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Correlation between brainstem and cortical auditory processes in normal and language-impaired children

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Summary

A functional relationship between brainstem and cortical auditory processing was shown to be abnormal in children with language-based learning problems (LP). Auditory evoked potentials were used to investigate brainstem and cortical responses to the speech sound /da/. The duration of the wave V–V_n complex of the auditory brainstem response was studied, as was the effect of noise on correlations between cortical responses to repeated stimuli. The group of LP children (n = 11) demonstrated abnormal encoding of speech sounds on both individual measures of brainstem and cortical processing; prolonged wave V–V_n duration and pronounced susceptibility of cortical correlations to degradation by noise were both interpreted as reflecting diminished synchrony of response generator mechanisms. Furthermore, the LP group as a whole failed to demonstrate a relationship between brainstem and cortical measures that was demonstrated to be quite strong across all normal children (NL, n = 9). However, a subset of roughly three-quarters of the LP children appeared to demonstrate the normal relationship between brainstem and cortical processing, suggesting that they share a common functional connection with NL children. This relatively normal relationship between brainstem and cortical auditory processing in most LP children, as well as the exceptions to this relationship reflected by a smaller portion of LP children, may delineate different subclasses of auditory-language-based learning problems. This suggests the potential for use of these measures as diagnostic tools.

Keywords: auditory brainstem response; cortical auditory evoked potentials; language impairment

Abbreviations: ABR = auditory brainstem response; IQ = intelligence quotient; ISI = inter-stimulus interval; ITI = inter-train interval; LP = children with language-based learning problems; NL = normal children

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Introduction

Many studies of language-impairment suggest that abnormal neural encoding of auditory information appears to play a major role in the disruption of normal language skills (Tallal and Piercy, 1974; Farmer and Klein, 1995), presumably by contributing to impaired perception of crucial acoustic cues contained in speech signals. For example, abnormal perception (Wright *et al*., 1997), and impaired cortical (Kraus *et al*., 1996; Nagarajan *et al*., 1999) and subcortical (McAnally and Stein, 1996; Cunningham *et al*., 2001) auditory neural processing, of both speech and non-speech stimuli, have been demonstrated in groups of children and adults who demonstrate various difficulties with language.

A primary finding from our previous study of cortical processing of speech sounds in normal (NL) and language-impaired (LP) children was that acoustic masking noise induced a pronounced degradation of the correlation between evoked responses to repeated stimuli in LP children only (Wible *et al*., 2002). This was interpreted as suggesting that, in LP children, the ability of the auditory system to consistently replicate the morphology or 'shape' of a response upon multiple repetitions of the speech sound was corrupted by noise.

In a study of auditory brainstem processing in a major subset of the children from the study of cortical processing

described above, we observed evoked auditory brainstem responses (ABRs) to the onset of a speech sound that were less 'sharp' in LP children, as reflected by a measure of response slope (Wible *et al*., 2004). This was interpreted as reflecting diminished synchrony of the generation and/or transmission, and subsequent scalp-recorded summation of underlying neural activity, likely originating in the lateral lemniscus and/or inferior colliculus (Møller and Jannetta, 1985).

While these previous findings by Wible and colleagues describe deficient timing of auditory encoding at the brainstem or cortical levels in LP children, we sought in the present study to determine whether systematic functional relationships may be observed between brainstem and cortical activity. In particular, we hypothesized that temporally degraded responses in the auditory brainstem, reflected by less synchronized activity that exhibits a shallower slope between peak features, would contribute to diminished integrity of encoding of temporal features in the auditory cortex, due to repetition and noise, as shown by measures of inter-response correlation.

In addition, we intended to determine whether such relationships could be observed across both NL and LP children. Consistent relationships across groups could imply common functional connections between brainstem and cortex for all children. This could suggest that auditory–perceptual and language problems result primarily from a sub-optimal degree of processing at lower levels of the auditory pathway, which then detrimentally affects processing—in a feed-forward fashion—throughout higher levels of an otherwise normal system. Alternatively, the data may suggest that different functional relationships, and thus different underlying mechanisms (e.g. cortically-localized processing deficits or compensatory processing via multiple, converging non-primary pathways) contribute to differences in auditory perception and language skills observed between LP and NL children. In light of these questions, a strength of the present analyses is that these brainstem and cortical measures were recorded from the same groups of NL and LP children, permitting meaningful interpretation of correlations between indices of processing from multiple levels of the auditory pathway.

Methods

Subjects

Subjects were 20 native-English-speaking children (mean age = 11.1 ± 2.1 years) with normal bilateral hearing (pure tone thresholds <20 dB hearing level for octaves 500–4000 Hz). Eleven children had received diagnoses of language-based learning problems prior to admission to this study. There were no significant group differences in age or male/female composition between groups of NL ($n = 9$) and LP children. These children were the same as those reported in a previous study of brainstem processing (Wible *et al*., 2004)—a subset of the children reported in a study of cortical processing (Wible *et al*., 2002). Given that (i) diagnoses were conducted by professionals who had no affiliation with our study and (ii) there can be considerable variability in diagnostic criteria across clinical settings, subject screening and data analyses were ultimately based on well-defined, study-internal behavioural measures (described below) rather than solely upon diagnostic classifications.

All children performed within or above 1 SD from the mean on a standardized measure of intelligence [all intelligence quotient (IQ) scores >85; standardized IQ: mean = 100, SD = 15; Brief Cognitive Index (Woodcock and Johnson, 1977)]. Although all children surpassed this threshold of normal intelligence, suggesting that they could be reasonably expected to understand and perform other behavioural tasks, 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). Given this difference, the potential effect of IQ on other behavioural measures was assessed.

Significant within-groups correlation between IQ and behavioural performance was demonstrated only for a composite measure of reading and spelling (Pearson correlations; LP: $r = 0.759$, $P = 0.007$; NL: $r = 0.817$, $P = 0.007$; composite score based on components from Wilkinson, 1993). Controlling for IQ on this measure of reading and spelling, LP children still demonstrated generally poorer scores than NL children [univariate ANOVA (analysis of variance: $F_{1,17} = 9.223$, $P = 0.007$, mean: NL = 116, LP = 84]. Children were selected such that there was no overlapping of scores between NL and LP groups on this measure.

Performance on a task requiring discrimination of synthesized speech sounds from along a continuum that varied only in the onset frequency of the third formant (F_3), spanning from /da/ (2580 Hz) to /ga/ (2180 Hz), was poorer in LP than NL children [independent samples t-test: $t_{18} = 4.289$, $P = <0.001$, mean just-noticeable difference between sounds in Hz (represents discrimination of sounds with 69% accuracy): NL = 87, LP = 198; see Carrell *et al*., 1999 for methodological details]. Children were selected such that there was no overlapping of scores between NL and LP groups on this measure. Performance on this same task, using a different continuum that varied only in the duration of the formant transition, spanning from /ba/ (10 ms) to /wa/ (40 ms), was no different between groups, and there was considerable overlap of scores between groups. Group similarities in discrimination along this /ba/–/wa/ 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 those stimuli. These screening procedures (i.e. differentiation on /da/–/ga/, similarities on /ba/–/wa/; described previously by Kraus *et al*., 1996) permit identification of children who are more likely to demonstrate auditory–perceptual bases for their language problems, thus enabling more focused study of such specifically-auditory phenomena.

In accordance with the Declaration of Helsinki and 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.

Stimuli and recording—general

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).

Stimuli were presented by a PC-based stimulus delivery system (Compumedics Gentask) that 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 sound pressure level. Silver-silver chloride electrodes (impedance <5 kΩ) were used. Data were collected at a sampling rate of 20 000 Hz, with a gain of 5000. Butterworth digital filters (22 dB/octave slope) were used for all recordings.

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 sound pressure level.

Stimuli and recording—brainstem

Stimuli were presented in trains consisting of four stimuli, separated within a train by 12 ms inter-stimulus intervals (ISI; time within a train between stimulus offset and subsequent stimulus onset). The inter-train interval (ITI; time between 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.

Electrodes were placed on the right mastoid, forehead, and at Cz. These acted as reference, ground and active electrodes, respectively. Data were digitally bandpass filtered online from 100 to 2000 Hz. Trials with artefacts that measured in excess of ±35 μV were online 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.

Stimuli and recording—cortical

Stimuli were presented in quiet and in background noise (signal-to-noise ratio +15 dB). White noise was generated by a PC-based stimulus delivery system (Bio-Logic). The speech and noise signals were combined in a mixing board (Optimus) and presented to the earphone transducer. Stimuli were presented in trains consisting of four stimuli separated by a 360 ms ISI. The ITI was 1060 ms.

Electrodes were placed on the nose, forehead, superior and outer canthus of the left eye, and at Cz. These acted as reference, ground, eyeblink monitor and active electrodes, respectively. Data were digitally bandpass filtered online from 0.05 to 50 Hz. Artefacts that measured in excess of 100 μV were online rejected from inclusion in the averaged response. The recording window was 405 ms, including a 5 ms pre-stimulus period. The final averages were composed of two blocks of 500 responses (a total of 1000 responses) per position in the stimulus train, per signal-to-noise ratio.

Data analysis—brainstem

Averaged responses to the first stimulus in the train are reported. 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 extremes. The peak-to-trough duration of the wave V–V_n complex, spanning ∼6.2–7.2 ms post-stimulus-onset, is reported here. This is a component of the composite measure of wave V–V_n slope, reported by Wible *et al*. (2004) (wave V–V_n slope = wave V–V_n amplitude/wave V–V_n duration). This measure is interpreted as reflecting the synchronization of the generation and/or transmission and subsequent scalp-recorded summation of underlying neural activity. Specifically, the wave V–V_n complex is thought to primarily reflect lateral lemniscal input to the inferior colliculus (wave V), and subsequent dendritic processing in the inferior colliculus (wave V_n) (Møller and Jannetta, 1985). A more detailed discussion of speech-evoked ABR analysis techniques is provided by Russo *et al*. (2004).

Data analysis—cortical

The latency range that was investigated for each response waveform was from 50 to 300 ms post-stimulus-onset. Within each subject and quiet/noise condition, Pearson correlation *r*-values were calculated between responses to the first and fourth (final) stimuli in the train. These correlations are interpreted as reflecting the degree to which the morphological features (e.g. peaks and troughs) of the response to the first stimulus are maintained in the response to the fourth stimulus. High correlation (approaching 1) indicates preservation of waveform 'shape'; the timing of peaks and troughs is consistently and synchronously maintained across responses to repeated stimuli. Low correlation (approaching 0) indicates alteration of waveform shape; timing of morphological features is altered between responses to first and fourth stimuli. This measure is relatively independent of overall response amplitude, in the sense that a waveform may have its amplitude increased or decreased by a scaling factor, without having any effect upon its correlation with another waveform.

Correlations between responses to the first and fourth stimuli in a train, presented in quiet (Q1Q4), reflect the relative instability of response morphology/timing due to repetition of stimuli. Correlations between responses to the first and fourth stimuli, presented in noise (N1N4), reflect this repetition effect in the presence of background noise. These correlations were compared in Wible *et al*. (2002). The data reported in this study are the differences between those correlations (Q1Q4 – N1N4), reflecting the degree to which the addition of noise affects the morphology of the cortical representation of repeated stimuli. A large positive difference score indicates a more pronounced effect of noise on reducing the correlation between repeated responses, which would thus suggest degradation of the system's ability to consistently and synchronously represent stimulus features across repetitions. To transform correlation values to an approximately normal distribution for the purposes of parametric statistical analyses, Pearson *r*-values were converted to z'-scores using Fisher's transformation $\{z' = 0.5 \times \ln [(1 + r)/(1 - r)]\}$.

Results

The duration of the wave V–V_n complex was more prolonged in LP children compared with NL children (independent samples *t*-test: $t_{18} = 2.474$, $P = 0.024$). There were no group mean differences in wave V or V_n latencies or amplitudes. Since (i) NL and LP groups did not differ in wave V latency or

amplitude and (ii) wave V–V_n duration is interpreted as the relative latency of wave V_n with respect to wave V, waveforms were normalized via the following procedure (for purposes of visualization only).

Each child's waveform was shifted along latency and amplitude axes so that the resultant, normalized wave V matched the average latency and amplitude calculated for unnormalized wave V for the entire group of combined NL and LP children. Averaged waveforms for NL and LP groups were then constructed from these normalized individual waveforms. These clearly emphasize the prolonged relative latency of wave V_n with respect to wave V in the group of LP children (Fig. 1, *top*). Group differences in wave V–V_n duration can be observed in the scatter plot of individual data, which also indicates the non-overlapping ranges of ±1 standard error from the group means (Fig. 2).

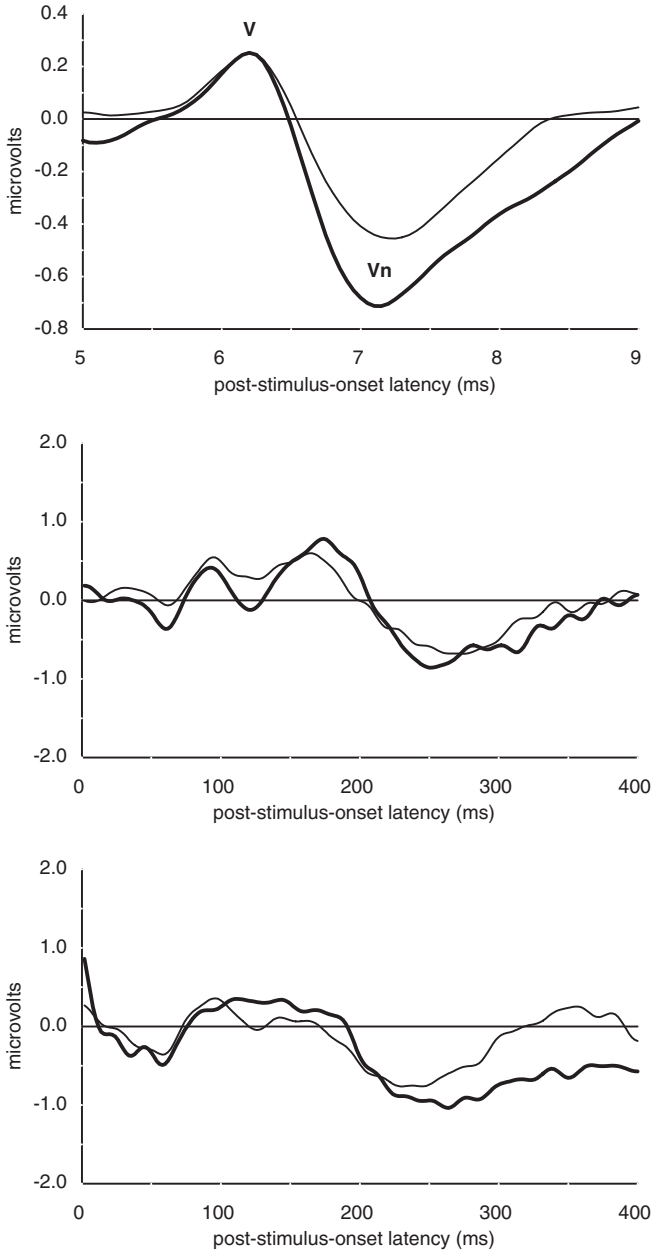

Fig. 1 *Top*: normalized mean auditory brainstem response waves, V and V_n, in response to the first stimulus in the train, recorded from NL (thick line) and LP (thin line) children. *Middle and bottom*: mean auditory cortical responses to the first (thick line) and fourth (thin line) stimuli in the train, presented in noise, recorded from NL (*middle*) and LP children (*bottom*).

The effect of noise in diminishing the correlation between cortical responses to repeated stimuli was more pronounced in LP children compared with NL children (independent samples *t*-test: $t_{18} = 2.470$, $P = 0.024$). The effect of noise on cortical inter-response correlations produced a significant degradation with respect to quiet in LP children only (i.e. the noise effect was significantly non-zero; one-sample *t*-test: $t_{10} = 5.059$, $P < 0.001$). Mean cortical waveforms are shown in Fig. 1 (NL, *middle*; LP, *bottom*). For more detailed inspection of cortical waveforms across repetition and noise conditions, and across slightly larger NL and LP groups which include the children in the present study, see Wible *et al*. (2002). Group differences in this effect of noise on cortical inter-response correlations can be observed in the scatter plot of individual data, which also indicates the non-overlapping ranges of ±1 standard error from the group means (Fig. 2).

A strong correlation between brainstem and cortical auditory processing was demonstrated by the NL children; decreased duration of the ABR wave V–V_n complex related to decreased differences in inter-response correlations between quiet and noise conditions [Pearson $r = 0.949$ ($r^2 = 0.901$), $P < 0.001$]

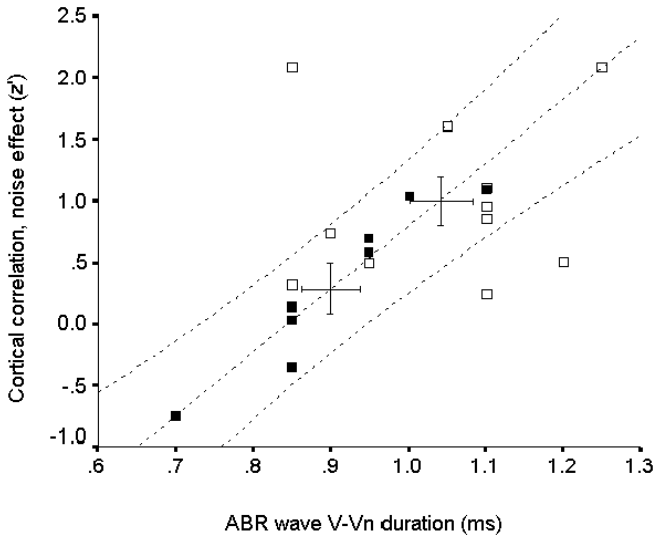

Fig. 2 Individual subject (NL = black, LP = white) and group mean and standard error data indicating duration of /da/-evoked ABR waves V–V_n and the effect of noise on the correlation between cortical responses to repeated /da/ stimuli (noise effect = correlation in quiet – correlation in noise; larger positive value indicates more pronounced degradation due to noise). Group mean data are indicated by the intersection of the standard error bars. Lower-left mean and error bars correspond to NL children, upper-right to LP children. The linear fit for the NL data is indicated by the central dashed line and is flanked by dashed lines indicating the limits of the range for prediction of individual data points with 95% certainty.

(Fig. 2). A significant correlation between the brainstem and cortical measures was not observed in the entire group of LP children. However, the relationship described for NL children was evident in a substantial portion of the LP children; a majority of the LP children (73%; eight out of 11) fell within the predicted interval with 95% certainty, based on the regression line that was fitted to the NL brainstem and cortical data (Fig. 2). Upon removal of the three children who fell beyond that confidence interval, a strong correlation between the brainstem and cortical measures was demonstrated among the remaining LP children [Pearson $r = 0.832$ ($r^2 = 0.692$), $P = 0.010$]. Removal of the three LP subjects also resulted in a strong correlation between brainstem and cortical physiology in the group that combined all NL children and the remaining eight LP children [Pearson $r = 0.919$ ($r^2 = 0.845$), $P < 0.001$]. This correlation describes 85% of the total children in this study in a sample that was essentially equal parts NL (53%) and LP (47%) children.

A test of homogeneity of regression confirmed that the slopes of the regression lines did not differ between the NL children and the eight remaining LP children (i.e. those who fell within the NL-defined range), thus satisfying a requirement for covariate analysis. Upon covarying ABR wave V–V_n duration, no difference was observed between NL children and the subset of eight LP children during between-groups comparison of the effect of noise on cortical inter-response correlations.

Although NL and LP children differed in IQ, there was no correlation between IQ and the measure of brainstem wave V–V_n duration, or between IQ and the effect of noise on correlation of cortical responses to repeated stimuli. Thus, there was no statistical motivation to believe that group differences in IQ contributed systematically to group differences on, or relationships between, these measures of brainstem and cortical processing. As a result, IQ was not incorporated as a covariate for any other analyses of these physiological measures.

Discussion

These findings suggest that, in the normal system, increased synchrony among mechanisms that encode transient acoustic information at the level of the brainstem contributes to more robust processing at the cortical level. The enhanced cortical processing reflects more consistently precise timing when representing rapidly presented signals in the presence of acoustic masking noise. Alternatively, prolonged duration of brainstem encoding of speech–sound onset, suggesting less precise timing of generation and/or transmission of responses in the lateral lemniscus and/or inferior colliculus, relates to 'weaker' cortical activity. This degraded cortical processing is more susceptible to pronounced disruption of timing of peak features when extracting and encoding rapidly presented acoustic signals that have been masked by noise.

Given this relationship between brainstem and cortical processing in a group of children who demonstrate normal language and auditory perceptual skills, the observed weakening of such a systematic relationship in a group of children who demonstrate difficulty with auditory perception and language is quite telling. A general hypothesis—motivating much research in this area of neuroscience—is that abnormal processing of the acoustic elements of speech contributes to abnormal development of language skills. Thus, the demonstration of a compromised relationship between brainstem and cortical processing of speech sounds could serve as a prime indicator of disrupted physiological mechanisms that may underlie abnormal perception of speech and subsequently poor development of language skills.

However, although apparently abnormal as a group, most LP children demonstrated measures of brainstem and cortical processing that were proportionally related in a manner similar to NL children. To emphasize the relative narrowness of those ranges, it should be noted that this confidence interval was somewhat restrictive, having been established for a sample that demonstrated very high correlation between the brainstem and cortical measures [$r = 0.949$ ($r^2 = 0.901$), as described above for NL children]. While responses from these LP children were generally degraded compared with NL children on both individual measures of brainstem and cortical auditory processing, the proportional relationship between these measures established by NL children was maintained. In this respect, most of the LP children demonstrated processing that fell toward a tail end of a continuum of normally coordinated processing, rather than representing the function of a completely novel system exhibiting markedly different transformations throughout the auditory pathway.

The lack of a group difference on the cortical measure when controlling for the brainstem measure further supports a model which posits that most language-impaired children share similar mechanisms with normal children that link brainstem and cortical auditory processing. Abnormal cortical processing in most LP children may primarily be a result of corrupted 'input' to the thalamo-cortical circuitry—possibly a result of degraded processing and/or transmission at the lateral lemniscus and/or inferior colliculus. Admittedly, this is somewhat at odds with evidence of abnormal anatomy at the thalamic and cortical levels in language impaired subjects (Galaburda, 1993). Alternatively, this relationship could suggest that processing in the lateral lemniscus and/or inferior colliculus is fairly consistent across all children, but that the signal is disrupted at even lower levels of the brainstem—or even the auditory periphery—and thus affects processing at all higher levels. Although our previous work describes apparently normal peripheral and low-brainstem auditory processing (Wible *et al*., 2004), others have suggested such regions as contributing to auditory-based learning problems (Muchnik *et al*., 2004).

Two of the three LP children who fell beyond the NL-defined prediction interval demonstrated particularly degraded brainstem processing with respect to their relatively robust cortical processing. These children would be prime candidates for investigation of compensatory mechanisms

by which intact cortical processes may have developed in spite of compromised brainstem processing—perhaps via converging input from multiple, parallel, non-primary pathways. The third LP child who fell beyond the prediction interval demonstrated particularly degraded cortical processing with respect to relatively precise brainstem encoding. This may reflect abnormal anatomy and/or physiology localized fairly exclusively to the level of the auditory thalamus and/or cortex beyond the essentially normal, low-level sensory processing in the auditory brainstem.

It would be reasonable to hypothesize that the learning problems experienced by these three children may be in some way rooted in the deviation from the typical functional linkage between brainstem and cortical representation of the acoustic structure of speech sounds demonstrated by the majority of the LP children and all the NL children. Given the heterogeneous composition of the population of children with learning problems, the delineation of LP children into groups that do and do not demonstrate relatively normal relationships between measures of brainstem and cortical processing could be immensely helpful in identifying different underlying causes of auditory-perceptually-based language impairment. Such classification could contribute to more refined development of rehabilitation programmes specifically tailored to effectively address different suspected causes.

This relationship between the timing of auditory brainstem encoding of speech sound onset and subsequent sensitivity of cortical processes to degradation by noise is especially interesting in light of related findings among groups of similar children (Hayes *et al*., 2003; Warrier *et al*., 2004). In these studies, children who demonstrated the most training-related improvement in correlations between auditory cortical responses recorded in quiet and noise were the same children whose ABR wave V_n latencies were delayed beyond previously established normative values (King *et al*., 2001). [(The peak referred to here as wave V_n is referred to as 'wave A' by King *et al*. (2001) and Hayes *et al*. (2003)]. Consistent with the present findings, we conclude that the cortical responses that were most degraded by noise were likely related to processing in the auditory brainstem which was the most temporally degraded.

While the studies by Hayes *et al*. (2003) and Warrier *et al*. (2004) suggested relations between brainstem timing and the efficacy of auditory training on cortical response morphology, there were no training-induced changes in the timing of this brainstem response. This suggests that phasic, brainstem processing of transient speech–sound onset was not malleable by training. However, recent work suggests that later portions of the auditory brainstem response, tonically encoding periodic features of the stimulus (e.g. vowels) in the frequency following response, are in fact sensitive to training (Russo *et al*., 2005). The ability to maintain synchronized representation of frequency following response in noise, with respect to quiet, was improved after auditory-based training, suggesting plasticity of early, low-level tonic encoding in the auditory brainstem. This disjunction between plastic, tonic encoding of periodic acoustic features and non-plastic, phasic encoding of transient acoustic features further illuminates the need for expanded investigation of low-level sensory encoding in the auditory brainstem. This would allow a description of which neuronal populations—and subsequently representations of which acoustic patterns—are more or less susceptible to modulation, and when, by what mechanisms, and in which populations of human listeners.

Acknowledgements

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