Altered pathways for auditory discrimination and recognition memory in preterm infants

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Preterm infants are at increased risk for cognitive disorders, including impairments in recognition memory. This study evaluated the effects of extreme prematurity on the neural pathway for auditory recognition memory using event-related potentials (ERPs), a neurophysiological technique widely used in cognitive neuroscience. ERPs were recorded at term postmenstrual age in 35 preterm infants born at less than 32 weeks' gestation (22 males, 13 females; mean birthweight ([BW] 1154g, SD 374g) with normal brain ultrasounds, compared with 40 healthy, term newborns (1 to 3 days of age; 20 males, 20 females; BW 3672g, SD 420g). Because infants must be able to detect and discriminate sounds before recognizing them, two paradigms were used to assess these functions. The first evaluated the detection and discrimination of speech sounds. The second tested recognition of the mother's voice compared with a stranger's. Results showed significantly different patterns of speech sound discrimination in preterm infants compared with term infants. No evidence of maternal voice recognition was elicited from the preterm infants. No specific patterns of auditory detection or discrimination were associated with patterns of recognition memory, suggesting that the function of multiple neural pathways may have been altered in this group of preterm infants. These results provide a functional corroboration of magnetic resonance imaging studies showing effects of prematurity on early brain development, even among preterm infants with normal cranial ultrasonography.

See end of paper for list of abbreviations.

Preterm infants are at high risk for a wide range of cognitive impairments (Rose et al. 1988, 1991, 2001, 2002; Koller et al. 1997; Luciana et al. 1999; de Haan et al. 2000; Saigal et al. 2000; Taylor et al. 2000; deRegnier et al. 2002; Aylward 2003). These problems appear to be due to perinatal brain injury; however, it has been difficult to understand the mechanisms underlying the disruption of discrete neural pathways, and how they result in specific cognitive impairments. These difficulties occur in part because of the prolonged maturation of cognitive function, and because some aspects of brain development are influenced by experience, not only during early childhood but also, to a lesser extent, throughout the lifespan (e.g. synaptogenesis; Nelson 2002). Developmental tests for young infants contain many motor- or sensory-based items (Bayley 1993) that cannot directly measure cognitive functions such as memory or attention. Thus, to understand further the effects of prematurity on cognitive development, it is important to develop methods that can assess the longitudinal development of specific neural pathways that are important for cognitive abilities.

Recognition memory is a cognitive ability that can be assessed from birth (DeCasper et al. 1988; deRegnier et al. 2000, 2002). The neural pathway for recognition memory has been relatively well described. It includes input through the sensory cortices, projecting to the hippocampus and surrounding medial temporal lobe structures, with reciprocal projections to frontal, temporal, and parietal association areas through thalamic relays (Nelson 1995, deUngria et al. 2000, Clark et al. 2002). Studying recognition memory in preterm infants is particularly important because several studies of older infants and children have demonstrated impairments in recognition memory, which contribute to learning difficulties as these children mature (Rose et al. 1988, 1991, 2001, 2002; Luciana et al. 1999, deHaan et al. 2000, Taylor et al. 2000, Curtis et al. 2002).

The purpose of this study was to investigate the neural network for auditory recognition memory in preterm newborns with no evidence of brain abnormalities on cranial ultrasound. Given that recent studies have shown subtle evidence of global brain injury in some preterm infants with normal brain ultrasounds (see Maalouf et al. 1999, 2002; Peterson et al. 2000, 2002), we hypothesized that these preterm infants would show impairments in multiple aspects of auditory processing, including auditory detection, discrimination, and recognition memory.

Method

PARTICIPANTS

The study was conducted at the Children's Hospital and Clinics in St. Paul, MN, USA, and was approved by its Institutional Review Board. Informed consent was obtained from each family. Control infants were healthy term newborns, born between 39 and 41 weeks' gestation, with Apgar scores of at least 7 and 8 at 1 and 5 minutes respectively, and no history of maternal complications of pregnancy. Preterm infants were born between 24 and 32 weeks' gestation and had normal brain ultrasounds with no evidence of intraventricular hemorrhage or periventricular leukomalacia at approximately 1 week and 1 month of age. Brain ultrasounds were obtained using an 8.5MHz transducer and interpreted by an experienced pediatric radiologist.

Neurobiological risk scores (NBRS) were calculated for each preterm infant. This scale assigns points to assess the

presence, severity, and duration of adverse neonatal medical events, and correlates them with abnormal developmental outcome. Three risk groups have been identified, including low (<4), intermediate (5 to 7), and high risk (>8) for developmental abnormalities (Brazy et al. 1993). Medical records were also reviewed to ascertain the incidence of chronic lung disease (defined as oxygen requirement at 36 weeks' postmenstrual age), patent ductus arteriosus requiring treatment with indomethacin or surgical ligation, sepsis, and necrotizing enterocolitis.

Infants were excluded from either group if the birthweight was less than the 10th centile for gestational age or if there were any congenital anomalies. Infants of diabetic mothers were also excluded as previous studies have demonstrated altered patterns of memory development in this group of infants (deRegnier et al. 2000, Doherty and Hepper 2000). Hearing was screened using an otoacoustic emissions test and only those infants who passed the test were included in the study.

STUDY DESIGN

All infants were tested at 39 to 42 weeks after the mother's last menstrual period (i.e. 39 to 42 weeks postmenstrual age) in a behavioral state of active sleep (Thoman 1990), using event-related potentials (ERPs). ERPs are neurophysiological recordings used by cognitive neuroscientists to evaluate learning and memory. ERPs are recorded at the surface of the scalp and are the portion of the electroencephalogram (EEG) that reflects cognitive processing of discrete stimuli. The ERP is embedded in the raw EEG and is extracted by time-locking the stimulus presentation and then averaging the EEG over multiple presentations. The stimuli are chosen to be similar in physical properties but different in cognitive attributes, such as familiarity (Nelson and Monk 2001).

For this study, two paradigms were used to evaluate different parts of the neural network for recognition memory. First, detection and discrimination of speech sounds were evaluated using an ERP auditory change paradigm. In the adult, this paradigm activates the primary and association auditory cortex, as well as the supramarginal gyrus, anterior cingulate cortex, and dorsolateral prefrontal cortex (Wible et al. 2001, Sevostianov et al. 2002). No studies have evaluated patterns of neural activation in infants, but it should be noted that the dorsolateral prefrontal cortex matures late and is not thought to be active in the newborn infant (Nelson 1995, Huttenlocher and Dabholkar 1997).

For the auditory change paradigm, ERPs were recorded during 600 presentations of the speech sounds /bi/ and /gi/. These sounds were synthesized consonant-vowel syllables in a male voice of 230ms duration and 75db sound pressure level (described in Molfese 2000). One speech sound served as the frequent sound and was presented for 88% of the presentations. It was interrupted by a novel stimulus in 12% of the presentations. The choice of the frequent stimulus (/bi/ vs /gi/) was counterbalanced so that half of each group received /bi/ as the frequent stimulus and the remaining half received /gi/. The stimuli were presented every 800ms, and data were recorded for 50ms prestimulus and 750ms post-stimulus (Fig. 1).

The second paradigm assessed auditory recognition memory. Auditory recognition memory in newborns has been demonstrated in response to the maternal voice with behavioral and neurophysiological methods (DeCasper and Fifer 1980; deRegnier et al. 2000, 2002). In addition to the sensory areas indexed with the auditory change paradigm, recognition memory also involves the hippocampus and surrounding medial temporal lobe structures, with reciprocal projections to frontal, temporal, and parietal association areas through thalamic relays (Nelson 1995, deUngria et al. 2000, Clark et al. 2002).

For the recognition memory paradigm, ERPs were recorded in response to the mother's voice alternating with a stranger's voice for 120 presentations. The stranger's voice varied for each infant and was the maternal voice from the previous infant. To determine if extra experience with the maternal voice would augment recognition memory, half of the infants also received a 'familiarization period' consisting of 60 presentations of the maternal voice before beginning the 'mother–stranger' task (Fig. 2). The stimulus was the word 'baby', digitized and edited to 750ms and 78db sound pressure level, using the Sound Blaster program (Creative Labs, Inc; Milpitas, CA). Stimuli were presented at random intervals of 3900 to 4900ms to prevent the infant from anticipating the presentation of the maternal or stranger's voice (Regan 1989). Data were recorded for 100ms prestimulus and 2000ms poststimulus. All stimuli were presented to the right ear with an EAR tone 3-A insert earphone (Cabot Corporation, Indianapolis, IN).

The raw EEG and electrooculogram (EOG) were recorded using previously described procedures (deRegnier et al. 2000, 2002; Nelson and Monk 2001). Briefly, disposable Ag–AgCl electrodes were placed over midline (Pz, Cz, Fz) and lateral scalp sites (T3, T4), according to the International 10–20 system of electrode placement (Jasper 1958) and referenced to the bilateral mastoids. To code the maturity level of the auditory cortical response, electrodes were also placed at two lateral sites denoted CM3 and CM4 (Novak et al. 1989). For the purpose of artifact rejection, a bipolar channel of EOG was recorded from electrodes placed obliquely above and below the outer canthus of the right eye. Data were considered artifactual whenever the voltage exceeded 99.5% of the full scale voltage (SD 100μV) for 50ms at the scalp sites and 100ms at the EOG

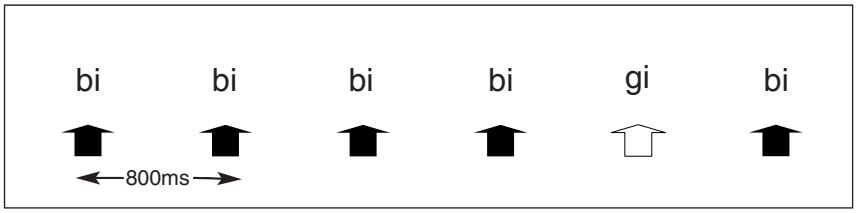

Figure 1: *Schematic representation of auditory discrimination paradigm. Event-related potentials were recorded as a frequent speech sound, in this case /bi/, and were interrupted by an infrequent sound, /gi/, on 12% of 600 trials. Stimuli were presented every 800ms.*

site. Mean artifact-free data were obtained by computer using previously described methods to create the mean ERPs (deRegnier et al. 1997, 2000; Nelson and Monk 2001).

DATA ANALYSIS

The ERP of newborn infants consists of peaks that occur early in the recording interval as well as slow wave activity that is often superimposed over the peaks but typically persists for the entire recording interval. Maturation of the early peaks follows a well-described sequence (Novak et al. 1989). The earliest response, seen in preterm infants and a small percentage of term infants, consists of a negative wave over both midline and lateral scalp sites (level I). With maturation, this component turns positive, first over the midline (level III), and then over the lateral scalp sites (level V). Most term newborn infants show maturity levels III to V, meaning that the midline positive component is typically seen but the lateral components may be negative or positive. The midline positive component (seen in levels III to V) appears to be the precursor of the adult P2 peak (Thomas and Crow 1994), and is thought to be generated in the primary auditory cortex. The lateral positive component is thought to be generated in the secondary auditory cortex (Novak et al. 1989). For this study, maturity levels were evaluated by examining the mean ERP obtained from the frequent stimulus in the auditory change paradigm at Cz and CM3 electrode sites during the time window 150 to 400ms, using the methods described by Novak et al. (1989).

Most newborn infants have achieved maturity levels III to V, and thus a positive midline component over Cz and Fz is a reliable finding in this age group. As in previous studies (deRegnier et al. 2000, 2002), the maximal positive peak amplitudes and latencies were measured by computer algorithm at Cz and Fz during the time window between 150 and 400ms.

Slow wave activity is seen at all electrode sites and over the entire recording intervals (Figs 3 and 4). Therefore, the remainder of the ERP data were analyzed by a computer algorithm integrating the positive and negative areas under the curve relative to baseline (Nelson and Monk 2001) at the five electrode sites (Pz, Cz, Fz, T3, T4) over the entire recording interval (0 to 750ms for the auditory change paradigm; 0 to 2000ms for the recognition memory paradigm).

Statistical analysis was performed using the Statview software (version 5.0). The percentage of infants achieving maturity level V was compared for the preterm and control groups using χ^2 tests. For each of the two paradigms, peak amplitudes and latency measurements (Cz, Fz) as well as areas under the curve (Pz, Cz, Fz, T3, T4) were evaluated by using repeated measures analysis of variance (ANOVA) using electrode site and stimulus type (frequent/infrequent stimulus or maternal/stranger's voice) as the repeated measures, and group (control, preterm) and order of testing (auditory change or recognition memory first versus second) as factors. For the recognition memory paradigm, familiarization period versus no familiarization period was included as a factor in the analysis as well. Follow-up statistical analyses were performed by using additional ANOVAs and/or Student-Newman–Keuls tests as specified in the results; *p* values were corrected for sphericity using Greenhouse–Geisser procedures where appropriate. All data are presented as mean and standard deviation (SD) or standard error of the mean (SEM).

Results

PARTICIPANTS

Of the 44 control infants tested, two were excluded for excessive artifacts and two for incorrect sleep state. Thus, 40 control infants (20 males, 20 females) provided data for both the auditory change detection task and the recognition memory task. Of the 40 preterm infants tested, four were excluded for excessive artifacts, and one because of insufficient data. Thus, 35 infants (22 males, 13 females) provided data for the recognition memory task and 33 (21 males, 12 females) for the

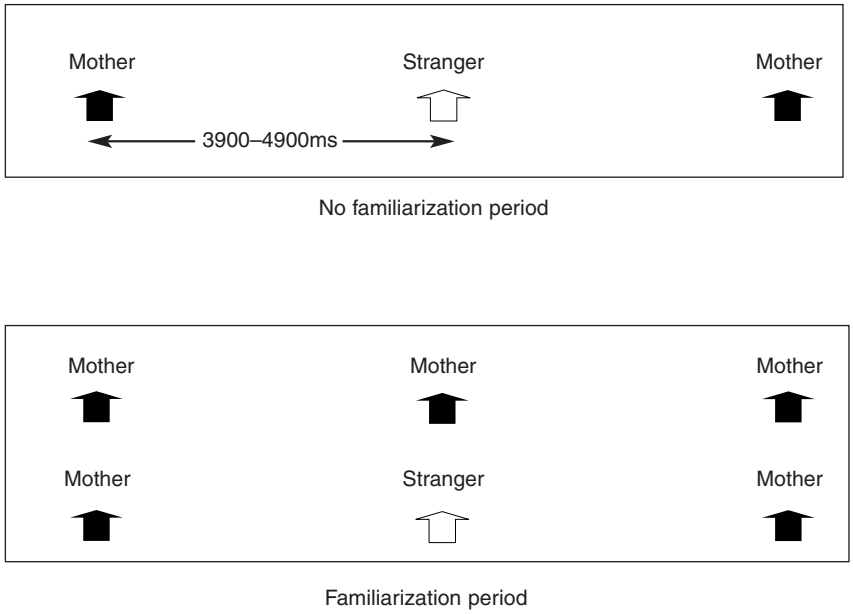

Figure 2: *Schematic representation of recognition memory paradigm. Event-related potentials were recorded as maternal voice alternated with a stranger's voice for 120 trials. Stimuli were presented at random intervals of 3900 to 4900ms. Half of infants received additional familiarization with maternal voice for 60 trials before alternating voices.*

auditory change detection task. Birthweights, gestational ages, ages at the time of the ERP test, number of interval days between discharge and the ERP test, incidence of chronic lung disease, patent ductus arteriosus, sepsis, and necrotizing enterocolitis, as well as NBRS are all shown in Table I. NBRS ranged from 0 to 9, with a mean of 2.7 (SD 2.2). As a group, these preterm infants scored in the low-risk category (NBRS score <4), although there were seven infants in the intermediate risk (NBRS score 5 to 7) and one in the high-risk category (NBRS score >8).

MATURITY LEVELS

The number of infants exhibiting level V maturity of the auditory cortex was similar in the control (23/40, 57%) and preterm groups (15/33, 45%, $p=0.309$).

Grand mean ERPs for the control and preterm infants to the frequent and infrequent speech sounds are shown in Figure 3.

SPEECH SOUND DISCRIMINATION, PEAK AMPLITUDES

Analysis of the peak amplitudes for the auditory change detection task revealed a main effect of group (preterm, control, $p=0.009$). This effect was due to lower mean peak amplitudes (summed across the Cz and Fz sites and both stimuli) in the preterm infants (2 SEM 0.3μV) compared with the control infants (3.6 SEM 0.4μV). There was also a main effect of electrode site. Summed across the preterm and control groups and stimuli, the mean peak amplitude at the Cz electrode (3.4 SEM 0.4μV) was larger than that seen at Fz (2.4 SEM 0.3μV, $p=0.03$), a typical finding for this age. There was no main effect of stimulus type or task order (auditory change before or after maternal voice recognition). There was no significant interaction in the ANOVA for peak amplitudes.

SPEECH SOUND DISCRIMINATION, LATENCY MEASUREMENTS

There was no main effect of group, stimulus type, electrode site, or task order. There was a significant interaction of stimulus and group ($p=0.044$). Follow-up of this effect using Student–Newman–Keuls testing showed that the latency to the peak elicited by the infrequent stimulus was shorter in the preterm group than in the control group (summed across the Cz and Fz sites; preterm group, 245ms SEM 10; control group, 285ms SEM 9.4; $p<0.05$), but the latency for the frequent stimulus was similar in the control and preterm group. This is likely to be a function of the early onset of the superimposed negative wave for the infrequent stimulus in the preterm group, described below and pictured in Figure 3.

SPEECH SOUND DISCRIMINATION, AREAS UNDER THE CURVE

For the areas under the curve, there was a significant group effect, with the preterm infants overall having more negative areas under the curve than the control infants across all five electrode sites and both stimuli (preterm group, 250μV-ms^2 SEM 116; control group, 251μV-ms^2 SEM 118; $p=0.014$). There were significant interactions of electrode site and group ($p=0.0324$) and stimulus and group ($p=0.0032$).

Follow-up stimulus × group ANOVAs were done at each of the five electrode sites to evaluate these effects further. At the Pz

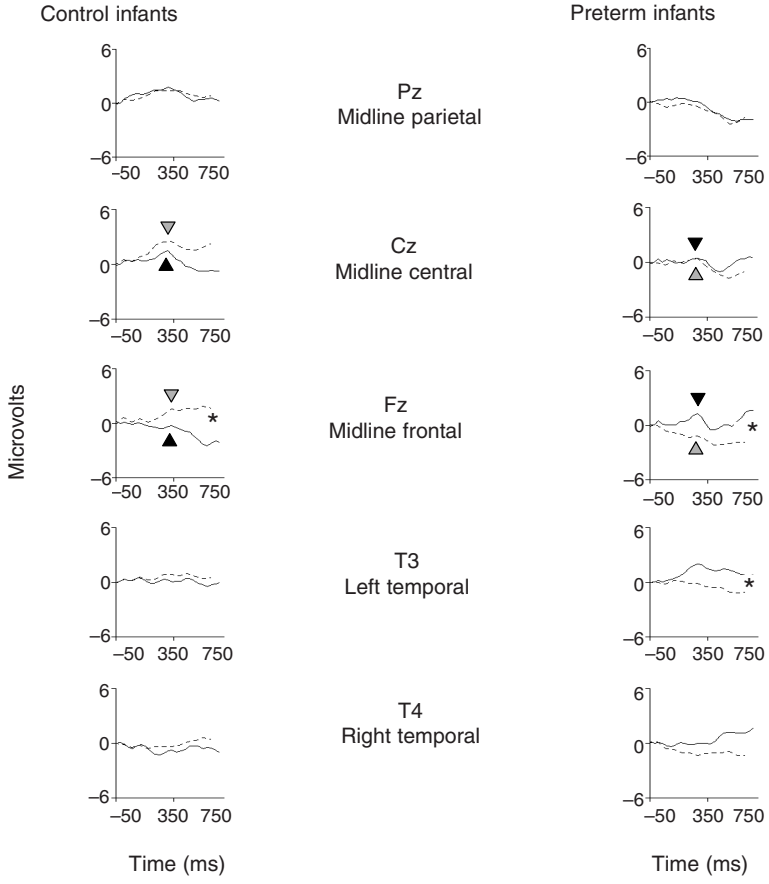

Figure 3: *Grand mean event-related potentials of auditory discrimination task for 40 control infants and 33 preterm infants in response to a frequent (solid line) and an infrequent (dotted line) speech sound. Arrowheads indicate , peak amplitudes to (▲) frequent and (▼) infrequent speech sounds at Cz and Fz. *Significant differences between areas under curve for frequent and infrequent stimuli (from Table II).*

and Cz electrode sites there was a main effect of group (Pz $p=0.004$, Cz $p=0.03$) with the preterm infants showing more negative areas under the curve for both of the stimuli (Table II). There was no significant interaction of stimulus and group at Pz and Cz.

At the Fz, T3, and T4 electrode sites, there was no significant main effect, but there were significant stimulus and group interactions (Fz, $p=0.001$, T3, $p=0.03$, T4, $p=0.037$). Post-hoc Student–Newman–Keuls tests at Fz showed significant differences between the stimuli in both the preterm and control groups, but the groups showed opposite patterns. In the control group, the infrequent stimulus elicited more positive activity than the frequent stimulus, whereas preterm infants showed more negative activity for the infrequent stimulus (Table II and Fig. 3). At the left temporal electrode site (T3), post hoc Student–Newman–Keuls testing showed more negative activity for the infrequent stimulus compared with the frequent stimulus in the preterm group (Table II and Fig. 3), whereas the control group showed no difference between the stimuli. At the right temporal electrode site (T4), the post hoc test showed no significant difference between the stimuli or groups.

RECOGNITION MEMORY, PEAKS AND LATENCIES

For the peak and latency measurements at Cz and Fz in the window from 150 to 400ms, there was no significant finding in the ANOVA, with no significant main effect or any significant interactions.

RECOGNITION MEMORY, AREAS UNDER THE CURVE

For the areas under the curve, the overall ANOVA showed no significant main effect for group, stimulus, task order, electrode site, or familiarization. There was a significant interaction of stimulus × group × task order ($p=0.0470$). Follow-up stimulus × task order ANOVAs were done in each of the control and preterm groups to further evaluate this interaction. This analysis showed a stimulus × task order effect in the term control infants ($p=0.021$). Post-hoc testing showed a main effect of stimulus in the control infants who received the recognition memory task first ($p=0.04$). These infants demonstrated the expected negative slow wave, with more negative activity to the stranger's voice than mother's voice (stranger, –2815μV-ms^2 SEM 882; mother, 977μV-ms^2 SEM 943; Fig. 4). There was no stimulus × lead interaction, and the effect is seen diffusely over the scalp. Control infants who were tested with the recognition memory task after the auditory change paradigm showed no significant stimulus effect nor interaction. For the preterm infants, the stimulus × task order ANOVA showed no main effects and no interactions. Thus preterm infants showed no difference between mother and stranger ERPs, regardless of whether the task was given first or second.

RECOGNITION MEMORY, FAMILIARIZATION ERP

Thirty-five infants (20 control, 15 preterm) had been given supplemental familiarization with 60 additional presentations of the maternal voice before the recognition memory testing. For

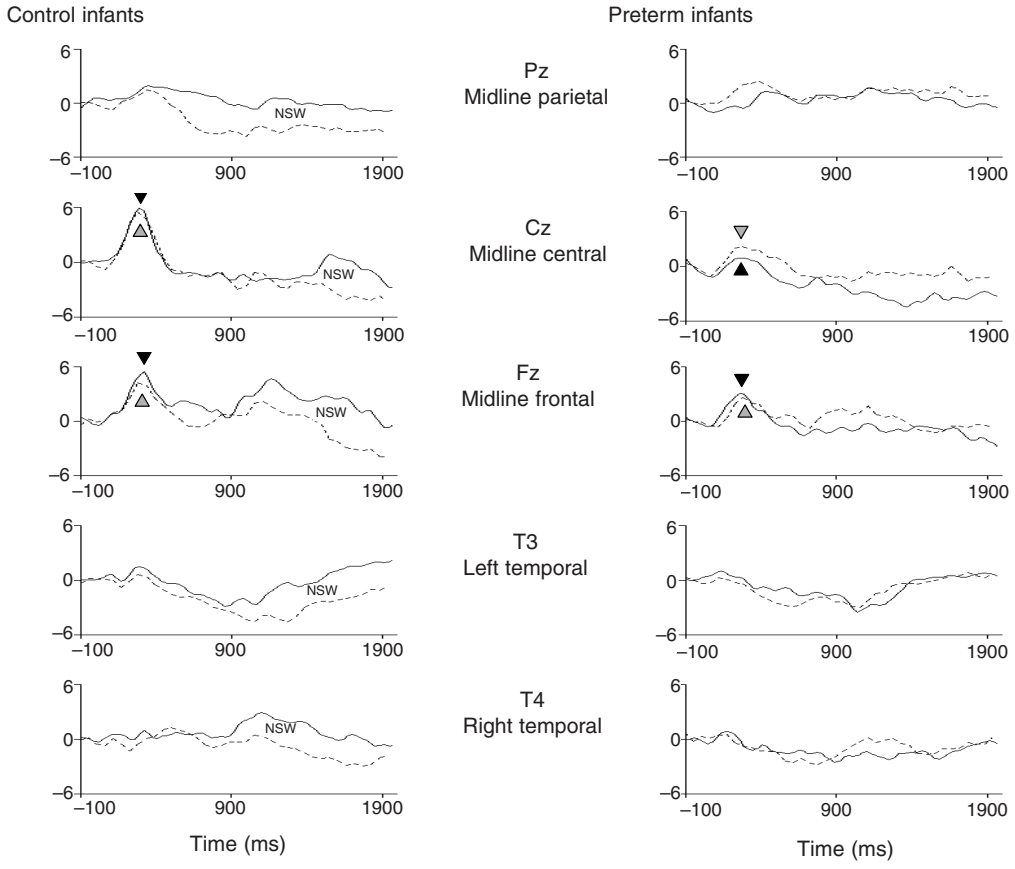

Figure 4: *Grand mean event-related potentials (ERPs) of recognition memory task for 40 control infants and 35 preterm infants in response to mother's voice (solid line) and a stranger's voice (dotted line). Arrowheads indicate peaks between 150 and 400ms at Cz and Fz. Control infants show evidence of a negative slow wave (NSW) to stranger's voice located diffusely over entire scalp (p=0.0400). Preterm infants show no difference between mother and stranger ERPs.*

the ERPs elicited during this familiarization period, separate evaluation of the peak amplitudes and latencies at 150 to 400ms (Cz and Fz) and areas under the curve (Pz, Cz, Fz, T3, and T4) were performed. In these ANOVAs, there was no significant difference between the groups, electrode sites, or task order (no main effect, no interaction).

CORRELATION OF DISCRIMINATION AND RECOGNITION MEMORY

A post hoc analysis was performed to determine if the patterns of results for the discrimination task and the recognition memory task were correlated. This analysis included only the 38 infants (20 control, 18 preterm) who were tested with the recognition memory task first, because those tested second did not show evidence of recognition memory. For each infant's auditory change task, the ERP areas under the curve for the frequent stimulus were subtracted from those for the infrequent stimulus at the Fz site (site of significant differences between the groups). For each infant's recognition memory task, the mean ERP area at each lead for the maternal voice was subtracted from the mean ERP area for the stranger's voice. Linear regression analyses were then performed by using the subtracted areas from the auditory change paradigm against the areas for the maternal voice recognition paradigm. This showed no correlation between the area scores for the auditory change task and the area scores for the recognition memory task ($p=0.9$). Furthermore, infants having either a positive or a negative wave for the speech sound discrimination task were capable of showing negative slow wave evidence of recognition memory (13/23 infants with a positive wave for discrimination, 10/15 infants with a negative wave for discrimination; χ^2 p value 0.39). This suggests that specific patterns of speech sound discrimination were not prerequisites for maternal voice recognition.

Discussion

Magnetic resonance imaging (MRI) studies of preterm infants have demonstrated a high incidence of brain abnormalities, even in those infants with normal brain ultrasounds. At term-corrected age, preterm infants have a high incidence of abnormal white matter (Maalouf et al. 1999) and decreased cortical volumes affecting many areas of the brain (Peterson et al. 2000). In addition to these anatomic abnormalities, this study shows that preterm infants with normal brain ultrasounds also have an altered cognitive function that can be demonstrated as early as 40 weeks postmenstrual age. Specifically, the preterm infants in our study showed altered discrimination of simple speech sounds and deficits in auditory recognition memory.

In the speech sound discrimination task, both term infants and preterm infants were able to discriminate between a frequent and infrequent speech sound over the frontal scalp, but the response to the infrequent sound was opposite in the two groups. Furthermore, in the preterm infants, the response was recorded over the frontal and temporal scalp sites, whereas the term infants localized the response to the midline frontal–central scalp. The differences in polarity and scalp distribution indicate that different neural structures probably

Table I: Characteristics of participants

Characteristics	*Control group n=40*	*Preterm group n=35*	*p*
Birthweight, mean (SD) g	3672 (420)	1153 (374)	<0.0001
Gestational age, mean (SD) wks	39.9 (0.79)	28.4 (2.57)	<0.0001
Postnatal age at ERP test, mean (SD) d	2.1 (0.14)	81.17 (18.9)	<0.0001
Postmenstrual age at ERP test, mean (SD) wks	40.1 (0.86)	40.1 (0.85)	0.957
Interval, discharge to ERP test, mean (SD) d	0	17.5 (12.0)	<0.0001
Chronic lung disease, *n* (%)	–	14 (40)	–
Patent ductus arteriosus, *n* (%)	–	5 (14)	–
Sepsis, *n* (%)	–	14 (40)	–
Necrotizing enterocolitis, *n* (%)	–	2 (6)	–
Neurobiologic risk score, mean (SD)	–	2.7 (2.2)	–

Table II: Areas under curve (μV-ms^2) in auditory change detection task

Electrode site	*Group*	*Frequent stimulus mean (SEM)*	*Infrequent stimulus mean (SEM)*	*Significant findings*
Pz	Control	619 (423)	239 (422)	Control>preterm*[a]
	Preterm	–524 (334)	–742 (352)	
Cz	Control	95 (442)	1132 (426)	Control>preterm**[a]
	Preterm	–21 (474)	–411 (332)	
Fz	Control	–614 (425)	723 (425)	Control: frequent<infrequent**[b]
	Preterm	–310 (309)	–1036 (358)	Preterm: frequent>infrequent**[b]
				Preterm infrequent<control infrequent*[b]
T3	Frequent	45 (244)	711 (228)	Preterm: frequent>infrequent
	Infrequent	388 (300)	–367 (310)	
T4	Frequent	–459 (286)	302 (447)	No significant difference
	Infrequent	–50 (283)	–722 (391)	

*$p<0.01$; **$p<0.05$. [a]Significant main effect in ANOVA; [b]Significance obtained by Student–Newman–Keuls post hoc testing.

generated the response in the two groups of infants (Nelson and Monk 2001). Other studies of healthy term infants suggest that several neural processes occur concurrently during this task, and that the appearance of the ERP reflects the dominant neural process (Pihko 1999, Kushnerenko et al. 2002). For example, Kushnerenko and colleagues showed that when newborn infants were tested using sounds that were very easily discriminated (tones versus bird chirps or speech sounds), the infants showed a large central–frontal positive wave (similar to our term newborns). However, when infants were tested using a more difficult task (discrimination of 500 and 750Hz tones), a small negativity was elicited. These authors speculated that the large positive wave in the ERP was a result of further neural processing of the stimuli beyond discrimination of the auditory change. Further investigation is required to evaluate the neural generators that are responsible for specific waveforms seen on neonatal ERPs, but the results of this study suggest that preterm and term infants may be processing the auditory information using different neural mechanisms.

Similar findings have recently been reported in older preterm children. Peterson et al. (2002) demonstrated functional MRI correlates of altered language processing in preterm 8-year-olds compared with term children. During a passive language comprehension task, preterm children used different neural pathways for semantic processing than term children, and this was associated with poor comprehension. Use of altered neural pathways for auditory processing may reflect perinatal brain injury, impaired brain growth and development, an effect of the altered sound environment ex utero, or a combination of these factors. Regarding development of the brain, the preterm and term infants studied here showed similar maturity levels of the auditory cortex, so it does not seem likely that these findings were simply the result of immaturity on the part of the preterm infants.

Evaluating the effects of the sound environment would be of practical and theoretical interest. Current understanding of the role of experience in brain development suggests that early brain developmental processes, such as early synaptogenesis, are under genetic control and that there is a limited effect of experience until the phase of synaptic pruning that begins in later infancy (see Nelson 2002 for a review). This suggests that the sound environment of the neonatal intensive care unit may have no effect on the early development of brain areas important for auditory processing. However, ERP studies of term newborns have shown that very early postnatal auditory experience is associated with changes in brain activity (Cheour et al. 2002, deRegnier et al. 2002). It will be important to evaluate the effects of the sound environment on preterm infants' auditory processing. The auditory environment of the neonatal intensive care unit (NICU) is very different than that experienced in fetal life, and if there were evidence that it would be of lasting benefit to preterm infants, the auditory environment in the neonatal intensive care units could be modified.

Turning to the results of the recognition memory task, healthy term newborns showed a negative slow wave for the stranger's voice when this task was given before the discrimination task. The negative slow wave for the stranger's voice was the expected finding as it has been previously described in term infants from 2 to 10 days of age. However, in past studies, the discrimination task has not interfered with the maternal voice recognition task (deRegnier et al. 2000, 2002). This may be due to the fact that the discrimination task given in this study was longer and more complex than the discrimination task used in previous studies, and it may have resulted in interference with the memory task. Interference with memory is a studied phenomenon in young infants (see Catherwood 1993, Gulya et al. 2002), and the susceptibility of maternal voice recognition to interference in the term infants studied here suggests that the recognition memory task used in this study may be relatively difficult, even for term infants.

For the preterm infants, there was no difference between the mothers' and strangers' voices, even when the memory task was given first and when a familiarization period was given immediately before the test in an attempt to 'boost' memory. Lack of evidence of maternal voice recognition may reflect a lack of exposure to the maternal voice or to a deficit in their memory abilities per se, with less ability to encode and retrieve memories. Regarding exposure to the maternal voice, preterm infants had less in utero exposure to the maternal voice than term infants, but more postnatal experience. Because of the filtering effect of the uterus, the maternal voice heard by the fetus in utero is very different from the voice heard postnatally. For term infants, it appears that prenatal exposure to the maternal voice provides sufficient experience to allow newborns to recognize the ex utero version of the maternal voice early in the postnatal period (DeCasper and Fifer 1988, Fifer and Moon 1995). However, there is evidence from ERPs that postnatal experience has potent effects on maternal voice recognition. Using ERPs, we demonstrated that 15-day-old infants had larger differences between the maternal and strangers' voices than 2-day-old infants tested at the same postmenstrual age of 40 weeks (deRegnier et al. 2002). In the current study, preterm infants actually had more experience with the ex utero version of the mother's voice than the term controls, because they were tested at 81 days of age versus 2 days for the control infants. Although the amount of time spent listening to the mother's voice while still hospitalized in the NICU varied among infants, 80% (28/35) of the preterm infants were discharged home for at least 6 days before the test, with the mean interval between discharge and ERP testing being 17.5 days. Though it is difficult to quantify the learning opportunities afforded by prenatal experience versus postnatal experience, the preterm infants had significant postnatal voice exposure that should have resulted in encoding of the maternal voice. Thus we speculate that our findings were indicative of a deficit in recognition memory in this group of infants.

Difficulties in recognition memory in preterm infants have been described in other studies of older preterm infants and children. We have previously reported evidence from ERPs of altered patterns of visual recognition memory in a group of NICU graduates that included a large proportion of preterm infants (see deRegnier et al. 1997). Rose and colleagues (Rose 1983; Rose et al. 1988, 1991, 2001, 2002) have described difficulties in visual and cross modal recognition memory extensively in 6- to 12-month-old preterm children, and have also shown that poor performance on these tasks correlates with later intellectual development. de Haan et al. (2000) have shown difficulties in immediate and delayed recall memory in preterm toddlers, and difficulties with spatial memory have been demonstrated at 8 to 12 years of age (Luciana et al. 1999, Curtis 2002). Finally, studies of former preterm adolescents and adults have shown hippocampal injury evidenced by

anatomic abnormalities on MRI and functional impairments in hippocampally based memory abilities (Isaacs et al. 2000, Vargha-Khadem et al. 2001). Thus, the body of evidence so far indicates that preterm infants are at risk for deficits in hippocampally based memory, and our study extends these findings to the neonatal period, close to the time of the presumed brain injury.

Preterm infants are at risk for hippocampal injury as part of a pattern of global brain injury or, rarely, as an isolated event (Isaacs et al. 2000, Vargha-Khadem et al. 2001). Global differences in brain function were implicated in this study, as preterm infants showed differences in both recognition memory and in the discrimination of speech sounds. Furthermore, there was no correlation between patterns of speech sound discrimination and recognition memory, suggesting that differences between the term and preterm groups reflected several areas of difference in the neural pathways. Preterm infants may experience repeated episodes of hypoxia and ischemia (Mattia and deRegnier 1998) and these may target the hippocampus and medial temporal lobe, later affecting recognition memory (Maneru et al. 2003, Nyakas et al. 1996). Nutritional or metabolic problems, such as iron deficiency or maternal diabetes, also affect the hippocampus and other parts of the brain (deUngria et al. 2000), so preterm infants may experience multiple factors resulting in damage to developing pathways for recognition memory. No studies have linked memory deficits with specific perinatal conditions in preterm infants. The infants in our study did not have intraventricular hemorrhage or periventricular leukomalacia detected by serial brain ultrasonography, and using the NBRS, most infants would be considered to be low risk for developmental problems. We did not have sufficient numbers of infants to evaluate our findings according to specific neonatal risk factors. Evaluation of specific obstetrical and neonatal risk factors with early ERPs and neuroimaging would be helpful in evaluating the causes of perinatal brain injury.

Overall, this study showed that processing of auditory information was altered in this group of preterm infants at term postmenstrual age. Although the maturity of the auditory cortex was similar in the preterm and term infants, this study noted differences in auditory discrimination processes in preterm infants. Additionally, evidence of maternal voice recognition could not be elicited from the preterm infants studied here. Although further replication is required to determine if these findings are applicable to the larger population of preterm infants, they are consistent with neuroimaging studies showing changes in brain anatomy between preterm and term infants (see Peterson et al. 2000, 2002). We speculate that many extremely preterm infants are discharged with brain anatomy and function that are very different from their term counterparts. Some of these differences may be plastic and potentially reversed or ameliorated as the brain continues to develop under conditions of optimal health, nutrition, and environmental experiences, resulting in normal cognitive function. Longitudinal ERP and anatomic studies would be helpful in learning more about perinatal brain injury, brain development, and recovery in this fragile population of infants.

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List of abbreviations

Cz	Midline central electrode site
EOG	Electrooculogram
ERPs	Event-related potentials
Fz	Midline frontal electrode site
NBRS	Neurobiological risk scores
Pz	Midline parietel electrode site
T3	Left temporal electrode site
T4	Right temporal electrode site