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Interaural Cross Correlation of Event-Related Potentials and Diffusion Tensor Imaging in the Evaluation of Auditory Processing Disorder: A Case Study

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Abstract

In a previous publication (Jerger et al, 2002), we presented event-related potential (ERP) data on a pair of 10-year-old twin girls (Twins C and E), one of whom (Twin E) showed strong evidence of auditory processing disorder. For the present paper, we analyzed cross-correlation functions of ERP waveforms generated in response to the presentation of target stimuli to either the right or left ears in a dichotic paradigm. There were four conditions; three involved the processing of real words for either phonemic, semantic, or spectral targets; one involved the processing of a nonword acoustic signal. Marked differences in the cross-correlation functions were observed. In the case of Twin C, cross-correlation functions were uniformly normal across both hemispheres. The functions for Twin E, however, suggest poorly correlated neural activity over the left parietal region during the three word processing conditions, and over the right parietal area in the nonword acoustic condition. Differences between the twins' brains were evaluated using diffusion tensor magnetic resonance imaging (DTI). For Twin E, results showed reduced anisotropy over the length of the midline corpus callosum and adjacent lateral structures, implying reduced myelin integrity. Taken together, these findings suggest that failure to achieve appropriate temporally correlated bihemispheric brain activity in response to auditory stimulation, perhaps as a result of faulty interhemispheric communication via corpus callosum, may be a factor in at least some children with auditory processing disorder.

Key Words: Auditory processing disorder, cross correlation, dichotic listening, event-related potentials, magnetic resonance imaging, twins

Abbreviations: APD = auditory processing disorder; CVC = consonant-vowel-consonant; DTI = diffusion tensor imaging; EEG = electroencephalographic activity; ERP = event-related potential; FA = fractional anisotropy; LI = lattice index; MRI = magnetic resonance imaging; ROI = region of interest

Sumario

En publicaciones previas (Jerger y col., 2002), presentamos información sobre potenciales relacionados con el evento (ERP) en un par de niñas gemelas de diez años de edad (gemelas C y E), una de las cuáles (la gemela E) mostró evidencia firme de un trastorno de procesamiento auditivo. En el presente trabajo, analizamos las funciones de correlación cruzada de las ondas de ERP generadas en respuesta a la presentación de estímulos meta, tanto al oído derecho como al izquierdo, en un paradigma dicótico. Existieron cuatro condiciones: tres que involucraban el procesamiento de palabras

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reales, tanto para metas fonémicas, semánticas o espectrales, y uno involucrando el procesamiento de señales acústicas no lingüísticas. Se observaron diferencias marcadas en las funciones de correlación cruzada. En el caso de la gemela C, las funciones de correlación cruzada fueron uniformemente normales en ambos hemisferios. Las funciones de la gemela E, sin embargo, sugieren actividad neural pobremente correlacionada en la región parietal izquierda, durante las tres condiciones de procesamiento de palabras, y en el área parietal derecha, para las condiciones acústicas no lingüísticas. Las diferencias entre los cerebros de las gemelas se evaluaron utilizando resonancia magnética nuclear por difusión de tensor (DTI). Para la gemela E, los resultados mostraron una anisotropía reducida a largo del cuerpo calloso sobre la línea media y de las estructuras laterales adyacentes, sugiriendo una reducida integridad de la mielina. Estos hallazgos sugieren que la dificultad de lograr, en respuesta a estímulos aditivos, actividad cerebral bi-hemisférica con apropiada correlación temporal, como resultado de una comunicación inter-hemisférica defectuosa a través del cuerpo calloso, puede ser un factor involucrado en al menos algunos niños con trastornos de procesamiento auditivo.

Palabras Clave: Trastorno de procesamiento auditivo (APD); correlación cruzada, audición dicótica, potenciales relacionados con el evento (ERP), imágenes por resonancia magnética, gemelos

Abreviaturas: APD = trastorno de procesamiento auditivo; CVC = consonante-vocal-consonante; DTI = imágenes por tensor de difusión; EEG = actividad electroencefalográfica; ERP = potenciales relacionados con el evento; FA = anistropía fraccionaria; LI = índice de celosía; MRI = imágenes por resonancia magnética; ROI = región de interés

More than 25 years ago, Sayers et al (1974) elegantly demonstrated that the waveform of a suprathreshold auditory evoked potential could be reproduced by modifying the spectral components of a subthreshold evoked response according to the phase spectrum of the original waveform. In other words, the evoked response to the suprathreshold stimulus could be created by simply reordering the phases of spectral components in the subthreshold stimulus condition, comprised presumably of spontaneous EEG (electroencephalographic) activity alone. Sayers et al concluded that "at least with some subjects, effective stimuli act by synchronising or controlling the phases of spectral components of the spontaneous EEG activity already present" (1974, 482).

More recent research has revisited and highlighted the importance of temporally correlated activity in neural processing. After reviewing a number of studies concerned with rhythmic and synchronous neural activity, Salinas and Sejnowski (2001) concluded that substantial variations in correlations between and among neural elements are observed even though mean firing rates are held relatively constant. They further noted that such rate-independent modulations in synchrony have been linked to changes in expectation, attention, response latency, and rivalry. Based on these findings, they suggest that the role of temporally correlated brain activity might be "to control the strength of a signal, and hence the downstream circuits that it reaches, rather than the nature of the information that it conveys" (2001, 548). In a subsequent study, Makeig et al (2002) analyzed electroencephalographic (EEG) data from a visual selective attention task in an effort to identify the neural mechanisms underlying the event-related potential (ERP). In contrast to the prevailing view that ERPs represent neural activity within discrete, functionally defined cortical regions, they concluded that ERP features derive from changes in the dynamics of ongoing neural synchrony within scalp-recorded EEG activity, specifically "phase resetting" of ongoing EEG processes.

Is it possible that at least one factor underlying auditory processing disorder (APD) in children may be failure to achieve appropriate temporally correlated brain activity in response to auditory stimulation? Is it further possible that such failure may be related to faulty communication between the two hemispheres via the corpus callosum? In the present paper, we seek answers to these questions by applying temporally sensitive correlation techniques to data derived from twin 10-year-old girls, one of whom showed strong symptoms of APD. We have reported conventional behavioral and electrophysiological data for these twins in a previous publication (Jerger et al, 2002). In the present paper, we have subjected the electrophysiological data to cross-correlational analysis. In addition, we studied the brain of each twin in the region of the corpus callosum and adjacent lateral structures by means of diffusion tensor magnetic resonance imaging (DTI).

METHODS

Correlation Analysis

A useful technique for describing and quantifying relations among temporally varying events is the cross-correlation function (Stanley, 1975; Stearns, 1975; Beauchamp and Yuen, 1979; Regan, 1989). Consider two event-related potential waveforms, A and B. Each waveform is defined by a voltage level at each of 1000 1 msec time intervals. Thus, the two waveforms can be represented by 1000 pairs of voltage levels. From these 1000 pairs of numbers, a standard Pearson product-moment coefficient of correlation (r) can be computed. Now suppose that one of the waveforms is displaced in time relative to the other waveform by a specified time interval (e.g., 1 msec) and the Pearson r is recomputed. Let "tau" represent the amount of time displacement, and let tau vary in 1 msec intervals in both directions. Now we can plot the coefficient, r, as a function of time displacement, tau. If the two waveforms being correlated are identical, the resulting function is called the "autocorrelation function." If, on the other hand, the two waveforms are different, then the resulting function is called the "cross-correlation function."

Figure 1 illustrates these two concepts. The functions are based on the data from a 10-year-old boy with normal hearing and no auditory complaints. ERP waveforms were generated in an "oddball" paradigm in which the nontarget stimulus was a pair of dichotically presented, unrelated CVC words. The target stimulus was a CVC word chosen from the semantic category "names of animals" (e.g., "cat," "dog," "pig," etc.). It was paired with a randomly selected CVC word

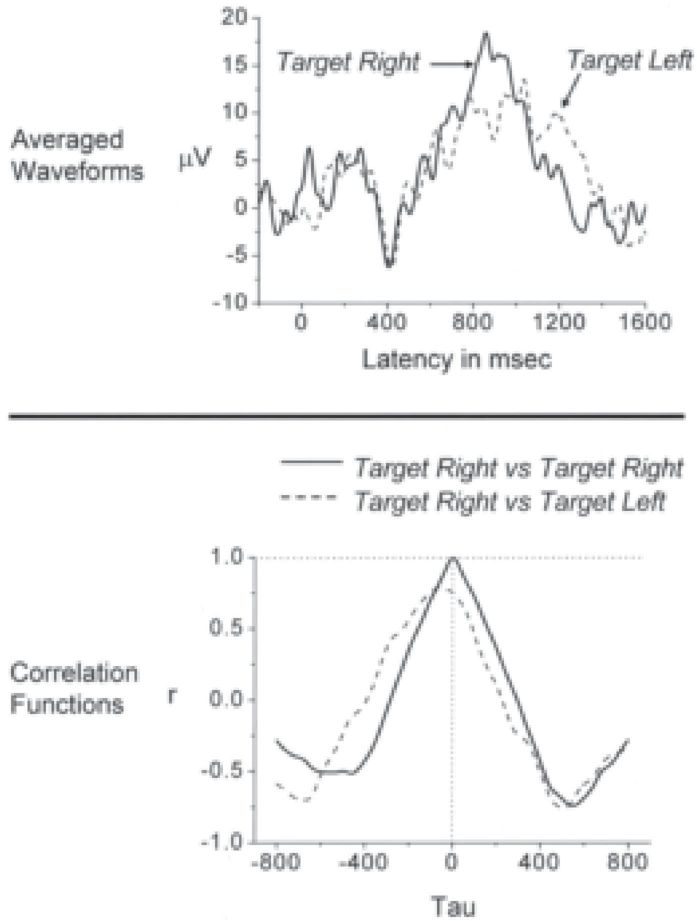

Figure 1. Examples of autocorrelation and cross-correlation functions. Functions are derived from ERP waveforms generated by a ten-year-old boy in a dichotic listening task. Upper panel shows averaged waveforms at electrode Pz in target-right and target-left conditions. Lower panel shows correlation functions derived from these waveforms. When the target-right ERP waveform is correlated with itself at varying time displacements (tau), the result is an autocorrelation function. When the target-right waveform is correlated with the target-left waveform at varying time displacements, the result is a cross-correlation function.

in the opposite ear. In half of the target pairs the target word was presented to the right ear, in the other half to the left ear. Responses were separately averaged for target-right and target-left pairs. Both the original averaged waveforms, and the correlation functions derived from them, are shown for ERP responses at electrode Pz. In order to generate an autocorrelation function, the target-right waveform was correlated with itself as a function of the time displacement, tau. To generate a cross-correlation function, the target-right waveform was correlated with the target-left waveform as a function of tau.

In the case of the autocorrelation function, r = 1.0 at tau = 0. Then, as tau increases, either in the positive or negative direction, the correlation coefficient declines systematically and symmetrically. The cross-correlation function, relating the waveforms for target-right and target-left conditions, follows the autocorrelation function closely but fails to reach perfect correlation and is slightly asymmetric around tau = 0. It reflects the extent to which brain activation in response to right-sided targets correlated with brain activation in response to left-sided targets. The relatively high correlation in the vicinity of tau = 0 is not unexpected. In the absence of brain disorder, activation patterns should be similar irrespective of side stimulated. The slight displacement in the peak of the cross-correlation function quantifies the extent to which the target-right waveform must be delayed, relative to the target-left waveform, in order to achieve maximum synchrony (i.e., the right-ear advantage in this dichotic listening task).

In the remainder of this paper, we have applied cross-correlation analysis to dichotic listening data gathered on twin girls, one of whom showed strong evidence of APD. All cross-correlation functions were computed between target-right and target-left data. They ask to what extent the ERP waveforms generated by dichotic targets presented from the right side were temporally related to ERP waveforms generated by dichotic targets presented from the left side.

Diffusion Tensor Imaging

In recent years, a type of magnetic resonance imaging (MRI), called diffusion tensor imaging (DTI), has been applied to identification of white matter disease, such as multiple sclerosis. Typically the white matter of the brain normally allows water to diffuse preferentially in the direction of the fiber tract. Using DTI, it is possible to quantify, in particular brain structures, the degree to which diffusion anisotropy or tendency for diffusion occurs in a certain direction (see, e.g., Bammer et al, 2003). Destruction of the white matter, as occurs in multiple sclerosis, for example, results in reduced anisotropy, reflecting a demyelinating process (Filippi et al, 2001). Based upon our electrophysiological findings, we hypothesized that differences in the myelinating process between the twins might also be detectable using DTI.

Imaging Protocol

Diffusion tensor images were obtained from both twins after receiving consent from the Institutional Review Board. The imaging was performed on a General Electric Signa Horizon LX NV/i MRI scanner at 1.5 Tesla (General Electric, Waukesha, Wisconsin). Images were gathered in an axial plane with the following parameters: TR/TE = 6000/90, FOV = 220 x 220 mm, 3 mm slice thickness, NEX = 2. The diffusion tensor acquisition was performed using 25 diffusion-sensitized directions. Diffusion tensor and diffusion anisotropy values were calculated using software created locally. We chose to use the Lattice Index (LI) (Pierpaoli and Basser, 1996) as the measure of anisotropy due to its inclusion of neighboring voxels in the measurement value, which tends to improve SNR over the (more widely used) Fractional Anisotropy (FA) measure.

Imaging Analysis

Following the reconstruction and calculation of the LI, a region of interest (ROI) was created to include the corpus callosum along its length and from its most superior to inferior extents. From this a histogram was constructed of the Lattice Index across the region for each twin. Two ROIs were selected, one which included more lateral structures such as the internal capsule and pyramidal tracts, and one which contained only midline corpus callosum.

Participants

The twins were 10-year-old girls. One (Twin C) was doing well academically and was free of any APD symptoms. The other (Twin E) was doing less well academically and was rated by both parent and teacher as "at risk for APD" on the Children's Auditory Performance Scale (CHAPS; Smoski et al, 1998). Both twins scored within the normal range on tests of cognitive and language competence.

Behavioral tests failed to differentiate the twins, but ERPs generated by gap-detection tasks and dichotic listening tasks showed dramatic differences in amplitudes and topographic distributions. Results were interpreted to indicate a probable deficit in the interhemispheric transfer of auditory information. Complete details are available in our previous publication (Jerger et al, 2002).

Dichotic Listening Tasks

In this paper, we report data generated by the twins on four dichotic listening tasks. The participant was seated in a sound-treated room between two loudspeakers situated directly to the right and to the left of the participant's ears at a distance of 1.5 m. ERPs were generated in an oddball paradigm in which target events occurred on 30% of trials, 15% to the right side and 15% to the left side. The nontarget event was always a pair of unrelated single-syllable, consonant-vowel-consonant (CVC) words, one from each side.

There were four different types of target events: acoustic, phonemic, semantic, and spectral. Except for the spectral condition, all words were recorded by the same male talker. To produce an acoustic target, one of the words was replaced by a burst of sawtooth noise with a fundamental frequency of 120 Hz. Phonemic targets were words that rhymed with "jet" (e.g., "met," "get," "set," etc.). Semantic targets were names of animals (e.g., "cat," "dog," "pig," etc.). Spectral targets were randomly selected words spoken by a different male talker.

In all conditions the task was to press a button labeled "yes" whenever a target (noise burst or word) was heard from either side, and "no" if no target was heard.

Electrophysiological Recording Techniques

Event-related potentials (ERPs) were collected using the Neuroscan electrophysiological data acquisition system (SCAN 4.2, Neurosoft, Inc.). Continuous electroencephalographic activity (EEG) was recorded from 32 silver-silver-chloride electrodes mounted in an elastic cap (Neurosoft) affixed to the scalp according to the International 10-20 system. Electrode impedances were always less than 5 kohms. Eye movements and eye blinks were monitored via electrodes placed above and at the outer canthus of the left eye. EEG channels were referenced to linked mastoid electrodes with a forehead electrode as ground. Ongoing EEG activity was sampled at 1000 Hz, amplified, analog-filtered from 0.15 to 70 Hz (except 1.0–100 Hz for the eye channel), digitized, and stored for off-line analysis. Off-line, individual epochs, encompassing -200 to 1800 msec relative to stimulus onset, were derived. Individual epochs were rejected if the activity in the eye channel exceeded ±50 μV. Following artifact rejection, epochs were separately averaged for target and nontarget stimuli. Only epochs corresponding to correct behavioral responses were averaged. The average number of acceptable sweeps was 31 for Twin C and 40 for Twin E. Successfully averaged evoked-potential waveforms were then linearly detrended, baseline corrected relative to the 200 msec pre-stimulus interval, and digitally low-passed filtered at 20 Hz (-48 dB/octave). Cross-correlation functions between target-right and target-left conditions were constructed over a 1600 msec interval beginning at stimulus onset and extending from tau = +800 msec to tau = -800 msec.

RESULTS

Cross-Correlational Analysis

Figure 2 shows cross-correlation functions at 24 electrode locations for each twin. Each function represents the coefficient of correlation as a function of the time displacement (tau) between the waveforms in the target-right and target-left conditions. Data are from the phonemic condition. In the case of Twin C, functions are similar at all electrode locations. Each shows the expected peak in the vicinity of tau = 0 and declines systematically and relatively symmetrically from this peak. In the case of Twin E, however, cross-correlation functions are similar to Twin C for midline and right-hemisphere electrode sites but dramatically different in the posterior region of the left hemisphere. The superimposed boxes indicate electrode sites where the difference is particularly evident.

On the basis of this finding, we chose three electrode sites, P3, Pz, and P4, for more detailed presentation. Figures 3–6 compare cross-correlation functions at these three electrode sites for each of the four experimental conditions. Figure 3 shows the results for the phonemic condition. Twin C shows similar functions at all three electrode sites. In the case of Twin E, however, functions are similar at electrode P4 (right hemisphere), less similar at the midline Pz electrode, and substantially different at the P3 (left hemisphere) site.

Figure 4 shows similar findings for the semantic feature. Again, the functions are most similar to the right of midline (electrode

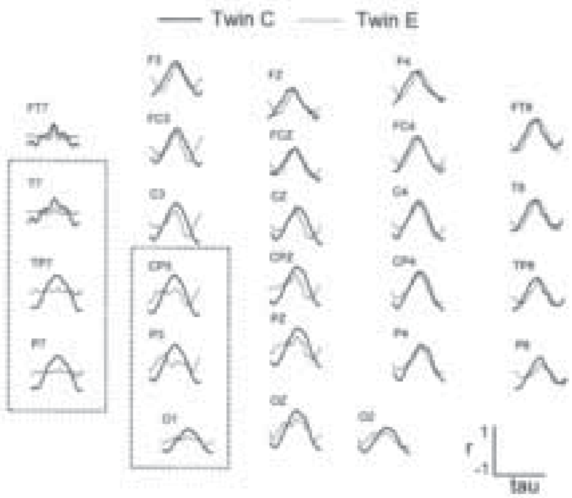

Figure 2. Cross-correlation functions for each twin at 24 electrode positions in the phonemic target condition. Rectangles indicate left-hemisphere regions in which there is a marked difference between the functions for the two twins. Note relatively normal functions for Twin E at P4 and CP4 electrode sites.

P4) and least similar to the left of midline (electrode P3). Figure 5 shows the same general result for the spectral feature. Functions are most similar at the P4 site and least similar at the P3 site.

In the case of the acoustic feature (Figure 6), however, the pattern is reversed. Now the functions are almost identical at the P3 and Pz electrode sites but less similar at the P4 site.

Table 1 summarizes the actual value of the coefficient r at the peak of the cross-correlation function at each electrode site for each twin in each of the four experimental conditions. Figure 7 plots these data graphically. Two conclusions seem evident. First, in the three conditions involving the processing of words (phonemic, semantic, and spectral), the coefficients for Twin E are uniformly lower than for Twin C. At the P3 site, for example, Twin C's coefficient of 0.862 contrasts sharply with Twin E's coefficient of 0.145. Only in the acoustic condition (sawtooth noise buzz) are Twin E's coefficients comparable to Twin C's. Indeed at Pz and P3 sites, they are actually larger. The second conclusion is that, in the three conditions involving word processing, Twin C's coefficients are relatively uniform across the three electrode sites, but Twin E's coefficients are higher on the right side of midline and lower on the left side. In the acoustic condition, however, the decline is in the opposite direction, higher correlation on the left side, lower on the right side.

Diffusion Tensor Imaging

Figure 8 shows histograms of Lattice Index (LI) values obtained over the ROI for each twin. Here focus is on the corpus callosum, the internal capsule and the pyramidal tracts. The values for Twin E show consistently less anisotropy, implying reduced myelin integrity, than the values for Twin C.

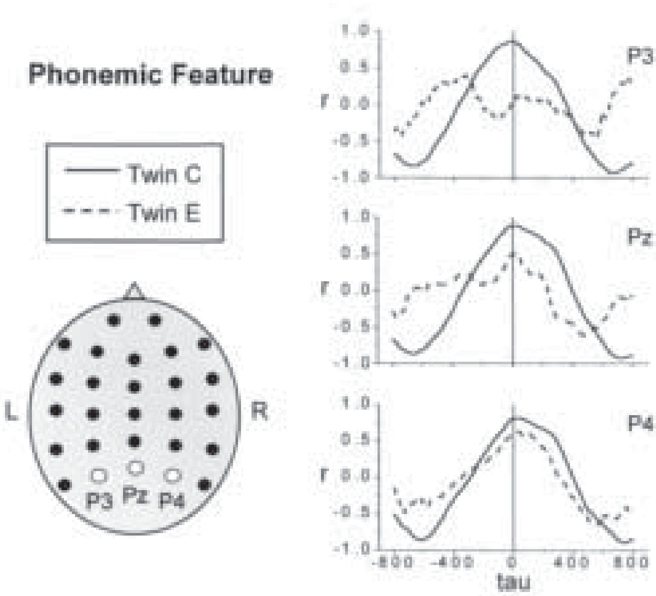

Figure 3. Comparison of cross-correlation functions for Twins C and E at three electrode positions, P3, Pz, and P4 in the phonemic condition.

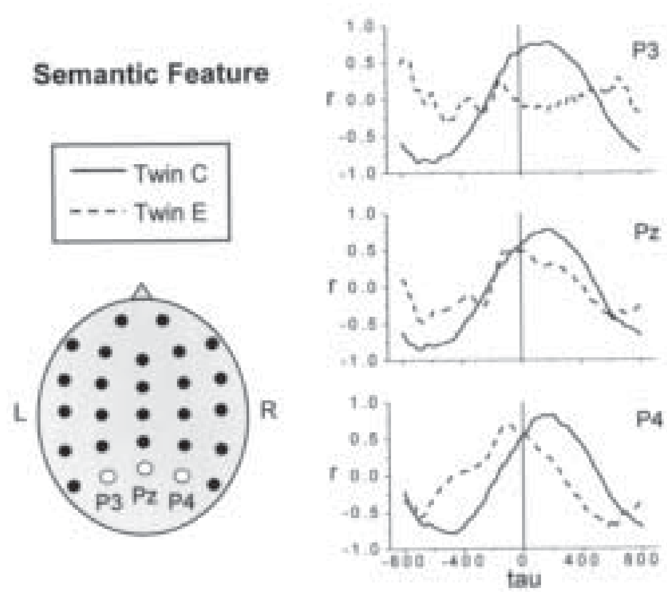

Figure 4. Comparison of cross-correlation functions for Twins C and E at three electrode positions, P3, Pz, and P4 in the semantic condition.

Table 1. Maximum Coefficients of Cross Correlation at Three Electrode Sites across Four Experimental Conditions

Condition	Electrode	Twin c	Twin E
Phonemic	P4	0.819	0.630
	Pz	0.885	0.523
	P3	0.862	0.145
Semantic	P4	0.815	0.685
	Pz	0.778	0.502
	P3	0.772	0.268
Spectral	P4	0.889	0.608
	Pz	0.927	0.559
	P3	0.882	0.307
Acoustic	P4	0.738	0.433
	Pz	0.710	0.800
	P3	0.629	0.857

Note: Pz is midline parietal electrode. P4 is to right of midline, P3 to left of midline.

In Figure 9, the region of interest is restricted to the corpus callosum. Results are similar to those of Figure 8, reduced anisotropy in Twin E. While it is difficult to judge the significance of these inter-twin differences statistically, the finding of reduced anisotropy in the region of the corpus callosum in Twin E is consistent with the hypothesis that her poorer interaural correlations may have derived from faulty interhemispheric communication.

DISCUSSION

The present results suggest that failure of temporally correlated activity in the two hemispheres of the brain may be a distinguishing feature of auditory processing disorder in some children. In the case of Twin C, cross-correlation functions between brain activity in response to target-right and target-left conditions was uniformly normal across the two hemispheres in all test conditions. In the case of Twin E, however, cross-correlation functions showed poorly correlated activity between target-right and target-left conditions. The abnormality was evident over the left parietal region in three conditions involving the dichotic processing of words and over the right parietal region in one condition involving the dichotic processing of nonword, acoustic targets.

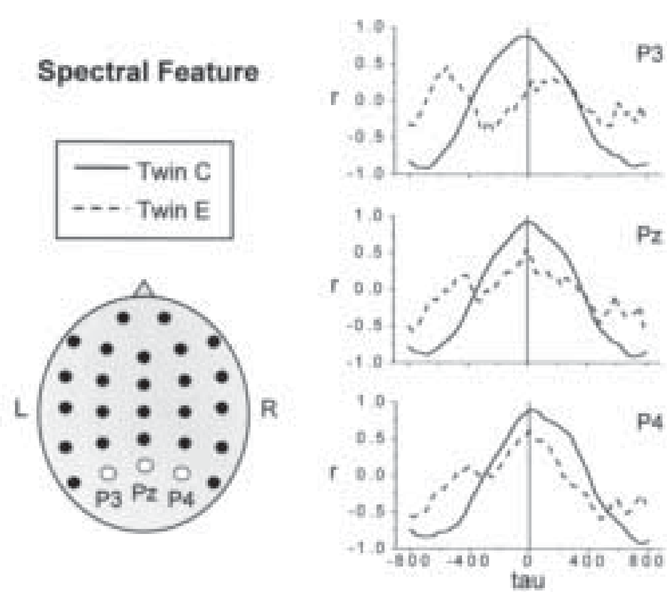

Figure 5. Comparison of cross-correlation functions for Twins C and E at three electrode positions, P3, Pz, and P4 in the spectral condition.

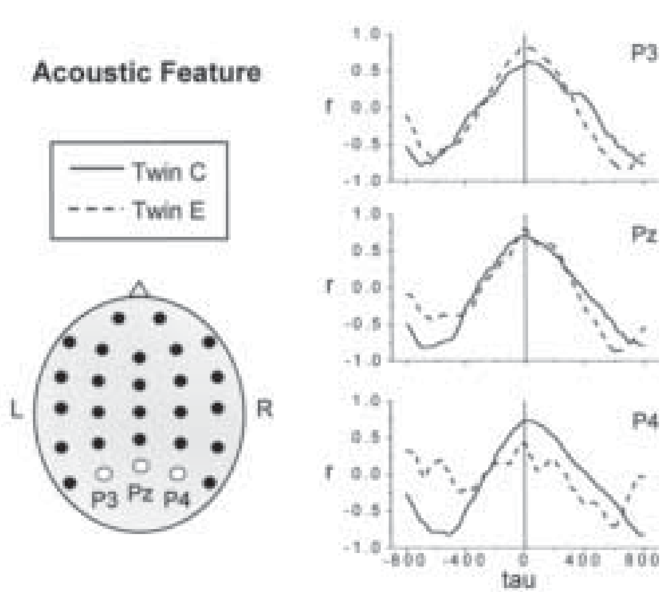

Figure 6. Comparison of cross-correlation functions for Twins C and E at three electrode positions, P3, Pz, and P4 in the acoustic condition.

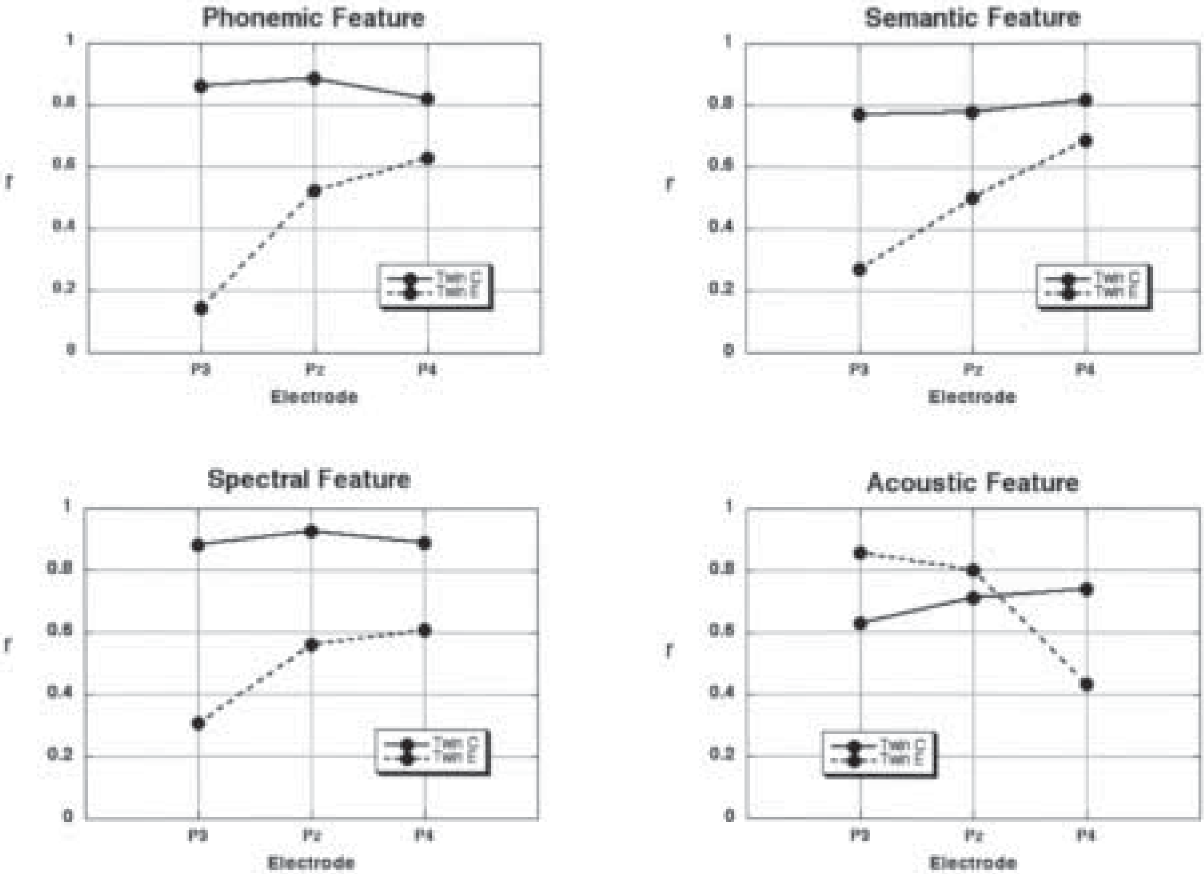

Figure 7. Correlation coefficients at peaks of cross-correlation functions for both twins at three electrode locations in four experimental conditions.

It could be argued that the degraded cross-correlation functions observed in Twin E were the simple consequence of poorer response amplitude. Arguing against this interpretation, however, is the fact that, in Twin E, cross-correlation functions were relatively normal over the right hemisphere in the three conditions involving word targets and over the left hemisphere in the one condition involving the acoustic target (see Figures 3–6). If low response amplitude accounted for the degraded cross-correlation

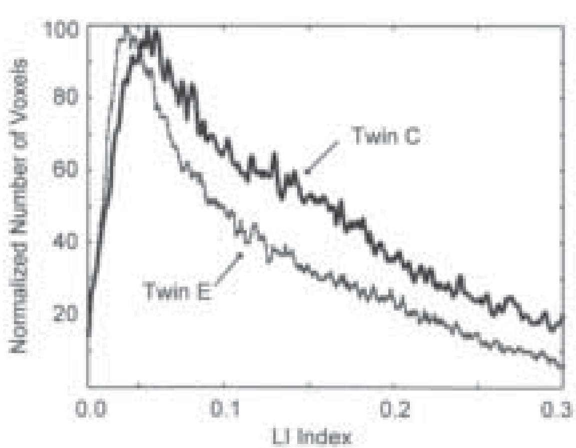

Figure 8. Results of diffusion tensor imaging. Histograms of Lattice Index (LI) values obtained from both twins. Large region of interest includes corpus callosum, internal capsule and pyramidal tracts. Note consistently lower anisotropy for Twin E.

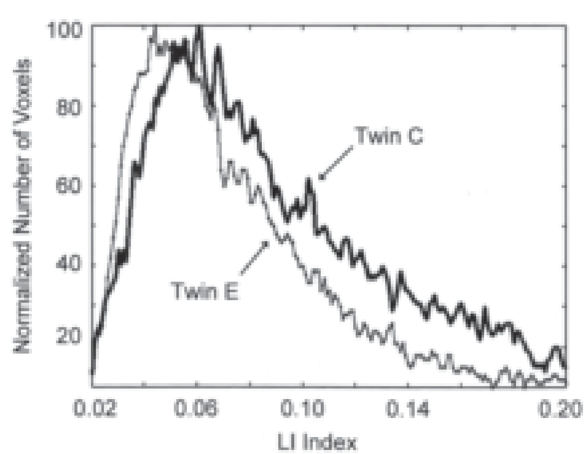

Figure 9. Results of diffusion tensor imaging. Histograms of Lattice Index (LI) values obtained from both twins. Smaller region of interest is restricted to corpus callosum. Note consistently lower anisotropy for Twin E.

functions, the effect should have been observed over both hemispheres.

Another source of potential concern is the possibility that electrodes in the P3 region of the scalp were in some way faulty in Twin E. Arguing against this possibility is the fact that, in the acoustic condition, the cross-correlation function was normal in Twin E at the P3 electrode (see Figure 6).

The importance of temporally correlated activity in the two hemispheres is underscored by the likelihood that the participation of both hemispheres may be required in difficult dichotic tasks. Banich (1998) has elaborated an earlier concept of Kinsbourne (1982) that, as task difficulty increases, the corpus callosum will shift from concentrating activation in one hemisphere to distributing activation between hemispheres. Banich's theory is well summarized by Liederman as follows:

> as task difficulty increases beyond the capacity of the resources of a single hemisphere, or when information engenders conflict, then bihemispheric processing is advantageous. As one hemisphere's resources or capacity is overtaxed by the processing requirements placed upon it, the other side of the brain will be recruited or activated to underwrite the processing. Banich conceptualizes this as the role of interhemispheric interaction, mediated by the corpus callosum, in dynamically modulating the processing capacity of the whole brain. [1998, p. 195]

Within this frame of reference we may hypothesize that a lack of temporally correlated activity in the two hemispheres interferes with bihemispheric processing in difficult listening tasks. Such a failure of bihemispheric correlation may be related, in Twin E, to evidence of faulty interhemispheric transfer via corpus callosum (Jerger et al, 2002), a conclusion buttressed by the present finding of reduced myelin integrity as demonstrated by the diffusion tensor imaging data, illustrated in Figures 8 and 9. Thus, the symptoms of auditory processing disorder, in at least some children, may reflect a fundamental deficit in the transfer of information between the hemispheres, leading to poorly synchronized activity from the two ears in a difficult dichotic listening task. To the extent that cross-correlation functions reflect such bihemispheric asynchrony, they may serve as biological markers of at least some auditory processing disorders.

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