Biobehavioral Pain Responses in Former Extremely Low Birth Weight Infants at Four Months' Corrected Age

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ABSTRACT. *Objective.* **To compare biobehavioral responses to acute pain at 4 months' corrected age between former extremely low birth weight (ELBW) infants and term-born controls.**

Methodology. **Measures of facial behavioral and cardiac autonomic reactivity in 21 former ELBW infants (mean birth weight = 763 g) were compared with term-born infants (n = 24) during baseline, lance, and recovery periods of a finger-lance blood collection. Further, painful procedures experienced during neonatal care were quantified in both groups.**

Results. **Overall, behavioral and cardiac autonomic responses to the lance were similar between groups. However, the ELBW group seemed to have a less intense parasympathetic withdrawal in the lance period and a more sustained sympathetic response during recovery than the control group. Further, in the recovery period, two behavioral patterns (early recovery and a late recovery) were apparent among the ELBW group.**

Conclusions. **Biobehavioral pain responses were similar overall between both groups of infants. Subtle differences were observed in cardiac autonomic responses during the lance period and in behavioral recovery among ELBW infants. Whether these findings represent a long-term effect of early pain experience or a developmental lag in pain response remains unclear. The lack of an overall difference runs counter to previously reported findings of reduced behavioral response in former ELBW infants.** *Pediatrics* **2000;105(1). URL: http://www.pediatrics.org/cgi/content/full/105/1/e6;** ***biobehavioral pain response, premature infants, repetitive pain, heart rate variability.***

ABBREVIATIONS. NICU, neonatal intensive care unit; PCA, postconceptional age; ELBW, extremely low birth weight; FBW, full birth weight; CCA, corrected chronologic age; HR, heart rate; NFCS, Neonatal Facial Coding System; ECG, electrocardiogram; RP, respiratory power; LF, low frequency; HF, high frequency.

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Received for publication Feb 1, 1999; accepted Aug 21, 1999.

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Pain experienced at times of neurobiologic vulnerability in premature infants may affect subsequent pain responses.[1] This observation has raised intriguing questions about the role of early adverse experience influencing neurologic development, and concerns regarding the effects of the care provided in the neonatal intensive care unit (NICU). While in the NICU, preterm neonates seem to have a lower pain threshold than term infants, with further decreases in pain threshold (windup phenomenon) after exposure to painful stimuli.[2,3] This altered excitability spreads to multiple levels of the spinal cord and may cause nonnoxious stimuli (handling, physical examination, and other nursing procedures) to be perceived as noxious stimuli and stimulate the systemic physiologic responses to stress. This scenario sets up established and long-term responses to tissue injury that outlast the initial noxious stimulus, leading to chronic noxious stimulation (classified as chronic pain or discomfort).[4]

Altered local tactile and nociceptive responses in preterm infants have been reported. Fitzgerald and colleagues[5] compared the development of the cutaneous flexor reflex in preterm infants born at 25 to 34 weeks gestation, and tested at 27 to 39 weeks' postconceptional age (PCA), compared with full-term infants. They found thresholds were lower in infants [2] demonstrated cutaneous hypersensitivity when flexion reflex was tested in areas of previous tissue damage. Such hypersensitivity is thought to reflect a change in the way afferent nociceptive stimuli are processed in the spinal cord after early nociceptive stimulation.

Increased cardiovascular responses and decreased behavioral responses to blood collection by heel lance were found in 4-week-old neonates born at 28 weeks compared with neonates born at 32 weeks.[6] Differences in these response patterns were correlated with the total number of invasive procedures experienced since birth, rather than other clinical factors (eg, age, Apgar score, birth weight, severity of illness, or body weight), suggesting pain system immaturity or an altered pain response.

There is also emerging evidence that effects of early pain experience may extend into infancy and perhaps beyond. In a study of the remote effects of circumcision pain in term-born infants, Taddio et al[7] reported that circumcised infants had a greater pain response to subsequent immunizations than uncir-

cumcised infants. As well, they reported that among the circumcised group, infants pretreated with eutectic mixture of local anesthetics (Astra Pharmaceutical Products, Inc), subsequent pain response was attenuated. There is indirect evidence suggesting that the effects of early pain extend beyond infancy into childhood in former extremely low birth weight (ELBW) infants. Parent ratings of child sensitivity to everyday pain at 18 months of age showed they regarded their ELBW premature toddlers (birth weight <1000 g) as significantly less sensitive than heavier preterm (1500–2499 g) and full birth weight (FBW) toddlers.[8] One quarter of former ELBW (<1001 g) children at age 4.5 years compared with full term children, showed clinically higher ratings of physical complaints of no known medical cause.[9] At 8 to 10 years of age former ELBW children rated the pictures of painful events in recreational settings higher than FBW children and emotional response ascribed to the children in the pictures was correlated with time spent in the NICU.[10] Whereas these studies suggest there may be long-term effects of early pain experience, they have the limitation that they used indirect measures such as parent report or child ratings of pictures.

Previous studies of direct observation of pain reactivity in former ELBW children have been limited to the neonatal period,[8,9] usually at sites of previous injury.[2,3] To the best of our knowledge there are no published studies which have directly examined pain responses between ELBW compared with FBW children, beyond discharge from the nursery or at a site remote from the site of original repeated injury.[11] In the present study, physiologic and behavioral responses to an acute noxious stimulus (finger lance for blood collection) at 4 months' corrected age of former ELBW infants (birth weight <801 g or ≤25 weeks' gestational age) were compared with a cohort of term-born control infants. In particular, we sought to investigate whether pain reactivity (facial behavior and cardiac autonomic responses) would be altered in former ELBW infants receiving a noxious stimulus at a site distal (the finger) to the site of original repeated injury (the heel). We hypothesized that extreme preterm birth, and NICU care, would result in a reduced global/generalized pain response at 4 months' corrected age when compared with the response of term-born control infants.

METHODS

Study Participants

With approval from the University of British Columbia Clinical Research Committee, British Columbia's Children's Hospital, and British Columbia Women's Hospital Scientific Review Committees, and written informed parent consent, a consecutive cohort of 24 former ELBW infants (mean birth weight, ≤800 g) were recruited from the NICU at British Columbia's Children's Hospital and studied at 4 months' corrected chronologic age (CCA). Criteria for inclusion of the ELBW infants in the study was birth weight or 2 grade intraventricular hemorrhage, no history of maternal drug abuse. During the study period 71 infants were eligible for recruitment, however, 9 moved and 37 parents refused blood collection for study purposes. The remaining 4 infants were excluded because of technical reasons. A control group of term-born healthy infants (n = 21) were recruited after delivery at British Columbia Women's Hospital and studied at 4 months of age. None of the term-born infants was receiving any medication, had neurologic, cardiac, or respiratory problems, or had a history of prolonged exposure to pain (Table 1).

Procedure

The study was conducted in a specially designed room in the Biobehavioral Research Unit in the Center for Community Child Health Research for videotaping, physiologic data recording facilities. Infants underwent a finger lance for blood collection (0.5 mL) for a concurrent study of iron metabolism among former ELBW infants. The infant was seated on his/her mother's lap and connected to the Respitrace monitor (Wims, Miami, FL). Recording began when the infant was in an awake, alert, noncry state.[12] Blood was drawn from a lance of the middle finger by 1 of 3 lab technicians. Each of the lab technicians conducted blood collection on equal proportions of ELBW and control infants.

Measures

To identify biobehavioral markers of an altered pain response, we used measures of facial reactivity[13] and cardiac autonomic responses.[14] Time segments for data analysis were selected by a priori criteria suitable for the nature of the measures. Videotape and autonomic recordings were conducted simultaneously throughout the study. Facial activity changes very quickly to ongoing events in infants,[15] thus 20-second time periods were used for each event. In contrast, analysis of heart rate (HR) variability requires relatively prolonged periods of stability, without movement artifacts, thus time segments of 2.2 minutes per event were used.

Behavioral Data Acquisition

A camera technician conducted video recording. The Neonatal Facial Coding System (NFCS) was used to provide detailed facial activity. The NFCS[13,16] is an objective, reliable behavioral measure of acute infant pain that has recently been validated for use up to the age of 18 months.[17] NFCS trained coders, blind to the subject group and all information about the infants, coded the presence or absence of a discrete set of precisely defined facial actions, using slow motion and stop-frame playback technique. From the NFCS, 7 facial actions were coded (brow bulge, eye squeeze, nasolabial furrow, open mouth, vertical mouth stretch, horizontal mouth stretch, taut tongue), as they have been related to pain in full-term healthy neonates,[13,18] premature neonates,[19,20] and in infants up to the age of 18 months.[17] The data for 1 ELBW infant were missing for the recovery event, because the face was not clearly in view. The infant's scores were replaced with the mean value for that cell, ie, the mean for ELBW infants during the recovery event.

The first 20 seconds from each of 3 events (baseline, lance, recovery) were coded in random order. One coder conducted the main NFCS coding, with 11 (24%) of the infants scored indepen-

TABLE 1. Subject Characteristics (Mean and Range)

	ELBW	Controls
Gestational age at birth (wk)	25.9 (24.0–28.4)	39.9 (38.3–41.6)
Birth weight (g)	763 (515–865)	3641 (2676–4320)
Corrected age at test day (mo)	3.9 (3.4–4.3)	4.1 (3.6–4.4)
Weight at test day (kg)	5.2 (4.1–6.6)	7.2 (6.3–8.3)
Days in the NICU	82.8 (45–214)	0
Procedures	86.7 (9–286)	1.2 (1–5)

Abbreviations: ELBW, extremely low birth weight; NICU, neonatal intensive care unit.

dently for inter-rater reliability. Reliability was calculated according to the formula described elsewhere[13] that assesses the proportion of agreement on actions occurred recorded by 2 coders relative to the total number of actions coded as occurring. The reliability coefficient was 0.86.

Physiologic Signal Acquisition

Three standard surface chest electrodes were used to record continuous electrocardiogram (ECG), and a 2-belt microprocessor-controlled inductance plethysmograph system was used to acquire a respiratory signal (Respiratrace-Plus, NonInvasive Monitoring Systems, Miami FL). Both signals were digitally sampled to disk at 360 Hz using a personal computer-based data acquisition system.[21] Calibration of the respiratory signal was performed using a previously described algorithm,[22] assuming an infant tidal volume of 7 mL/kg. Respiratory volumes were normalized to a standard body surface area of 1.73 m^2 to enable comparisons between previous adult and infant respiratory data.[23,24] One lead of surface ECG and respiratory activity were recorded continuously during baseline, lance, and recovery periods.

R waves were detected from the sampled ECG and used to form a smoothed instantaneous 4-Hz HR time series.[25] The inductance respiratory signal (RP) was digitally low-pass filtered and decimated to 4 Hz. Segments of HR and respiratory activity (2.2 minutes each) were selected from: 1) the resting baseline period within 5 minutes before the lance, 2) a lance period starting within 20 seconds after the finger prick blood collection, and 3) a recovery period within 7 minutes after the lance. The epoch duration of 2.2 minutes was based on the need for stable behavioral state and the absence of gross movement artifact as previously reported.[23,24]

Power spectral estimates of HR were quantified using the area (power) of the spectrum in a low-frequency (LF) region (LF, 0.04–0.15 Hz) and a high-frequency (HF) region (HF, 0.15–0.80 Hz), as well as by the ratio of LF and HF power (LF/HF), as previously described.[26] Similar measures of respiratory activity were tabulated from the RP spectrum to yield total RP (LF-RP and HF-RP).

To determine the contribution of both sympathetic and parasympathetic components to HR modulation, the effect of respiratory activity on HR was assessed using transfer function analysis, as previously reported in infants[23,24] and adults.[26] Autospectra of the HR and respiratory signals and the cross spectrum between them were estimated for each 2.2-minute (512 point) segment as previously described.[27] The complex transfer function, or frequency response, between respiratory activity and HR was quantified using the cross-spectral method to yield magnitude (gain) and phase components. A squared coherence spectrum was also computed to define the degree of the linear relation between respiratory activity and HR. The coherence varied between 0 and 1.

Quantitative measures of cardiac parasympathetic and sympathetic cardiac control were derived from the average coherence weighted transfer gains of the 2.2-minute segments of data. Using this technique, previous work during pharmacologic treatment of adults with either atropine while upright, or propranolol while supine, demonstrated transfer gain and phase plots characteristic of pure parasympathetic and pure sympathetic modulation of HR, respectively.[26] A pure sympathetic HR response (during standing with atropine) was characterized by a reduced gain at frequencies 0.01 Hz and a phase delay. In contrast, under pure vagal conditions (supine plus propranolol), the HR responses were characterized by higher gain at all frequencies and no phase delay. From the transfer gain we derived measures of $LF_{transfer\ gain}$ (0.04–0.15 Hz) and $HF_{transfer\ gain}$ (0.15–0.8 Hz).

Statistical Analysis

Behavioral Data

The facial data were examined in two ways: 1) a single index of pain for each event was derived from principal components analysis, using a method described previously.[17] Repeated measures analysis of variance was conducted on the facial activity pain scores, to examine the role of group (ELBW versus FBW), and event (baseline, lance, recovery). 2) The distributions of individual face actions were examined during each time segment of each event. To examine the pattern of facial response throughout time, occurrence of each of the 7 NFCS facial actions were summed within each 2-second time segment in each event.

Physiologic Data

The mean and SEM of HR, respiratory activity, and power spectra for each data segment were calculated. A repeated measures analysis of variance was used to compare outcome measures across study periods. To determine the significance of differences of change of a measure, analysis of covariance was used to examine the effect initial or starting measure had on lance response. For the purposes of display, group average transfer function estimates of both gain and phase from each experimental epoch were computed as previously described.[26] A difference was considered statistically significant for $P < .05$. Post hoc comparisons were done where appropriate using Tukey tests.

RESULTS

All infants underwent the finger lance blood collection without complications. Infant and demographic characteristics are presented in Table 1.

NFCS Facial Activity

There were no overall statistical differences in facial pain scores between the ELBW and control groups ($f_{1,43} = .1$, $P = .91$), or the interaction of group by event ($f_{2,86} = .97$, $P = .38$). Event was statistically significant ($f_{2,86} = 170.31$, $P < .001$), and post hoc comparisons showed significantly increased facial activity from baseline to lance, followed by significantly decreased facial activity from lance to recovery (Fig 1).

The distribution of individual NFCS face actions was examined for each group in each 2-second phase period of time in each phase of blood collection. There were no differences between the groups apparent on inspection of the baseline and lance phases. However, during the recovery phase, two patterns emerged for the ELBW infants. During the first 2 seconds of the recovery phase, 43% of the infants in the ELBW group showed no facial activity in the first recovery time segment, suggesting a more rapid return to baseline after termination of the lance procedure. In contrast, only 12% of the control infants' scores were at 0 in time segment 1 (χ^2 df 1 = 5.28; $P = .05$). The mean number of face actions in each time segment is presented graphically for baseline, lance, and recovery phases of blood collection (Fig 2). An overall trend toward less facial activity in the recovery period was evident for the ELBW infants compared with term-born controls.

Physiologic Data

Mean HR

Mean HR rate increased significantly from baseline to lance period and declined again in recovery

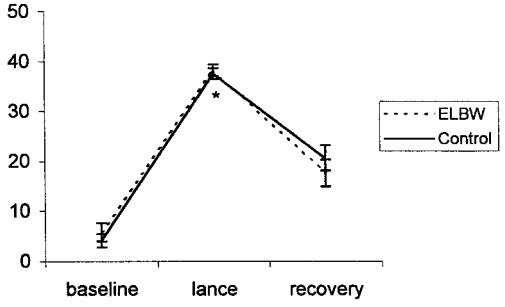

Fig 1. Mean facial pain scores across events (mean ± SEM) $P < .05$ repeated measures analysis of variance across time epochs.

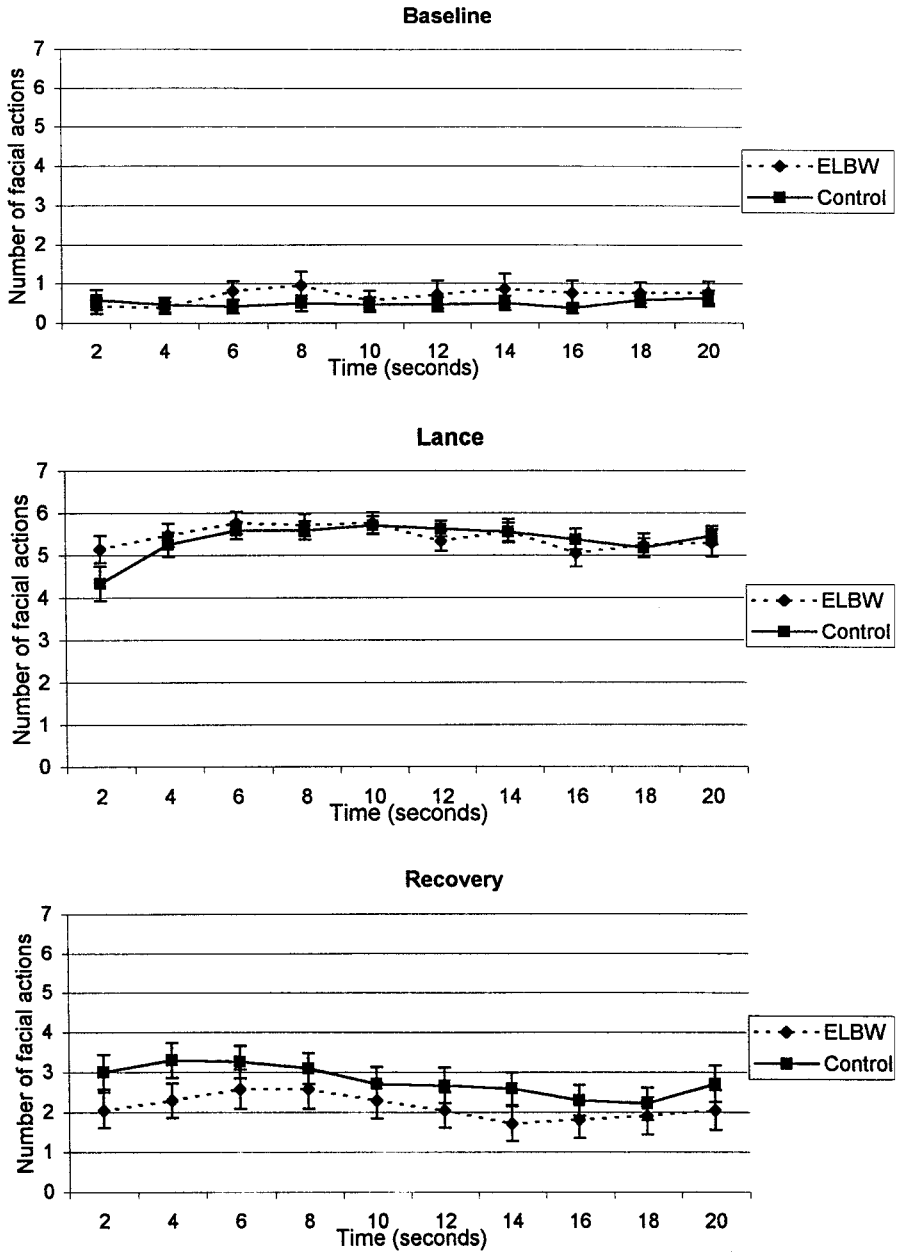

Fig 2. Facial response to lance at 4 months corrected age (mean facial actions ± SEM)

periods in both groups ($f_{2,90}$ = 111.3, $P < .05$; Fig 3), however, overall changes with time were not significantly different between groups ($f_{2,90}$ = 2.5, $P = .08$).

Power Spectral Estimates

In both groups, LF and HF power decreased significantly ($f_{2,90}$ = 6.7, $P = .002$ and $f_{2,90}$ = 11.8, $P < .01$, respectively) from baseline, and increased again in the recovery period (Fig 3), however, the differences between ELBW and control groups were not significant. The ratio LF/HF remained stable in both groups across study periods with minimal changes ($f_{2,90}$ = .4, $P = .7$) and no differences between groups ($f_{2,90}$ = .327, $P = .57$; Fig 4). Finally, total RP increased significantly from baseline with the lance and decreased in the recovery period in both groups, ($f_{2,90}$ = 110.7, $P < .01$; Fig 5). Importantly, respiratory spectral power changes were significantly smaller among the ELBW infant group ($f_{2,90}$ = 6.6, $P = .02$), particularly at the lance period.

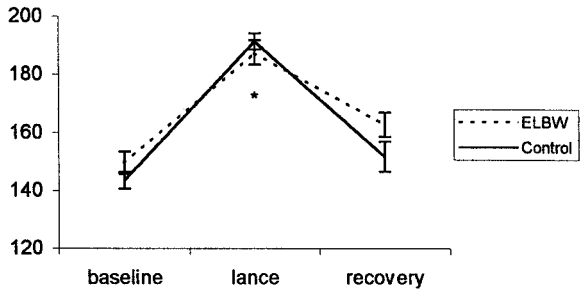

Fig 3. Mean heart rate response to lance (bpm ± SEM). *$P < .05$ for repeated measures analysis of variance across time epochs

Transfer Function Estimates of Respiratory Sinus Arrhythmia

In both groups the high- and low-frequency transfer gain decreased significantly with the lance and increased in the recovery period ($f_{1,43}$ = 116, $P < .01$ and $f_{1,3}$ = 66.4, $P < .01$, respectively), with no group differences demonstrated ($HF_{Transfer\ gain}$ and $LF_{Transfer\ gain}$ in

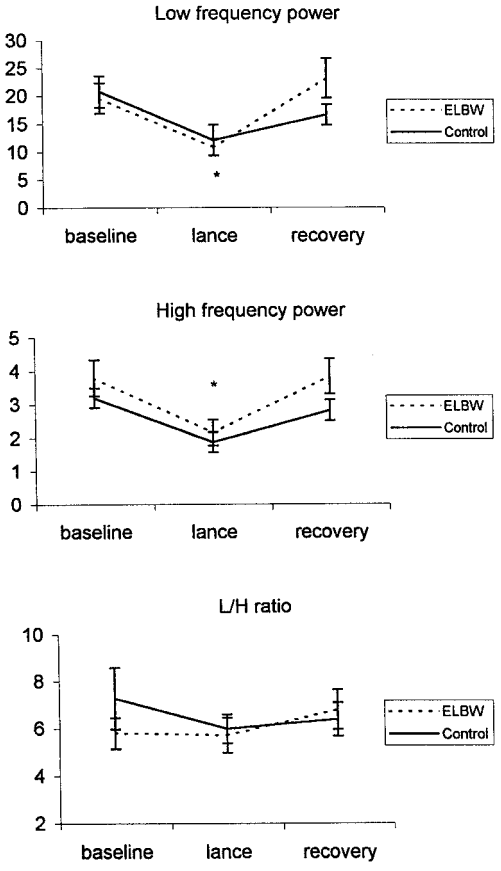

Fig 4. Low frequency, high frequency, and low frequency/high frequency ratio response to lance (bpm/l²/Hz ± SEM). *$P < .05$ for repeated measures analysis of variance across time epochs.

Table 2). Qualitatively, (Fig 6) the transfer gain was high at all frequencies during the baseline period, with the phase beginning near 0 degrees at 0 Hz and decreasing slightly with increasing frequencies, reflecting a predominance of vagal cardiac modulation in the baseline condition in both groups. In response to the lance, transfer gain decreased across all frequencies, and became very low in the HF range. Among control infants it fell to levels below that observed among the ELBW infants during the lance period ($P = .01$, for differences between group mean $HF_{transfer\ gain}$). The LF transfer gain also decreased, but stopped at levels similar to those in the ELBW group. In contrast to the ELBW group, transfer phase fell more consistently among control infants with increasing frequency, suggesting a greater withdrawal of parasympathetic activity accompanied by increased sympathetic cardiac modulation. In the recovery epoch, transfer gain increased again across all frequencies while phase remained and actually approached 0 degrees at frequencies up to 0.5 Hz, consistent with a return of sympathetic and parasympathetic modulation to near baseline levels. However, in the ELBW group gain increased across all frequencies and phase declined, consistent with a return of parasympathetic modulation as well as a persistent sympathetic response.

In summary, from the transfer function results, both ELBW infants and control infants responded to the lance with increased cardiac sympathetic and reduced cardiac parasympathetic modulation. However, for the ELBW infants there seemed to be less intense parasympathetic withdrawal in the lance phase and a sustained sympathetic response remained in recovery, compared with term-born control infants.

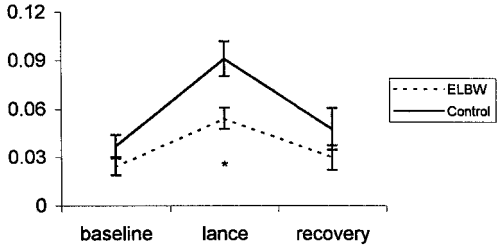

Fig 5. Total respiratory power and response to lance (l²/Hz/m² ± SEM). *$P < .05$ for repeated measures analysis of variance across time epochs and between groups.

ELBW Subgroup Analysis

Based on the distribution of facial activity during the first 20 seconds of recovery, the ELBW infants were divided into early facial recovery and late facial recovery subgroups. Infant characteristics of the subgroups are summarized in Table 3. Changes in HR and HR spectra were statistically similar between subgroups (Table 4). However, transfer gain and phase changes were qualitatively different between early facial recovery and late facial recovery groups (Fig 7). Overall, the early facial recovery infants seemed to have increased gain at all frequencies, a smaller decline with the lance and increased gain in recovery when compared with the pattern observed in the late facial recovery group. Together these results suggest increased vagal modulation and less sympathetic response among the early recovery group (ie, less responsive to the painful event).

Early recovery infants seemed to be sicker, had longer stays in the NICU, experienced more procedures, and received more intravenous morphine (Table 4). Given the small sample size in each subgroup however, further analysis was not possible to determine the precise association between pain response and previous experience.

DISCUSSION

In contrast to our original expectation and previous research, the physiologic and behavioral responses among former ELBW infants to an acute noxious event were similar to term-born control infants at 4 months' CCA. In particular, a finger lance resulted in an increase in respiratory-related sympathetic HR control and a significant decrease in respiratory-related parasympathetic control in both groups. However, subtle differences were noted in cardiac autonomic and facial responses. During the lance period, ELBW infants responded with less parasympathetic withdrawal than control infants. Further, the increase in RP that accompanied the lance was significantly less among ELBW infants. Finally, during recovery, the sympathetic response seemed to be more sustained among ELBW infants. Together, these results suggest former ELBW infants seemed less able physiologically to modulate their

TABLE 2. Transfer Function Magnitude Autonomic Measures (Means ± SEM) (bpm/L/m^2)

	ELBW			Controls		
$LF_{transfer\ gain}$	29.03 ± 6.1*	9.14 ± 1.3	30.38 ± 6.9	30.12 ± 8.3*	6.71 ± 1.0	26.00 ± 5.2
$HF_{transfer\ gain}$	13.10 ± 2.8*	3.77 ± 0.6	9.87 ± 1.6	8.19 ± 1.1*	2.33 ± 0.2	8.95 ± 1.8

Abbreviations: ELBW, extremely low birth weight; LF, low frequency; HF, high frequency.
* $P < .05$ repeated measures analysis of variance across time epochs for each group.

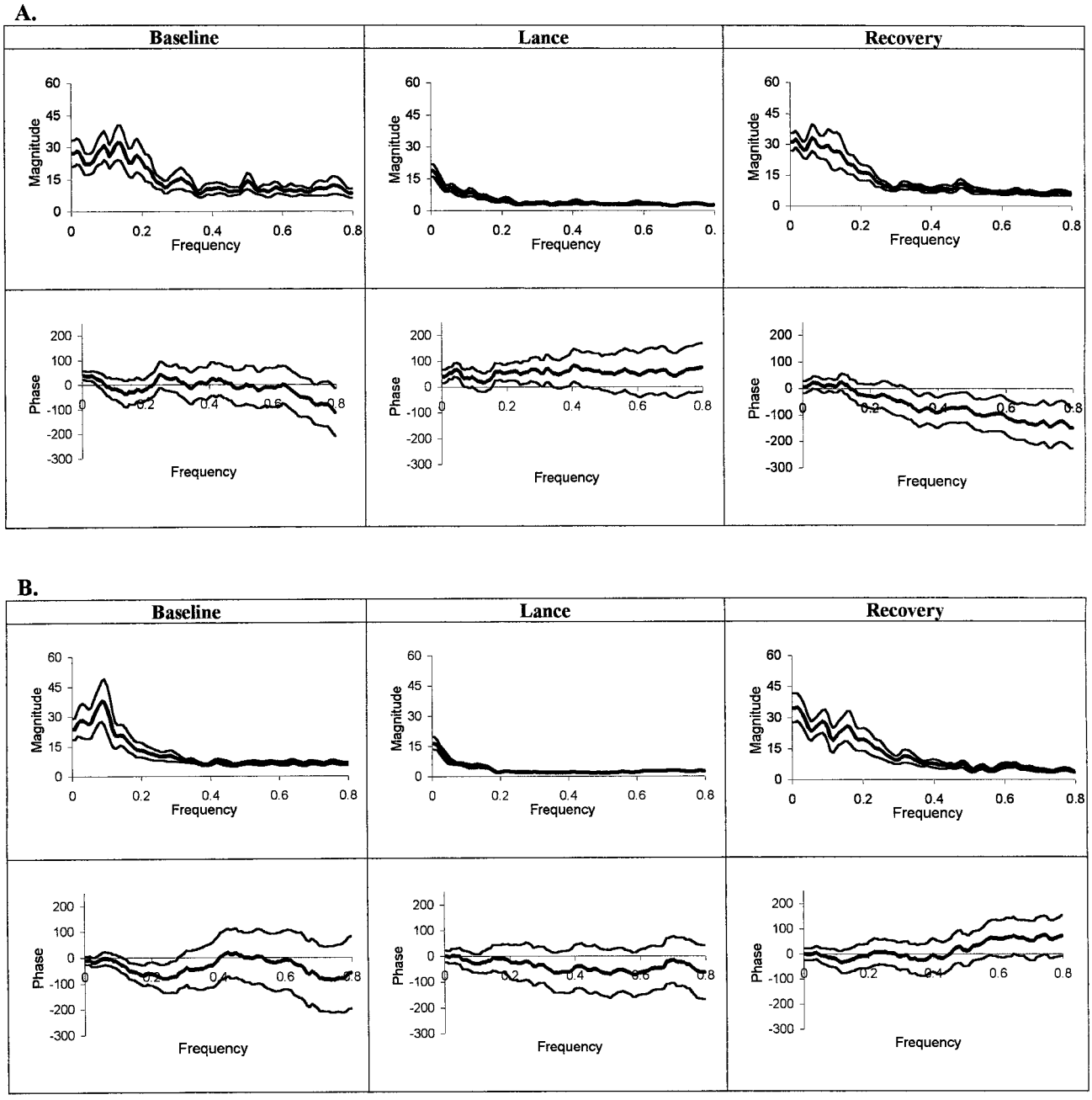

Fig 6. Mean transfer function magnitude and phase in ELBW infants (A) and control infants (B) (± SEM). Axis for magnitude is bpm/L/m^2.

immediate and recovery response to an acute noxious event. Further, facial reactivity to heel lance did not differ significantly between the ELBW and termborn control infants. However, more ELBW infants (43%) had fully recovered behaviorally as soon as contact by the lab technician was completed, compared with only 12% of the control group. ELBW infants who recovered quickly, as a group, had increased parasympathetic modulation in the baseline period, less parasympathetic withdrawal during the lance, and increased vagal modulation in the recovery period when compared with infants in the late recovery group.

The infants in the ELBW group had been subjected to prolonged periods of neonatal intensive care involving many necessary noxious procedures, leading

TABLE 3. ELBW Subgroup Characteristics and NICU Treatment Variables (Means and Range)

	Early Facial Recovery Group (n = 7)	Late Facial Recovery Group (n = 14)
Birth weight	750.0 (515–845)	770 (720–865)
Gestational age (wk)	25.8 (24.6–27.6)	25.9 (24–28.4)
Days in NICU	98 (56–207)	75.1 (45–214)
Opioid analgesia:		
Morphine (mean mg/kg/d)	0.50† (.00–1.34)	0.27 (.00–0.69)
fentanyl (mean mcg/kg/d)	10.9 (.00–52.6)	3.0 (.00–18.7)
Invasive procedures*	98.6 (32–192)	80.8 (9–286)

Abbreviations: ELBW, extremely low birth weight; NICU, neonatal intensive care unit.
* Invasive procedures: combine number of intravenous starts, lumbar punctures, PICC lines, chest taps/chest tubes inserted, surgeries, total blood collections.
† $P < .05$ for differences in morphine received.

TABLE 4. Heart Rate Spectral Power and Transfer Function Magnitude Autonomic Measures (Means ± SEM) in ELBW Subgroups

	Early Facial Recovery Group (n = 7)			Late Facial Recovery Group (n = 14)		
	Baseline	Lance	Recovery	Baseline	Lance	Recovery
LFP	21.3 ± 5.3*	12.5 ± 2.9	29.4 ± 8.5	18.72 ± 3.2*	10.0 ± 1.8	20.13 ± 3.2
HFP	2.9 ± .56*	2.39 ± .42	4.0 ± .8	4.27 ± .74*	2.1 ± .55	3.78 ± .7
LFP/HFP	7.9 ± 1.3	5.99 ± 1.9	7.9 ± 1.4	4.75 ± .62	5.6 ± .7	6.28 ± 1.1
$LF_{transfer\ gain}$	34.4 ± 12.2*	11.6 ± 2.0	47.3 ± 17.0	26.34 ± 7.1*	7.91 ± 1.7	21.94 ± 5.0
$HF_{transfer\ gain}$	12.25 ± 4.7*	4.9 ± 1.3	13.6 ± 3.4	13.52 ± 3.6*	3.23 ± .6	8.00 ± 1.4

Abbreviations: ELBW, extremely low birth weight; LFP, low-frequency power; HFP, high-frequency power.
* $P < .05$ repeated measures analysis of variance across time epochs for each group.

to our hypothesis that these early experiences would have modified the normal development of pain behavior. Such a modification has been suggested in previous studies of similar children in the neonatal period and at later ages, where this question has been investigated through both parental reporting[8,9] and the use of responses to pictures.[20] The present study, which found only small differences between the ELBW and control infants, is the first to observe ELBW infants undergoing a procedure after discharge from the NICU. The infants in the earlier studies likely received less analgesia in the NICU than current cohorts of ELBW infants because of changes in practice patterns. In addition to the later age of observation, another difference between the Johnston and Stevens[6] study at 32 weeks' PCA, and our study at 4 months' CCA, was that the previous study used heel lance, which was a site already used for blood collection during the infants' time in the NICU. In the present study a previously unused site, finger lance, was the location. There are assumptions that repeated pain to one site may lead to widespread alteration in the entire pain system. The reduced parasympathetic withdrawal during the lance and sustained sympathetic activity in the recovery period among ELBW infants seems consistent with the less mature acute pain response reported by Johnston and Stevens[6] in preterm neonates studied at 32 postconceptual weeks after 4 weeks in the NICU. However, in the current study, overall differences were minimal at the pain-naïve site. In a study of term-born infants, circumcised boys showed different responses to inoculation at age 4 months, suggesting a generalized alteration of the subsequent pain response. Although it is likely that the ELBW infants in the present study received analgesia in the initial adjustment to the ventilator, subsequently many painful procedures (eg, heel lance blood collection) were conducted on these ELBW infants without pharmacologic pain intervention. Therefore, the present findings are at odds with the effects of a single untreated pain experience as suggested by the observations of Taddio et al.[7] The relationship between hyperalgesia at one location and alterations to the systemic pain response after a noxious event at a remote location remains to be determined.

Previous work examining the effects of subsequent pain response in a region of previous repeated early injury[2] has demonstrated an altered pain response. The subtle nature of our observations might reflect the robust nature of the developing pain system and the continuing capacity to overcome the effects of early repeated noxious events. In addition, we may have not found an overall altered reaction because we examined the pain response at a site remote (finger) from the area of predominant initial early injury (heel) in ELBW infants. The relationship between hyperalgesia at one location and alterations to the systemic pain response after a noxious event at a remote location remains to be determined (ie, hyperalgesia at one site could represent changes to the peripheral nervous system only, and may not represent any alteration on a global level).

Time frames and gestational ages of infants in previous studies may make direct comparisons between studies difficult. The work of Fitzgerald and colleagues[2] examined effects of previous pain/injury throughout hours or days; whereas Johnston and Stevens[6] reported on the effects of previous pain that had occurred weeks or even months before. Similarly, Fitzgerald and colleagues[2] examined the effect of repeated pain experienced at the same site of original injury; in the study by Johnston and Stevens[6] the site was not clear. In the current study we exam-

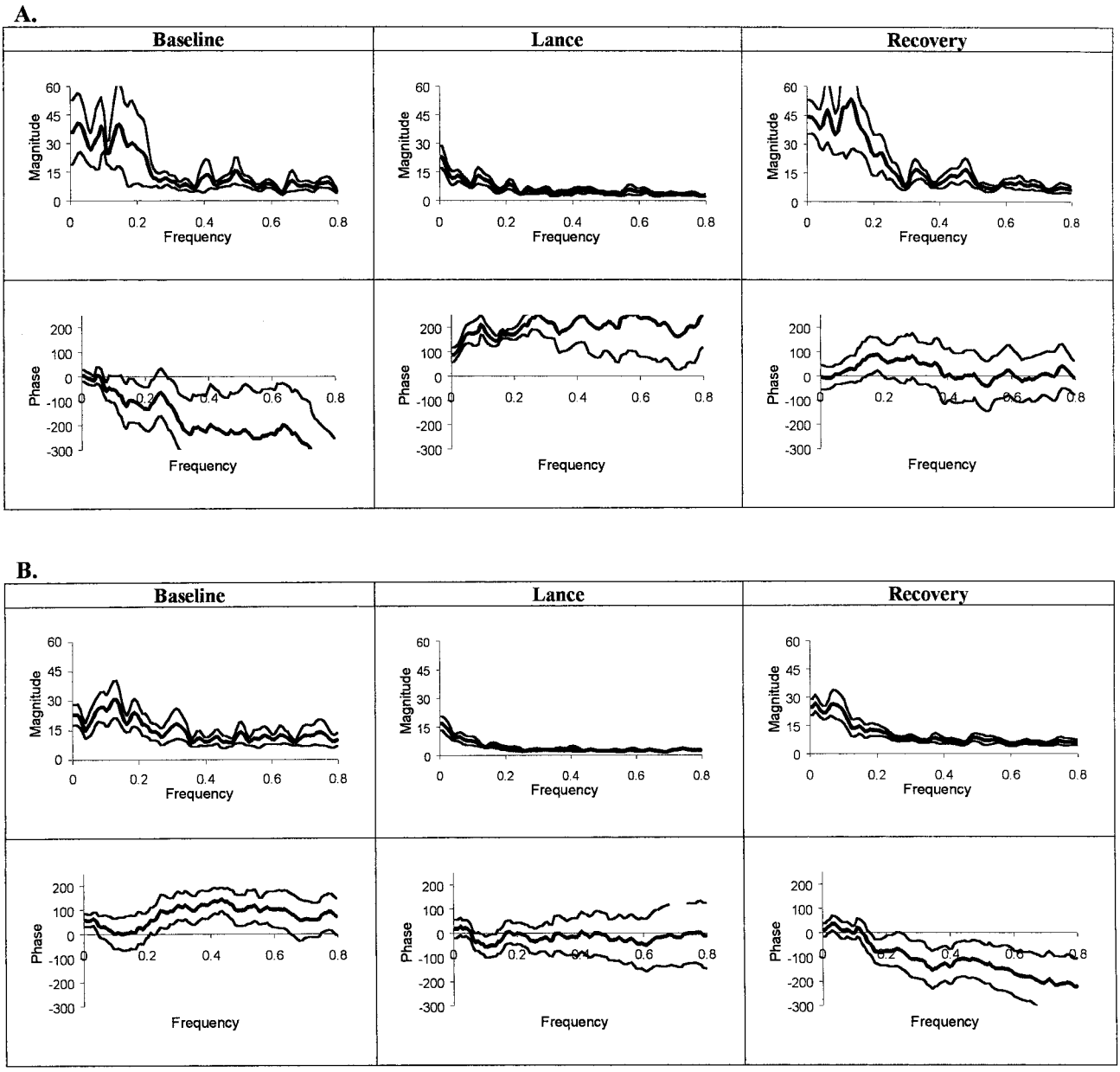

Fig 7. Mean transfer function magnitude and phase in ELBW infant subgroups: early facial recovery (A) and late facial recovery (B) (± SEM). Axis for magnitude is bpm/L/m^2.

ined response at a pain-naïve site well beyond the time of initial injuries (5 months).

The inference is frequently made that the younger preterm infants are less capable of modulating their pain response.[6] It is not clear whether this continues beyond 40 weeks' PCA. Our data suggest that such differences seem to persist beyond term, but are relatively small, and seem unlikely to be of clinical importance for most infants. However, there may be subgroups of infants who have been more affected by their NICU stay than others.

A number of concurrent factors among ELBW infants may also contribute to altered pain reactivity. Neurologically impaired individuals, such as adults with cognitive impairments,[28] frail elderly,[29] and adolescents with cerebral palsy[30] may have blunted acute pain reactions. In this study we sought to avoid these neurologic confounds by excluding infants with a history of clinically significant abnormalities on neonatal head ultrasound (intraventricular hemorrhage >2 and/or absence of periventricular leukomalacia).

The current study suggests some subtle, but perhaps important differences in the global pain response between ELBW and term-born infants that will require future study. Among the ELBW infants during the recovery period 2 behavioral patterns emerged (early-facial and late-facial recovery) which suggest the importance of looking beyond the immediate postlance period. Examination of cardiac autonomic responses in these 2 subgroups also yielded distinct differences in the characteristics of their pain responses. Infants in the early recovery group began with increased parasympathetic modulation in the baseline period, less parasympathetic withdrawal during the lance, and increased vagal modulation in the recovery period when

compared with infants in the late recovery group. These differences in autonomic response to the lance may illustrate a lag in maturity of the developing pain system rather than an altered response secondary to early pain experience.

Infants in the early recovery group received more morphine during longer NICU stays. Although the number of infants in this subgroup was small, this observation does raise the possibility that early morphine exposure in ELBW infants may itself influence subsequent pain response. The effects of early analgesia and pain exposure has been recently demonstrated by Rahman and coworkers[31] investigating the effects of inflammatory pain and morphine use during the first day of life on subsequent pain response in rats. They found that early pain treated with morphine led to a typical adult opioid analgesic response in adult rats. In contrast, however, morphine given in the absence of pain shifted the opioid dose-response curve in the adult, raising the threshold for its effects. These results suggest that both early pain and opioid exposure have long-term implications in animal models, depending on whether they occur alone or together.

Our data may have implications for our current approach to blood collection in the NICU. Although there are few suitable cutaneous sites for blood collection in the premature neonate, sites should probably be rotated. Further, because there may be long-term and unwanted consequences of early pain exposure, the need for every procedure should be considered, even ones considered routine.

Derived physiologic parameters possibly reflecting pain must be interpreted with care. If HR spectral data are considered alone, the reduction in both LF and HF and the lack of change in their ratio could be interpreted as a pain-related decrease in parasympathetic HR modulation with little or no change in sympathetic activity. This interpretation would be inconsistent with the expected increase in mean HR and sympathetic arousal accompanying a noxious event. However, we also found a significant increase in respiratory signal power. Because LF and HF fluctuations are strongly influenced by both the frequency and amplitude of respiratory activity,[32] changes in respiratory activity must be accounted for when interpreting spectral results. When the transfer function between respiration and HR was used to account for the effects of changes in respiratory activity, transfer gain and phase demonstrated that sympathetic HR control increased with the lance, whereas parasympathetic control decreased significantly in both groups. The inclusion of the influence of respiration and the transfer function to account for sympathetic and parasympathetic changes leads to results which are more consistent with both the expected physiologic response.

A number of limitations to the current study need to be mentioned. Given the differences in life experience, many aspects of which may influence patterns of central nervous system development, we should ask whether term infants at 4 months CA are appropriate controls for former low birth weight infants at 4 months' CCA, when in fact they are 7 months ex utero. Detailed work is needed to investigate the neurologic differences between infants of the same PCA but different ages after birth. Second, the biobehavioral measure used is study, although sophisticated, may not have tapped into the same aspects or expression of pain captured by the parent questionnaire in our previous studies,[8–10] thereby, presenting 2 plausible but discordant views of an infant's pain response. These differences also require detailed examination. Finally, the current investigation studied pain response at one moment in time and therefore failed to tell us where this response falls into the developmental course among former ELBW infants. In particular, it remains unclear whether the pattern of pain response among the former ELBW infants we observed was indeed a part of a typical course of development of pain reactivity, a temporary pattern or part of a continued developmental lag. Further longitudinal studies are required to address these questions.

Our data are reassuring in that there are few lasting differences in pain response at least at 4 months, despite quantum differences in previous pain experience between ELBW and control infants. This may suggest analgesic use in this cohort has protected the ELBW infants from overt longstanding side effects of repeated pain exposure. But that remains to be seen and at present we do not know what effects early and prolonged opioid exposure have in other developmental domains in infancy or later.

CONCLUSION

In summary, this is the first study to directly observe ELBW infants undergoing an invasive procedure after discharge from the NICU. Overall behavioral and physiologic reactivity to an acute noxious event were similar between former ELBW and term-born infants at 4 months of age. However, differences in the degree of the parasympathetic reaction during the lance period were found. Further differences in the sympathetic reaction and initial behavioral responses during the recovery period were noted in the ELBW infants. Thus, our data suggest subtle alterations to acute pain reactivity, which were still present 4 months beyond the term period, but were relatively small. Differences apparent to finger lance seemed unlikely to be of clinical importance for most infants. However, because finger lance is a relatively innocuous procedure, the results cannot be generalized to more pervasive pain experiences during childhood. Further, there may be subgroups of ELBW infants who have been more affected by their NICU stay than others. It remains to be determined whether differences in pain responses between ELBW and term-born infants represent a developmental lag inherent to preterm birth, or cumulative effects of early and prolonged pain exposure with varying conditions and amounts of analgesia exposure. The longer-term differences in biobehavioral pain response between ELBW and term-born infants require further study.

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