: Reading; Speech; Auditory brainstem response; Frequency following response

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doi:10.1016/j.biopsycho.2004.02.002

1. Introduction

Nearly 2 of every 20 American school children are diagnosed with learning problems (Torgeson, 1991). A substantial portion of these children demonstrates difficulty in perceiving and discriminating auditory information, including speech sounds (Kraus et al., 1996; Tallal, 1981). The current study examined neural brainstem responses to speech sounds in normal children and children with learning problems.

The work of Jewett and Williston (1971) and Jewett et al. (1970) was the first to definitively describe far-field scalp-recorded auditory brainstem responses (ABR). The ABR is a phasic response to a transient acoustic event, occurring within the initial 10–15 ms after the event (e.g., stimulus onset). In the years since Jewett's work, advancements in recording and analysis techniques, in combination with corroborating evidence of generator loci from animal, imaging, and intra-operative studies, have fostered development of ABR into a highly sensitive index of the integrity of the auditory periphery and brainstem. This sensitivity results from the high replicability and temporal precision of ABR components commonly identified as waves I–VII, demonstrated to represent activity at distal auditory nerve (I), proximal auditory nerve (II), cochlear nucleus (III), superior olivary complex (IV), lateral lemniscus (V) and inferior colliculus (V_n, VI, VII). It should be made clear, however, that scalp recorded far-field responses most certainly reflect overlapping responses from multiple generators, so these loci of activity, while likely responsible for primary parts of the respective ABR components, are probably not the sole generators. The replicability of these features within and across subjects, their relatively early maturation and their independence from higher cognitive function (e.g., they can be recorded in sleeping or anesthetized subjects), have allowed establishment of normative data to which subjects suspected of auditory dysfunction can be compared. Absolute and relative latencies of these peak features are used to diagnose conductive hearing loss, cochlear lesions, tumors on the auditory nerve, lesions of the lower and upper brainstem, etc. Differences in brainstem responses to sounds on the order of fractions of a millisecond commonly distinguish clinical populations. While peak amplitudes are not as commonly used clinically as latencies, they too have been described as providing crucial information with respect to timing of generation and propagation of auditory responses along the pathway. This conception is inherent to the nature of evoked potentials (Hall, 1992): "Evoked responses directly depend on temporal synchronization of neuronal activity. AERs are optimally generated by action potentials or synaptic potentials arising almost simultaneously from many neurons within a specific anatomic region." (Information culled from excellent overview provided in Jacobson (1985)).

Frequency following responses (FFR) in humans were first reported by Moushegian et al. (1973). The FFR is a tonic response, phase-locked to the harmonic structure of the stimulus. Thus, while ABR consists of an initial, single series of phasic peaks in response to the onset of a stimulus, the FFR demonstrates periodic activity, with repeated peaks observed at periods (wavelengths) corresponding to those occurring in the acoustic stimulus. Though not nearly as widely investigated as ABR, the FFR has been purported to have its generators localized in the inferior colliculus (Møller and Jannetta, 1982; Faingold and Caspary, 1979; Sohmer et al., 1977), though alternate suggestions of lower-brainstem origins have been proposed, such as lateral lemniscus (Galbraith, 1994), superior olivary complex, or cochler nucleus (Hoormann et al., 1992).

A shared locus of generation for phasic ABR waves V and V_n, as well as tonic FFR, likely the lateral lemniscus and/or inferior colliculus, can be appreciated in parallel with related animal literature. Describing several species, there are numerous accounts of single- and multi-neuron recordings in inferior colliculus (or the particular species' analogous structure) that have described multiple, distinct populations of neurons, some of which typically respond phasically to transient aspects of stimuli, such as onsets and/or offsets, and some of which respond tonically to periodic aspects of stimuli, such as vowels (Wilson and Walton, 2002; Irvine, 1992).

Studies of EEG activity have indicated abnormal cortical activity in learning-disabled subjects while they performed various reading and verbal processing tasks (Ackerman et al., 1994; Galin et al., 1992). In the evoked response literature, there are several studies of learning-disabled subjects that investigated not only higher cognitive functions such as reading, but also more basic sensory processing. Some people with language-based learning problems exhibit abnormal central neural encoding of the spectral and temporal information crucial for accurate perception of sounds (King et al., 2001; Cunningham et al., 2001; McAnally and Stein, 1996; Jerger et al., 1987). Some also experience abnormal susceptibility to the demands placed on the auditory system by rapidly presented temporal information (Wible et al., 2002; Temple et al., 2000; Nagarajan et al., 1999; Kraus et al., 1996). The acoustic structure of speech is marked by such rapidly changing spectral patterns, thus diminished ability to process, perceive and distinguish rapid sounds could impair one's ability to develop normal language skills. Temporal processing deficits in the visual system have also been described in learning-disabled subjects, and have contributed to proposed pan-sensory temporal processing deficits in language disabilities (Tallal et al., 1993; Livingstone et al., 1991). Some propose that abnormal cellular structure might contribute to these processing deficits (Livingstone et al., 1991); for example, decreased membrane flexibility in thalamic magnocellular nuclei, which could limit the rapid conformational changes of channel proteins, may reduce the ability of cells to accurately and precisely respond to the rapidly changing features of incoming signals (Stein, 2001). Other research has proposed decreased myelination, and thus diminished integrity of axonal communication between crucial sensory and language areas, as a basis for these language problems, very possibly related to delayed signal transmission times during rapid sensory processing (Klingberg et al., 2000). Most of these and similar studies investigated disrupted processing at the level of the cortex. The interest of the present study lies at a much lower level, the auditory brainstem, reflecting encoding of sounds at much earlier latencies.

Some studies have used the precise timing of auditory brainstem responses to describe abnormal encoding in learning-impaired populations. Abnormal transient responses to stimulus onset (Purdy et al., 2002; Jirsa, 2001; Gopal and Kowalski, 1999; Jerger et al., 1987) and abnormal phase-locked representation of stimulus harmonic structure (McAnally and Stein, 1996) have been reported in subjects diagnosed with learning or auditory-processing problems. Some recent studies have used speech stimuli, which are much more spectrally and temporally complex than clicks and tones that are typically used. These studies reported abnormal representation of stimulus onset and harmonic structure in children with learning problems (Cunningham et al., 2001), and in some cases noted that the abnormalities in response to speech were not observed in response to simpler stimuli (King et al., 2001).

The intent of this study was to investigate whether the ABR and FFR, measures that reflect the highly synchronized representation of transient (e.g., onset) and harmonic (e.g., vowel) elements of speech (Boston and Møller, 1985), could implicate abnormal desynchronization of the neural mechanisms underlying speech sound encoding in learning-impaired children. More specifically, based on the growing body of literature describing temporal processing abnormalities in learning impaired children, we hypothesized that differences in neural responses to the acoustic structure of speech between normal and learning-impaired children, should any be observed, would be exacerbated by demands placed on the system by rapid stimulus presentation. Effects of stimulus repetition have been characterized for click-evoked ABR in normal subjects (Burkard and Sims, 2001; Burkard and Hecox, 1983, 1987), with peaks exhibiting delayed latencies in response to rapidly repeated stimuli. We hypothesized that children demonstrating abnormally poor performance on behavioral measures of auditory perception and higher-level language skills would likewise demonstrate abnormal timing of brainstem activity in response to rapidly presented speech. Given the results of previous studies that describe findings in wave V and in FFR, both of which are thought to originate in lateral lemniscus and/or inferior colliculus, we focused our analyses on those response features, though we recognized the need to evaluate earlier-latency ABR indices of the integrity of the lower-brainstem, auditory nerve, and ear. Ultimately, we hoped that our paradigms of stimulation, recording and analyses would reveal measures that, to some degree, predict or relate to relevant language skills, and that could thus prove useful in the earliest possible stages of identification of children likely to experience language-learning problems, thereby providing earlier opportunities to develop and implement appropriate, effective remediation strategies.

2. Methods

2.1. Subjects

Subjects were 20 native-English-speaking children (mean age = 11.1 years, S.D. = 2.1) with normal bilateral hearing (pure tone thresholds <20 dB HL for octaves 500–4000 Hz). Based on behavioral measures described below, these children were chosen from a pool of subjects who participated in earlier related studies conducted by this laboratory. In accordance with the approval of this research by the Northwestern University Institutional Review Board, all children and their legal guardians signed forms that acknowledged their informed consent.

Eleven children were diagnosed with a language-based learning problem (LP) prior to inclusion in the study. These were professional diagnoses, performed external to, and independent of, the current study, by clinical psychologists, school psychologists, neurologists, etc. Subject selection and classification, and further analyses, were ultimately determined based on performance on a battery of study-internal measures, but these external diagnoses provided an initial, gross classification upon which more specific criteria were then imposed. There were no significant group differences in age or male/female composition between groups of normal (NL, $n = 9$) and LP children.

All children performed within or above one standard deviation from the mean on a standardized measure of intelligence (all IQ scores >85; standardized IQ: mean = 100,

S.D. = 15; brief cognitive index, Woodcock and Johnson (1977)). Performance above this threshold, which is commonly used to describe normal intelligence (i.e., non-retarded), ensured that no children suffered mental deficiencies that may have hindered the ability to understand or perform other behavioral tasks. Though all children surpassed this threshold of normal performance, mean intelligence was lower in LP than in NL children (independent samples *t*-test: $t_{18} = 3.794$, $P = 0.001$; mean IQ: NL = 125, LP = 102). That these groups would differ in performance on an intelligence measure that requires verbal skill, such as the one utilized in this study, is thus not entirely unexpected. This discrepancy may in part be a consequence of our seeking to test children who exhibit pronounced deficits in language skills; even some measures of non-verbal intelligence describe some relationships between intelligence and measures of reading and spelling ability (Brown et al., 1997).

NL and LP children were selected on the basis of their performance on a measure of reading/spelling ability (composite score based on components from Wilkinson (1993)) and measures of speech–sound discrimination (/da/–/ga/ and /ba/–/wa/ speech–sound continua; described below and in Carrell et al. (1999)). Children were selected such that there was no overlapping of scores between NL and LP groups on measures of reading/spelling or /da/–/ga/ discrimination; there was considerable overlap of scores on the /ba/–/wa/ discrimination task, which was specifically intended to act as a task control. In spite of such clear differences in performance, group differences in mean IQ necessitated comparison of groups on these behavioral measures while covarying IQ, in order to isolate the contribution of the particular task and associated skills, independent of intelligence. Controlling for IQ, univariate ANOVAs constructed to compare groups on reading/spelling and /da/–/ga/ discrimination indicated strong group differences on both measures (reading/spelling: $F_{1,17} = 9.223$, $P = 0.007$, mean: LP = 84, NL = 116; /da/–/ga/: $F_{1,17} = 16.147$, $P = 0.001$, mean just-noticeable difference (represents discrimination with 70% accuracy), in Hz: NL = 87, LP = 198). As designed, performance on the /ba/–/wa/ discrimination control task reflected no such group difference.

Performance on the /da/–/ga/ perception task required discrimination of auditory stimuli along a speech–sound continuum that varied the onset frequency of the third formant (F_3), with endpoint phonemes /da/ and /ga/. The continuum having /ba/ and /wa/ as endpoints varied the duration of the formant transition. Discrimination along this continuum served as a control to ensure that all subjects could understand and perform the task, and thus indicated that group differences in /da/–/ga/ discrimination were due to differences in ability to distinguish specific acoustic characteristics of the stimuli. These screening procedures (differentiation on /da/–/ga/, similarities on /ba/–/wa/) have been described previously by Kraus et al. (1996).

For screening/selection procedure, differences between NL and LP groups were considered significant when $P < 0.008$ (six comparisons (sex, age, IQ, reading/spelling, /da/–/ga/, /ba/–/wa/); per-comparison alpha level = 0.05/6 = 0.008).

2.2. Stimuli and recording

Evoked potentials were elicited by the speech stimulus /da/. The 40 ms phoneme was generated with a digital speech synthesizer (SenSyn) at a sampling rate of 10 kHz. The stimulus was composed of five formants that transitioned from the consonant /d/ to the vowel

/a/. The fundamental frequency (F_0) and the first three formants (F_1, F_2, F_3) changed linearly over the duration of the stimulus: F_0 changed from 103 to 125 (0–35 ms) to 121.2 Hz (35–40 ms), F_1 from 220 to 720 Hz, F_2 from 1700 to 1240 Hz and F_3 from 2580 to 2500 Hz. F_4 and F_5 remained constant at 3600 and 4500 Hz, respectively. The initial 10 ms of the stimulus contained an onset burst in F_3, F_4 and F_5 as described by Klatt (1980). The vowel /a/ was abbreviated to allow increased presentation rate, in order to better stress the system. Synthesized speech was used because very similar stimuli were used for perceptual measures, thus facilitating comparison of physiological and behavioral measures.

Stimuli were presented by a PC-based stimulus delivery system (Compumedics Gentask) that output the signals through a 16-bit converter. That system controlled the timing and intensity of stimulus delivery. It also triggered the PC-based evoked potentials averaging system (Compumedics Acquire).

Stimuli were delivered monaurally to the right ear through insert earphones (Etymotic Research ER-2) at 80 dB SPL. A schematic illustration of the stimulation paradigm is presented in Fig. 1. Stimuli were presented in trains consisting of four stimuli, separated within a train by 12 ms interstimulus intervals (ISI: time within a train between stimulus offset and subsequent stimulus onset). Pilot data indicated that this ISI was the shortest that could be used without presenting a subsequent stimulus while the response to the previous stimulus was still evolving. Such response overlap would have interfered with analyses. A previous study of repetition and ABR showed that a similar ISI (11.9 ms) was effective at eliciting repetition effects (Burkard and Hecox, 1983). That same study showed that repetition-induced effects were minimal beyond the fourth stimulus in the train. The motivation of the study was not to study the time course of repetition effects per se, but to investigate potential differences between NL and LP children under the stress of repetition. Thus responses to stimuli two and three were not studied, as the literature did not lead us to expect these responses to demonstrate maximal effects of repetition, and thus maximal differentiation between groups, compared to responses to stimulus four. For this reason, investigation of repetition effects was limited to responses to the fourth stimulus in the train, compared to the response to the first stimulus. The intertrain interval (ITI: time between

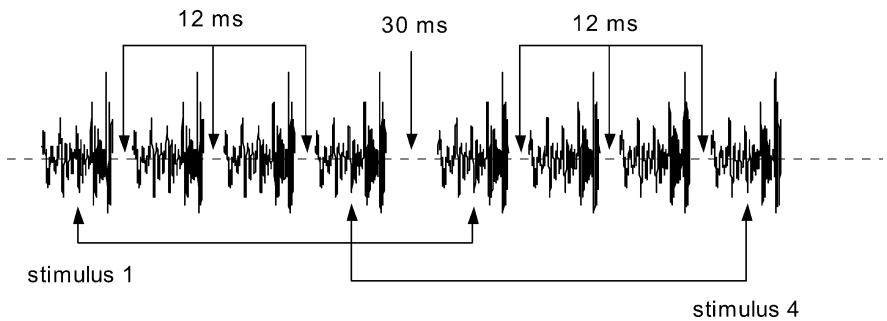

Fig. 1. Schematic description of stimulation paradigm. The synthesized-speech sound /da/ was presented in trains of four. Within each train, stimuli were separated by 12 ms. The interval between successive trains was 30 ms. Analyses focused on evoked potentials recorded in response to the first and fourth stimuli.

offset of final stimulus in a train and onset of initial stimulus in the subsequent train) was 30 ms.

An inverted polarity stimulus train was randomly presented 50% of the time. Addition of responses evoked by stimuli of opposing polarities facilitated isolation of neural contributions, while eliminating contributions from the cochlear microphonic response, a receptor potential generated by cochlear hair cells (Gorga et al., 1985). Responses were averaged separately for each position in the stimulus train (i.e., responses to first or fourth stimuli in train), for each polarity. Each child's final response was an average of 6000 stimuli (3000 each, positive and negative polarity), per stimulus position within the train (first or fourth).

Children were tested in a sound-treated booth and were instructed to ignore the stimuli in order to minimize effects of the child's state of attention or arousal on the responses being recorded. To diminish attention to the stimuli, as well as to promote stillness during recording, each child watched a videotape of his/her choice, with soundtrack presented in free field at 40 dB SPL. While this clearly presented a minor source of additional acoustic stimulation, the time-locked nature of brainstem response averaging minimized the contributions of any physiological or other electrical activity that was not precisely synchronized with the presentation of the stimuli. Also, any noise introduced by the video was greatly outweighed by the benefit it provided in ensuring that the children had an enjoyable experience and that they sat as still as possible in order to minimize muscle artifacts.

Silver-silver chloride electrodes (impedance $<5\,\mathrm{k}\Omega$) were placed on the right mastoid, forehead, and at Cz. These acted as reference, ground, and active electrodes, respectively.

Data were collected at a sampling rate of 20,000 Hz, with a gain of 5000, and were digitally bandpass filtered online from 100 to 2000 Hz. Trials with artifacts that measured in excess of $\pm 35\,\mu\mathrm{V}$ were rejected from the averaged response. A 52 ms epoch was recorded for each stimulus in the train, beginning at stimulus onset. The 25 ms epoch immediately preceding the onset of the first stimulus in the train was recorded for purposes of estimating system noise.

2.3. Data analysis

Averaged responses to the first and fourth (final) stimuli in the train were analyzed. A data-screening algorithm was used to objectively identify local maxima and minima to the nearest 0.05 ms. Peaks were then chosen from these extrema. Peak latencies (ABR waves I and III), interpeak latencies (I–III), peak-to-trough slopes (positive peak to following negative trough, I–I_n, V–V_n) and peak-to-trough areas (V–V_n) were calculated. Peak-to-trough slope was defined as peak-to-trough amplitude divided by peak-to-trough duration. Though not entirely similar to the measure of slope described here, an expanded, multidimensional ABR slope vector has recently been used by other researchers (Gopal and Kowalski, 1999). We interpret peak-to-trough slope as a composite measure of response timing. One factor contributing to waveform slope, peak-to-trough duration, explicitly describes the temporal course of generation and/or transmission of summed neural activity, likely reflecting, for example, the channel kinetics of neurons and/or the propagation of potentials along axons and dendrites. The other contributing factor, peak-to-trough amplitude, reflects the synchrony of underlying electrophysiological activity, in that summation of activity-related electrical

potentials into a larger waveform peak requires more precise integration over a shorter time course.

To calculate areas, wave V–V_n peak-to-trough waveforms were linearly shifted in the amplitude dimension so that the positive peak's amplitude was 0 μV. The amplitudes of each point in the digitized, shifted waveform, from peak to trough, were then summed. The duration of each sample period in the waveform was 0.05 ms; the summed amplitude value was multiplied by this per-sample duration, resulting in appropriate area units, μV ms. This area measure is interpreted as providing a general estimate of the overall activity underlying the generation of the peak-to-trough waveform. This measure, and other similar measures such as RMS amplitude, is commonly employed for assessment of overall response magnitude over a given time course. In general, we interpret area as describing "how much activity" contributed to the generation of the waveform, while slope describes "how the activity is shaped" over time, and by extension describes the temporal synchronization of the response generators.

Analyses of waves I, I_n and III, measures of the integrity of peripheral and low brainstem encoding, were limited to the response to the first stimulus in the train because these waves are typically not as robust as wave V and were therefore much more difficult to consistently identify in responses degraded by repetition (Jacobson, 1985). Wave III_n was excluded from analyses because its relatively high inter-subject variability, compared to waves I and V (Weber, 1985), made it difficult to consistently identify.

The FFR was measured over 35 ms, from 11.4 to 46.4 ms post-stimulus onset. Activity was fitted to 256 points, 5 ms Hamming ramps were applied to the beginning and end of the range, and the windowed responses were baseline-corrected to remove DC offset, for purposes of computing Fast Fourier Transforms (FFT). A 17.5 ms period immediately preceding presentation of the first stimulus in the train was fitted to 128 points and was identically Hamming ramped and baseline-corrected to compute an FFT that represented non-stimulus-related system noise. The amplitudes of the following frequencies, common to both FFR and pre-stimulus FFTs, were measured to describe activity corresponding to prominent features of the stimulus: F_0 was represented by peak activity at 114 Hz; F_1 was represented by the mean of activity spanning the 229–686 Hz range. Frequency ranges corresponding to higher formants F_2–F_5 were not investigated because they exceed FFR low-pass thresholds typically reported from 1000 to 1500 Hz (Hoormann et al., 1992; Gardi et al., 1979; Marsh and Worden, 1968). FFR analyses were limited to responses in which stimulus-evoked activity exceeded the system noise.

To our knowledge, there have been no reports of a modulatory effect of intelligence upon auditory brainstem processing. Much evidence has described use of auditory brainstem measures in subjects who were sleeping, under sedation or experiencing multiple handicaps (Stein and Kraus, 1985), suggesting that these methods of assessment of peripheral and brainstem auditory processing are unaffected by such factors. For such reasons, we did not recognize any clear conceptual motivation to account for variability in IQ when analyzing measures of brainstem physiology. In other words, the difference between NL and LP groups on IQ was not expected to be a factor contributing to any potential differences in brainstem physiology.

For the following analyses, unless indicated otherwise, all F and corresponding *P* values refer to main effects or interactions resulting from 2 factor levels (subject group: NL/LP) ×2

repeated measures (stimulus position in train: first/fourth) ANOVAs. Differences between NL and LP groups on these physiologic measures of speech sound encoding were considered significant when $P < 0.0125$ (four comparisons (wave V–V_n slope, FFR F_0 magnitude, FFR F_1 magnitude, control condition MANOVA incorporating features of waves I, III and wave V–V_n area); per-comparison alpha level $= 0.05/4 = 0.0125$).

3. Results

Averaged responses to the initial stimulus in the train are shown in Fig. 2 (NL = dark, LP = light). These consist of ABR waves I, I_n, III, V and V_n, occurring at roughly 2.1, 2.8, 4.4, 6.2 and 7.2 ms post-stimulus onset, respectively, followed by the phase-locked activity of the FFR, measured from 11.4 through 46.4 ms.

3.1. ABR wave V–V_n morphology

Children with learning problems demonstrated degraded morphology of wave V–V_n, compared to NL children: the mean LP wave V–V_n response was less steep, having a smaller slope, compared to NL children (main effect of NL/LP group: $F_{1,18} = 8.141$, $P = 0.011$). There were no group differences in sensitivity to repetition, reflected by the absence of significant interaction between subject group and response position. There was no main effect of repetition.

To illustrate the difference in wave V–V_n slope, data were plotted on a two-dimensional coordinate system using wave V–V_n duration and amplitude as axes (Fig. 3; data reflect responses to first stimulus in train). In this space, the slope of a line passing through the origin and a given data point represents the slope of that subject's wave V–V_n (slope =

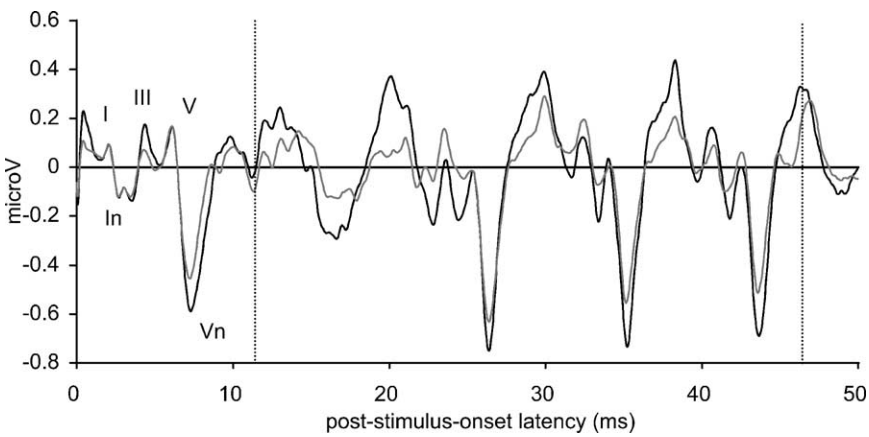

Fig. 2. Averaged brainstem and frequency following responses. Averaged, /da/-evoked auditory brainstem responses from NL (dark line, $n = 9$) and LP (light line, $n = 11$) children. ABR waves I, I_n, III, V and V_n are indicated. The FFR was measured over the region contained between the dotted lines, from 11.4 to 46.4 ms. Data reflect responses to the first stimulus in the train.

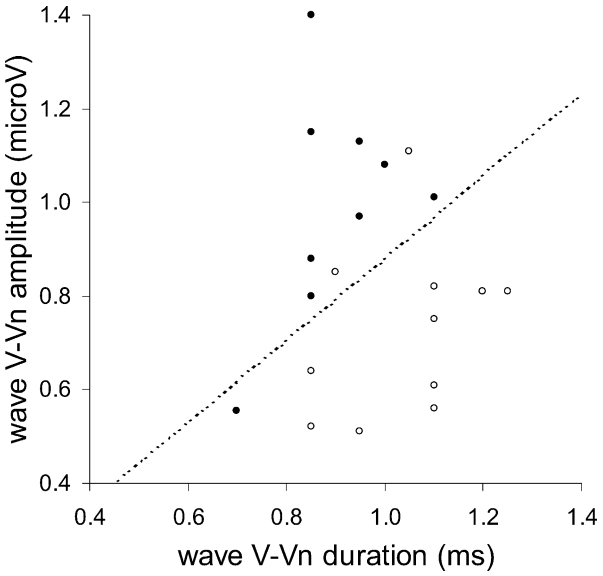

Fig. 3. ABR wave V–V_n durations and amplitudes in LP and NL children. The mean LP wave V–V_n response was less steep, having smaller slope, compared to NL children. Data are plotted on a two-dimensional coordinate system having wave V–V_n duration and amplitude as axes (NL = solid circles, LP = open circles). In this space, the slope of a line passing through the origin and a given child's data point represents the slope of that child's wave V–V_n (recall: slope = inter-peak amplitude/inter-peak duration). In this figure, the dotted line represents the mean slope of all children together (0.88 μV/ms). The majority of the LP children lie below this line, demonstrating generally longer duration for a given amplitude, generally smaller amplitude for a given duration, compared to the majority of NL children, who lie above the line. Data reflect responses to the first stimulus in the train.

peak-to-trough amplitude/peak-to-trough duration). In this figure, the dotted line represents the mean slope of all the children (0.88 μV/ms). Points above or below this line can be appreciated as having greater or lesser slope than the mean. It can be seen that the majority of the LP children lie below this line, demonstrating generally longer duration for a given amplitude, generally smaller amplitude for a given duration, compared to the majority of NL children, who lie above the line.

There were no significant within-group correlations between IQ and ABR wave V–V_n slope (LP: $r = 0.191$, $P = 0.573$; NL: $r = 0.228$, $P = 0.554$). Since these data were not correlated, and thus did not satisfy an important requirement for appropriate use of ANCOVA, IQ was not used as a covariate during analyses of ABR wave V–V_n slope. There were no theoretical or statistical motivations to hypothesize that group patterns of brainstem physiology were modulated by intelligence.

3.2. Spectral representation of F_0 and F_1 in the FFR

The spectral components of the FFR corresponding to F_1 of the /da/ stimulus were diminished in LP children compared to NL children (main effect of NL/LP group: $F_{1,18} = 13.153$, $P = 0.002$; Fig. 4). There was no group difference in the amplitude of the F_0

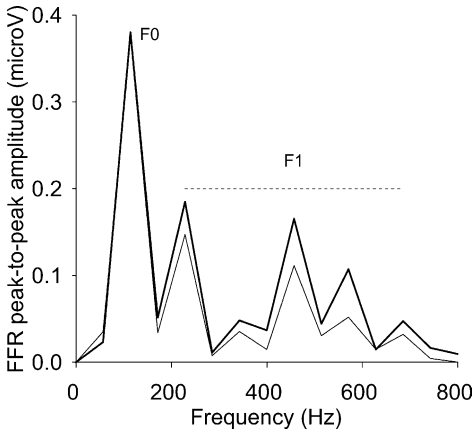

Fig. 4. Spectral representation of stimulus structure in LP and NL children. LP children (thin line) have diminished amplitude in the FFR over the 229–686 Hz range, compared to NL children (thick line). These frequencies (spanned by dotted line) correspond to the range over which F_1 transitions throughout the /da/ stimulus. There are no group differences in the amplitude of the neural representation of F_0, by far the largest spectral component, shown at 114 Hz. Data reflect responses to the first stimulus in the train.

component of the FFR (Fig. 4). There were no group differences in sensitivity to repetition for either F_0 or F_1 components, reflected by the absence of significant interaction between subject group and stimulus position. Main effects of decreased magnitude upon repetition were observed for both F_0 ($F_{1,18} = 8.269$, $P = 0.010$) and F_1 ($F_{1,18} = 12.995$, $P = 0.002$).

There were no significant within-group correlations between IQ and FFR F_1 amplitude (LP: $r = 0.327$, $P = 0.327$; NL: $r = 0.297$, $P = 0.437$). Since these data were not correlated, and thus did not satisfy an important requirement for appropriate use of ANCOVA, IQ was not used as a covariate during analyses of FFR F_1 amplitude. There were no theoretical or statistical motivations to hypothesize that group patterns of brainstem physiology were modulated by intelligence.

3.3. Periphery and low-brainstem components and overall response magnitude

A MANOVA was constructed that incorporated multiple control measures intended to confirm the integrity of peripheral and low-brainstem structures (/da/-evoked wave I and III absolute and interpeak latencies, wave I–I_n slope), and to rule out potential influence of overall response magnitude on group differences in wave V–V_n slope (wave V–V_n area). There was no significant difference between NL and LP groups. Recall, as well, that NL and LP children did not differ on the measure of F_0 amplitude, by far the largest component of the FFR. Similarity on these measures of robust, primary response components further suggests that observed group differences were not the result of differences in overall response magnitude, but were more specific to subtle differences in the synchrony of processing.

Fig. 5 depicts the similarities between NL and LP children on the measure of wave V–V_n area, and the differences between those groups on the measure of wave V–V_n slope.

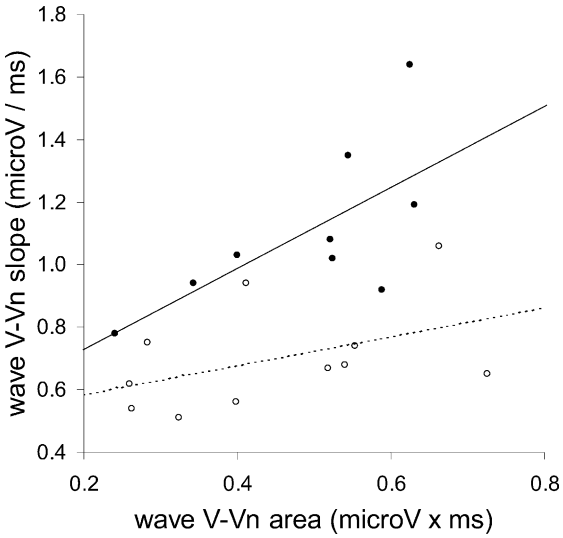

Fig. 5. ABR wave V–V_n slopes and areas in LP and NL children. Both NL (solid circles) and LP children (open circles) demonstrated similar overall wave V–V_n response areas, but LP responses were generally less "sharp" for a given area, reflected by smaller slopes. While the overall magnitude of underlying activation appears similar between both groups, the degraded temporal synchrony of the underlying generator and/or transmission mechanisms results in a shallower, less "sharp" response in LP children. Trendlines are fit through both NL (solid line) and LP groups (dotted line).

Linear fits are plotted through both NL and LP groups. Qualitative assessment of this figure corroborates the statistical findings reported above: both groups demonstrate similar overall response area, and for a given area, LP children tend to have smaller slopes compared to NL children. So while the overall magnitude of underlying activation is similar between both groups, the diminished temporal synchrony of the underlying generator and/or transmission mechanisms results in a shallower, less "sharp" response in LP children.

4. Discussion

Children with language-based learning problems exhibited abnormal responses to speech signals at the level of the auditory brainstem. Both transient, phasic responses to stimulus onset and phase-locked, tonic responses to the stimulus' harmonic structure were impaired. These data support theories that propose low-level sensory processing deficits as bases for some language-learning problems. Such low-level, basic sensory degradation in both transient and harmonic speech signal encoding in LP children may be passed on to higher neural/cognitive levels for identification, categorization and integration. These higher-level, later processes may in fact function normally in some LP children. However, as a result of deficient, basic, perceptual encoding, the cognitive manipulations involved in the task could be performed on substandard perceptual signals, thus limiting their effectiveness. Also, to

compensate for these degraded representations and any potential increase in cognitive load that may result, the abnormal system may devote more resources toward adequately manipulating the distorted perceptual signal, and thereby divert resources from other important aspects of processing, thus further hampering efficient, effective encoding and manipulation of information vital to successful use of language.

4.1. Selection of subject groups

The learning-disabled population is a heterogeneous one. Abilities are typically spread across a continuum of performance, and diagnoses are subject to variability depending on definition (Shaywitz et al., 1992a,b). This could be interpreted as suggesting that a single, common cause of such problems is less likely than multiple, interacting physiological processes. Several non-specifically auditory phenomena have been proposed to account for abnormal development of language skills (Ramus et al., 2003; Snowling, 2001; Livingstone et al., 1991). For these reasons, subject selection and classification was based largely on the study-internal battery of tests, rather than solely on clinical diagnoses. By including the speech–sound discrimination measure as a primary tool for selection and classification of subjects, LP children were chosen whose learning problems are more likely to have some bases in abnormal auditory perception, allowing us to focus our study on this subset of the learning-impaired population. We acknowledge that such selection does not lend itself to our being able to broadly define biological bases of learning problems in the population in general. When designing the study, we initially assumed, based on experience with a large population of children having learning problems, that of this entire population, only about one third would likely demonstrate abnormal auditory processing and perception. Given this assumption, then, our task was to best identify and study that subset of the population. Therefore we pursued a more clinically oriented approach, employing multiple measures to identify specific traits, allowing us to direct our resources toward children on whose problems we would most likely be able to shed the most insight.

4.2. Sensory versus cognitive processing, independence of ABR and FFR

Our general research aims are to investigate sensory processes that relate to higher levels of language ability. Many higher-level cognitive attributes, such as overall intelligence, certainly contribute to performance on measures of language ability. Though we appreciate these influences, we wish to isolate our behavioral investigations from those higher functions to the greatest extent possible, and instead focus on measures and skills specific to auditory processing and language. We account for the effects of IQ by incorporating it as a covariate during analyses on other behavioral measures. We also seek to minimize the extent to which effects such as attention are introduced in our physiological paradigms. We wish to instead focus on auditory sensory processing of the acoustic structure of speech sounds and the relations between these processes and language ability. The more dependent upon higher-level cognitive attributes an evoked response may be, the more one must be concerned about controlling for such states. A strength of the paradigm described here is that neither ABR nor FFR have ever been observed to relate to higher functions such as intelligence. For many years, these measures have provided excellent, objective tools with which one can

observe low-level auditory processing in the brainstem, with clinically relevant resolution in the sub-millisecond range, that is independent of many factors that confound research using longer-latency, cortical evoked potentials.

4.3. Timing of wave V–V_n is abnormal in LP children

Rather than reflecting overall group differences in response scale, the combined findings of group differences in wave V–V_n slope and similarities on wave V–V_n area suggest differences in response morphology, specifically differences in response timing. In order for wave V–V_n slope to be diminished in LP children with respect to NL children, without an accompanying group difference in wave V–V_n area, the duration of wave V–V_n must be both generally longer, and the amplitude of wave V–V_n generally smaller. This relationship between duration and amplitude, as well as the differences between NL and LP children despite similarities in response area, are shown in Figs. 3 and 5.

The wave V–V_n duration measure reflects timing of successive response components, and likely could be affected by differences in conduction velocity along the dendritic arbor and/or axonal projections, or by differences in the channel kinetics of the contributing neurons. Differences in wave V–V_n amplitude would also likely be based in large part on differences in synchronization of response generators. So both potential sources of differences in slope are either explicit (duration) or implicit (amplitude) indices of response timing. The shallower slope in LP subjects is thus a very strong indicator of diminished synchronization of ABR wave V–V_n generators, thought to reside in the lateral lemniscus and inferior colliculus. This complements much of the literature on abnormal cortical auditory processing in LP children that describes disordered responses to rapid temporal stimulations as substantial contributors to impaired auditory perception and difficulties with language skills (Nagarajan, 2002; Merzenich et al., 1996).

4.4. Frequency-specific degradation in LP children

The lack of group difference in F_0, by far the largest component of the FFR, suggests that the difference over the F_1 range was not the result of an overall response degradation in LP children. Given equivalent F_0, atypical activity observed over the F_1 range must reflect group differences in frequency-specific encoding, occurring primarily at higher frequencies that require more precise, rapid activation and recovery of neural mechanisms. Such abnormal encoding of rapid information among LP children is consistent with many other studies reviewed above that describe similar sensitivity to rapid temporal information.

4.5. Processing deficits appear to be central in origin

The NL/LP group similarities in waves I and III, thought to reflect activity from the auditory nerve to the cochlear nucleus (Møller et al., 1995, 1988; Jacobson, 1985; Møller and Jannetta, 1983), suggest that both groups similarly encode sounds at these low levels. This suggests that abnormal morphology of ABR wave V–V_n in LP children results from abnormal encoding in the region of the lateral lemniscus and/or inferior colliculus, thought to generate waves V and V_n. To adequately qualify these statements, however, it should

be noted that while localization of primary response generators is possible to a degree, these complex far-field responses most certainly reflect overlapping activity from multiple regions (Møller and Jannetta, 1985).

Group differences in FFR further support localized abnormalities in the region of the lateral lemniscus and/or inferior colliculus, as the FFR has been proposed to originate there (Galbraith, 1994; Møller and Jannetta, 1982; Sohmer et al., 1977). There is some skepticism about these proposed generators in light of alternate suggestions of lower-brainstem origins (Hoormann et al., 1992). However, if it is to be assumed that FFR is generated in lower regions of the pathway, group differences in encoding in the periphery and lower-brainstem levels, sufficient to contribute to NL/LP differences in FFR, likely could have also affected some of the /da/-evoked earlier waves I and III as well as the FFR. As such group differences on these early ABR measures were not observed, it is likely that abnormal FFR encoding was localized to a region higher up the auditory pathway, already suggested as abnormal in LP children based on ABR wave V–V_n findings. Our data and analyses, however, are by no means designed to certify the exact locations of response generation.

4.6. Main effects of NL/LP group

On measures of both ABR wave V–V_n slope and FFR F_1 amplitude, LP children demonstrated abnormal responses. These differences, it is worth discussing, were manifested as main effects (i.e., differences were evident regardless of stimulus repetition within the train). Our hypotheses were that differences between groups would likely be more obvious in response to the final stimulus in the train. So we are forced to speculate as to why the LP responses were abnormal in general, rather than specifically only after stimulus repetition.

One possibility is that LP children demonstrate overall diminished responses, period. Perhaps responses are generally smaller in LP children, regardless of specific aspects of temporal processing. However, measures of wave V–V_n area and FFR F_0 magnitude act as controls, to the extent that they demonstrate major relevant response features on which both groups appear similar. These demonstrate that to a great extent, both NL and LP children are capable of similar levels of activation, and that the group differences are somewhat less general. However, our data are unable to definitely support such conclusions.

Another possible explanation is that the group differences across both initial and final train positions are a result of differences in temporal sensitivity to the 30 ms interval separating the end of one stimulus train and the beginning of the next. Perhaps this interval was of sufficiently limited duration such that the neural systems in LP children were less able to fully recover prior to stimulation by the subsequent stimulus train, compared to NL children. Preliminary studies in this laboratory that are investigating processing in guinea pig inferior colliculus lend some support to this possibility. In the guinea pig model, FFR component F_0, on which NL and LP children do not differ, is relatively insensitive to gap durations similar to the ITI used in the present study, while the F_1 component, on which NL and LP children differ, demonstrates degradation from one response to the next when separated by similar gap durations. However, such frequency-specific differences in repetition sensitivity are not readily apparent in a review of the literature.

4.7. Previous studies of ABR and FFR

Measures of ABR and FFR have been studied in similar groups of children with learning problems. Abnormal click-evoked ABR morphology was observed in a child diagnosed with reading and writing problems (Jerger et al., 1987). While not specifically testing children with language-learning problems, some studies have demonstrated abnormally shallow click-evoked ABR slopes (Gopal and Kowalski, 1999) and prolonged wave V latencies (Jirsa, 2001) in children diagnosed with central auditory processing disorder, whose relationship to language impairments has been long recognized (Tallal and Stark, 1981). Neither Gopal and Kowalski nor Jirsa, however, reported any statistical group differences on measures of reading or spelling. Purdy et al. (2002) described decreased latency of wave V in learning-disabled subjects relative to normals, though they acknowledged an inability to provide any substantial, theoretically based explanation for this.

Adults with dyslexia demonstrated poorer representation of tone-evoked FFR (McAnally and Stein, 1996); these same subjects demonstrated normal ABR, but the control stimulus was a standard click, not a speech–sound. Similarly, another study reported no group differences in response to click stimulation, but in response to more complex, synthesized-speech stimuli, children with learning problems demonstrated significantly longer latencies of wave V_n in quiet (King et al., 2001). Similarly diagnosed children also demonstrated diminished spectral representation of the FFR over a range of frequencies that corresponded to crucial harmonic elements of the speech stimulus (Cunningham et al., 2001), though, unlike the current study, this difference was only observed in noise.

The lack of a repetition effect on ABR wave V–V_n processing is somewhat unexpected in light of previous work by Burkard and Sims (2001) and Burkard and Hecox (1987, 1983). This may certainly be a result of fundamental differences in stimuli (click versus speech) and measure (latency versus slope). We did not intend to explicitly replicate those studies, and thus did not use identical methods, therefore we cannot definitively state why findings in our normal children might not agree with those previously described effects of repetition.

4.8. Potential use as diagnostic tools

Motivated by interest in predicting reading ability via evoked potentials, Molfese (2000) described auditory-evoked cortical responses in newborn children that predicted future development of normal/abnormal reading skills. Benasich and Tallal (2002) recently found that auditory processing deficits in infants, no older than 3 years, preceded, and in some cases predicted, delayed language. Given these early ages of the initial stages of development of both normal and abnormal language and its underlying neurophysiology, and the young age of maturation of the ABR (Cox, 1985), early childhood ABR and FFR screening with specific emphasis on measures of speech-evoked transient and phase-locked synchrony could potentially increase the likelihood of identifying children at risk for auditory-based learning problems. Further, armed with our emerging understanding of the efficacy of auditory perceptual training and the nature of corresponding neural plasticity, such screening could potentially allow very early attempts at remediation.

Acknowledgements

We thank Cynthia King, Erin Hayes, Catherine Warrier, Dan Abrams, Krista Johnson, Nicole Russo, Gabriella Musacchia, Erika Skoe, Jason Eastman, Dottie Martin, Steven Zecker, Ann Bradlow and Jim Baker. This work was supported by National Institutes of Health Grants R01 DC01510-09, T32 DC00015-17 and F31 DC04546-01. We also thank the reviewers for their extremely helpful comments.

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