The Relationship Between Heart Rate Variability, Auditory Evoked Heart Rate Responses, and Performance on Recognition Memory Tests in Low Birth Weight and Normal Birth Weight Infant Macaques (*Macaca nemestrina*).

by

Dorothy Marie Patteson

A dissertation submitted in partial fulfillment
of the requirements for the degree of

Doctor of Philosophy

University of Washington

1994

Approved by _____
(Chairperson of Supervisory Committee)

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Date December 13, 1994

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Abstract

The Relationship Between Heart Rate Variability, Auditory Evoked Heart Rate Responses, and Performance on Recognition Memory Tests in Low Birth Weight and Normal Birth Weight Infant Macaques (*Macaca nemestrina*).

by Dorothy Marie Patteson

Chairperson of the Supervisory Committee: Professor Kathryn Barnard
School of Nursing, Department of Parent-Child Nursing

This study describes heart rate variability (HRV) in the first two months of life and explores the relationships between HRV, auditory evoked heart rate responses and performance on tests of visual recognition memory (VRM). A sample of 9 low birth weight (LBW) and 15 normal birth weight (NBW) infant monkeys was studied.

Measures of HRV including heart period, standard deviation, and RMSSD were obtained from five minutes of heart period data collected during sleep at six estimated postconceptional days of age: 175, 180, 190, 200, 210, and 230. Spectral analysis HRV measures were also computed. Heart rate responses to a series of auditory stimuli were tested at age 200. Performance on visual recognition memory problems was assessed at 180, 190, 200, and 210 days of age.

The NBW group had a developmental pattern for heart period and HRV which started out higher at the early ages of 175 and 180, dropped to a low level at age 190 and began to rise again at 200 days of postconceptional age. The LBW group had a similar pattern which was not statistically significant. Values for LBW and NBW groups did not differ significantly. HRV measures were not stable for individuals across time for either group of infants.

LBW infants had a more marked biphasic HR response to the auditory stimuli and habituated more slowly. Infants with higher HRV during sleep had a greater response to the auditory evoked heart rate testing. No relationship was found between measures of HRV and performance on VRM.

The failure to find differences in HRV measures between groups or to find individual differences which were stable across time mitigates against concluding that HRV is indicative of inherent autonomically based self-regulatory abilities or predictive of future cognitive outcomes. A macaque model for studying HRV was supported.

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ACKNOWLEDGMENTS

Many people contributed to the process and completion of this project. Dr. Kathryn Barnard, as adviser and chairperson of the PhD committee was incredibly patient and persistent in her support. Her intellectual capacity for assimilating and processing information is prodigious. Dr. Susan Blackburn and Dr. Pamela Mitchell , PhD committee members, offered insightful suggestions for revision and completion of the manuscript. It has been a privilege to have the benefit of association with three such exceptional nursing scholars. Dr. Gene Sackett, the Graduate Faculty Representative, provided access to the equipment, facilities, and subjects in the Infant Primate Research Laboratory. He also provided invaluable assistance in analyzing and interpreting data.

Members of the staff at the Infant Primate Research Laboratory were always forthcoming with information and assistance related to the facilities, equipment, supplies, and working with baby monkeys. Gerald Ruppenthal, Colleen Walker, and Annie Washington deserve special mention. Vince Henderson provided the expertise in computer programming and instrumentation necessary for data collection and answered many a panicked call regarding equipment problems Dr. Virginia Gunderson and Dr. Kim Grant-Webster generously shared their knowledge and experience with Visual Recognition Memory testing.

Dr. Robert Burr devoted an extraordinary amount of time and energy assisting with data analysis. His willingness to share his depth of knowledge in the fields of computers, statistical analysis, and heart rate variability was absolutely indispensable for the completion of this dissertation.

Many colleagues and friends have provided an incredible amount of support from the beginning of my educational program through completion of this project. Dr. Sandra Eyres and Dr. Constance McDonald befriended and encouraged a very distressed pre-

doctoral student and Sandy "has been there" with wise, gentle, and nonjudgemental support and assistance on numerous occasions ever since. Dr. Monica Jarrett (alias, "if you don't know, ask Monica") could always be counted on for information, advice, and sympathy on all kinds of logistical, statistical, and personal issues.

The support and encouragement received from friends and family, near and far, helped me to see this process through to completion. Special appreciation goes to Rosemary Neff, my best friend and partner, who assisted from the beginning of the proposal process, through data collection, to preparation of slides for the dissertation defense. Both her sense of humor and her tolerance for tears provided opportunity for tension relief.

Non-human support came from several sources including the infant pig-tailed monkeys in the Infant Primate Research Laboratory as well as canine (Lucky) and feline (Patiwack) friends at home.

To

ROSEMARY ROMANS NEFF

With Gratitude and Love

In Recognition of

Your Tolerant and Generous Spirit

CHAPTER 1

CONCEPTUAL FRAMEWORK AND LITERATURE REVIEW

Background and Significance

Each year an estimated 6 to 10 percent of all births in the United States are premature. Infants born prematurely each year number in the hundreds of thousands, perhaps over 300,000 (Blackburn, 1982; Gottfried, 1985; U. S. Bureau of Census, 1994). Most of these infants require admission to neonatal intensive care units (NICU). The average length of stay is from 15 to 20 days with the time period extending to 40 to 50 days for infants weighing between 1000 and 1500 grams (Gottfried, 1985). The prematurely born infant has long been known to be at risk for a large number of long term problems including abnormalities in neurological development, poor physical growth, sustained intellectual impairment, retarded language development, learning disabilities and deviant social behavior (Caputo & Mandell, 1970; Escobar, Littenberg, & Petitti, 1991; DeHirsch, Jansky, & Langford, 1966; Drillien, 1964; Fitzhardinge, et al., 1976; Fitzhardinge & Ramsey, 1973; Hack & Fanaroff, 1989; Lubchenco, 1976; Rose, 1983). Advances in the field of neonatal care in the last decade have vastly improved survival rates especially for very low birth weight infants and have apparently decreased the incidence of some of the most severe problems including spastic diplegia, blindness from retinopathy of prematurity, and the CNS effects of hyperbilirubenemia (Rose, 1983). However, follow-up studies continue to show that premature infants remain at developmental risk in perceptual-motor skills, language, cognition, and social interaction (Gorski, 1983; Halsey, Collin, & Anderson, 1993; Rose, 1983).

With survival goals largely achieved, there has been a change in focus toward achieving more long term quality of life outcomes. It has become apparent that it is necessary to begin to differentiate between those long term negative effects related to prematurity itself versus those which may be secondary to an environment/neurological development interaction occurring in an environmentally nonsupportive NICU. An

environment designed to be highly successful in terms of basic life support may well be less supportive of the neurological maturation and environmental interaction needs of a developing premature infant.

Conceptual Framework and Literature Review

Infant-Environment Interaction

Environmental stimulation is thought to be essential for development of organization and integration of the central nervous system which has an impact on cognitive functioning and the behaviors which make the infant accessible for positive interactions with other people and for optimal psychological and social functioning. Although earlier studies of premature infant environments were based on theories of sensory deprivation, there is now evidence that premature infants in NICU's may instead be experiencing sensory overload. Investigators have proposed that the more accurate assessment of NICU physical and caregiving environmental stimulation is that it is inappropriate in the sense of being nonpatterned, unpredictable, noncontingent, intrusive or painful, unremitting, and often unimodal (Barnard & Bee, 1983; Blackburn & Barnard, 1985; Brazelton, 1983; Gorski, 1983).

In addition to the problems inherent in the NICU environment, the premature infant has characteristics which pose unique problems in attempting to analyze the supportive or nonsupportive nature of infant-environment interactions. The first and most obvious problem derives from the fact that infant is "prematurely born". Als, Lester, Tronick, and Brazelton (1982) state that the developmental level of physiological organization is species appropriate and species parsimonious for the organism's particular adaptive niche relative to organism-environment fit. They further postulate that, in most circumstances, the organism is capable of eliciting and seeking the physiological, motoric, state, and interactive organizational perquisites from the environment which are necessary for its ongoing survival and development. The dilemma confronting prematurely born infants

and their caregivers is that the infant is not developmentally prepared for the environment with which he or she is confronted. In addition, the very event of birth has promoted developmental acceleration in some systems which would make the former intrauterine environment inappropriate even were it possible to recreate it.

Another characteristic which makes it difficult to assess the supportive or nonsupportive nature of the environment for premature infants is their limited ability to communicate their response to the environment. Many of their physiologic and behavioral cues are global and nonspecific making it difficult to assess or interpret environmental effects. The infants are also comparatively vulnerable to environmental input since they are motorically unable to either escape or exert any control over it.

It is also probable that there are individual differences in the degree to which the infant is vulnerable to environmental demands. Degree of vulnerability may relate to the infant's ability to self-regulate. Self-regulation refers to the infant's ability to maintain his or her own ongoing level of organized behavior or to regain his level of homeostasis in the face of external manipulation and/or internally or environmentally induced perturbations. Self-regulation may also be described as the ability to keep oneself together and respond in an appropriate manner to meet one's well-being or survival needs. Self-regulation in the infant may be an early analog to coping in the adult.

The ability to be self-regulating is seen as a developmental phenomenon which is related to neurological maturation and organization. Sander and his associates (Sander, 1969, 1974; Sander, Julia, Stechler, Burns, & Gould, 1975; Sander, Stechler, Burns, & Julia, 1970) conceptualize the newborn infant as a composite of semi-independent physiological subsystems each with its own rhythm such as those controlling heartbeat, respiration, and body movement. They suggest that infants arrive with varying degrees of coherence or phase synchrony between these component subsystems which must become internally harmonized and coordinated. The adaptive task for the infant is to achieve

phase synchrony between these internal rhythms and also with rhythms or periodicities in the environment around them. Self-regulation for the newborn may then be interpreted as the ability to achieve phase synchrony and homeostasis with his own subsystem rhythms and to obtain an harmonious, synchronous, participatory relationship with his external environment.

Als, Lester, and Brazelton (1979) suggest that behavioral organization and self-regulation arise as hierarchical levels or stages. The premature infant is still at a stage of physiological differentiation and must master regulation of autonomic functions such as temperature control, digestion, and respiratory and cardiovascular control. Inability to tolerate or process external stimulation (especially when it is unpredictable, abrupt, or prolonged) may be reflected in signs of physiologic autonomic instability such as apneas, bradycardias, gagging, spitting, etc. Autonomic instability related to environmental stimulation may have immediate detrimental repercussions which influence developmental prognosis through mechanisms such as hypoxia, increased susceptibility to intraventricular hemorrhage, or feeding intolerances leading to nutritional deficits.

Autonomic vulnerability to environmental stimuli may also have longer term influences by producing alterations in the patterns of behavioral response thereby influencing the ongoing processes of neurological development including the CNS mechanisms of cell migration, synaptogenesis, and neurotransmitter specification which are highly active in the premature infant. Premature infants are noted to have difficulty in achieving alertness or attention from lower states of arousal but once aroused also have difficulty decreasing their level of arousal even after the stimulus is removed. Lack of autonomic self-regulation may manifest as either an obligatory dependence for physiological stability on predictable and cyclical environmental stimuli or an inability to ignore or shut out unpredictable, disruptive stimuli resulting in great physiological expenditure. A later, learned response may be to self-regulate autonomic or physiologic

functions by shutting down responses to environmental stimuli at the expense of developing the ability to appropriately regulate state and social interaction. Thus self-regulatory functions may be distorted. Animal models have given substantial evidence of the fine-tuned specificity of environmental inputs necessary in the course of sensitive periods of brain development to support normal cortical ontogenesis (Duffy, Mower, Jensen, & Als, 1984; Goldman & Rakic, 1979, Kandel, 1985; & Weisel, 1982). Conditions providing for either lack of sensory input or the provision of supplemental stimulation during critical periods of development have been shown to result in changes in anatomical and physiological properties of the CNS and subsequent malfunctioning.

It would be especially useful if a reliable and valid indicator of autonomically based self-regulatory ability could be identified which would reflect individual differences in vulnerability to environmental events and/or be useful in studies to determine what aspects of the environment infants were apt to respond to with adverse effects and under what conditions.

There is some information in the literature that heart rate patterns, especially patterns of heart rate variability (HRV), may offer such possibilities. Beyond an intrinsic rate determined by characteristics of cardiac cells, heart rate and heart rate variability result from sympathetic and parasympathetic input to the heart mediated through the higher central nervous system in response to feedback designed to maintain physiologic homeostasis in the face of internal and external environmental demands. It seems possible that an indicator of autonomic balance within the cardiovascular system may offer hope of reflecting a predisposition for autonomic responsivity and balance for the organism as a whole. Lower heart rates and higher heart rate variability have been reported to be associated with better morbidity and mortality outcomes in infants with respiratory distress syndrome (Cabal, Siassi, Zanini, Hodgman, & Hon, 1980; Kero, 1974), better cognitive

outcomes (Fox & Porges, 1985), and less inhibited behavior in strange situations (Kagen, 1982).

The rest of this chapter presents (1) a review of the phenomenon of heart rate variability; (2) a summary of results of studies using heart rate and heart rate variability as indicators of developmental outcomes in infants; and (3) the specific aims of this study to explore the relationships between heart rate variability measures, a physiologic behavioral response to a discrete environmental stimulus, and a measure of cognitive outcome in low-birth weight and normal birth weight infant pig-tailed monkeys in the first two months of life. A significant relationship between these variables in this age group and population would provide support for continuing research with a population of premature infants in an NICU setting.

Heart Rate Variability

Heart rate variability is simply change in heart rate. The duration of a heart beat changes from one beat to another--sometimes increasing and sometimes decreasing. The length of a heart beat in milliseconds is measured by the time between R waves on an electrocardiogram. This measurement is termed the heart period. The inverse of heart period is heart rate which is expressed in units per time measure or beats per minute. The basic purpose of cardiac activity is to provide an adequate blood supply for delivery of oxygen and removal of carbon dioxide from body cells. The amount of oxygen and carbon dioxide exchange necessary varies with metabolism, activity, etc. Heart rate varies in order to accommodate changing needs. The variation occurs as a result of nervous system control based on information from a variety of physiological feedback mechanisms including temperature sensors, blood pressure, and chemoreceptors. Heart rate changes are primarily mediated through the autonomic nervous system with sympathetic inputs to the heart increasing heart rate and parasympathetic inputs decreasing heart rate.

Because heart rate changes are based on physiologic mechanisms designed to maintain homeostatic limits, many heart rate changes are cyclic or repeated at fairly constant intervals, i.e., there is a periodicity to heart rate variability. When time series analysis techniques are used to analyze heart rate variability and decompose it into its various components, several periods or frequencies of variability can be identified. There is a low frequency (LF) range extending from 0.02 Hz to 0.2 Hz which, in the adult literature, has been attributed to blood pressure influences. There is a very low frequency (VLF)--a slow cycling--region of variability below the low frequency range to DC. This VLF component has been associated with thermoregulatory activity in adults. Stochastic and non-periodic variability may also be captured in the VLF range. The remaining component of heart rate variability occurs at a high frequency (HF) extending above the low frequency region to the Nyquist frequency of 2.5 Hz. This high frequency region is associated with respiratory activity and has been labeled respiratory sinus arrhythmia (RSA) (Chess, Tam, and Calaresu, 1975; Dykes, Ahmann, Baldzer, Carrigan, Kitney, and Giddens, 1986; Kitney, 1980; Porges, 1986). There is some question in the literature as to whether the relationships of the physiological phenomena associated with the heart rate variability frequencies are cause and effect or correlational in nature. A correlational relationship perhaps implies a higher CNS influence than does a direct cause and effect relationship. Regardless of the nature of the relationship between the other physiological phenomena and heart rate variability frequencies, there is evidence to suggest that the very low (VLF) and low frequencies (LF) cycling is under the influence of both sympathetic and parasympathetic input while the highest frequency is predominantly controlled by the parasympathetic branch of the autonomic nervous system (Chess, Tam, and Calaresu, 1975; Giddens and Kitney, 1985; Porges, 1986; Woodson, 1988; Snidman, 1989).

Heart Rate Variability and Developmental Outcomes

Because of the nature of the sympathetic and parasympathetic influences on heart rate variability it seems possible that heart rate variability could provide a nonintrusive measure of autonomic balance in the individual's response to both internal and external environmental stimuli. The heart rate variability literature on infants provides some interesting support for the theory that heart rate variability may have some predictive value for a variety of outcomes. Early studies of heart rate variability, using standard statistical measures such as means, standard deviations, average of mean differences, etc., demonstrated that infants with high heart rates and low variability were more ill with respiratory distress syndrome and that improvement in heart rate variability presaged improvement in health while further decreases or continuing low levels of heart rate variability presaged mortality (Cabal, Siassi, Zanini, Hodgman, and Hon, 1980; Jenkins, McC. Reid, and McClure, 1980). A study by Fox and Porges (1985) using discriminant function analyses found the respiratory component of heart rate variability in sick newborns to be predictive of cognitive outcomes at eight and twelve months of age. Cusson and McCarthy (1987) found positive relationships between heart rate variability (including RSA) and infant performance on the regulation of state and autonomic regulation clusters of the Brazelton Neonatal Assessment Scale at time of discharge from the hospital for preterm infants with bronchopulmonary dysplasia. They also found a positive association between discharge measures of heart rate variability and cognitive performance on the Bayley MDI at seven months.

Kagan and his associates (Kagan, 1982; Kagan, Resnick, Clarke, and Snidman, 1984; Kagan, Reznick, and Gibbons, 1989) have found that young children who are inhibited and shy in novel situations have a high heart rate and low heart rate variability. They attribute this to a "sympathetic" overreactivity or defensiveness to stressful situations. A number of studies have found that infants who have low heart rates and high

variability overall and, in particular, have a large amount of heart rate variability in the high frequency (HF) range (which is associated with respiratory activity and referred to as RSA) have better attentional abilities, perform better on recognition memory tasks, and have better cognitive outcomes developmentally (Fox and Porges, 1985; Linnemeyer and Porges, 1986; Porges, 1983; Richards, 1987). They propose that the mechanism involves a preponderance of parasympathetic influences which facilitate attentional capabilities.

There has been a spate of more recent studies examining the relationship of heart rate variability (especially RSA) with infant behaviors and infant outcomes in both temperament and cognitive development. In a study of preterm infants, DiPietro and Porges (1988) reported that baseline measures of RSA correlated positively with the intensity of behavioral response to insertion of a tube for gavage feedings. Porter, Porges, and Marshall (1988) reported that newborn infants with higher RSA preoperatively exhibited the most dramatic responses during circumcision: They characterized these infants as more reactive.

A number of studies have been done with older infants. Richards and Cameron (1989) studying healthy infants at four time periods between 14 and 26 weeks of age with both cross-sectional and longitudinal methods, found that there was no predictive relationship (either with earlier measures or concurrent measures) between RSA and cognitive performance on the Bayley. However, they did find consistent positive relationships between RSA and infant scores on the approach subscale of the Infant Temperament Questionnaire for both early and concurrent measures. Conversely, Healy (1989), studying infants between 11 and 35 months cross-sectionally, found that infants with low heart rates and high variability (including high RSA) showed greater latency to approach a robot in the laboratory setting and were rated as more "difficult" by their mothers on the Toddler Temperament Scale. Stifter, Fox, and Porges (1989) reported that, in five month old infants, high RSA was associated with more facial expressivity

(interest, joy, look away behaviors) with mothers and strangers in a laboratory approach paradigm. There was no relationship between heart rate variability and facial expressivity in 10 month old infants. Fox and his associates (Fox, 1989; Stifter and Fox, 1990) have reported a number of outcomes from a longitudinal study of physiologic correlates of infant emotional reactivity during the first year of life. They found no relationships between heart rate variability measures and response to removal of a pacifier (expected to generate a negative response) in newborn infants. However, in five month old infants, there was a significant positive relationship between amount of RSA and infant negative reaction to gentle arm restraint. Infants with high RSA were also reported by their mothers to have higher levels of activity and smiling behavior. After categorizing infants as having either high RSA or low RSA at fourteen months and then looking retrospectively at other measures from earlier and concurrent time points, Fox reported that their data suggests that infants with high RSA were more reactive to both positive and negative events at 5 months and more sociable and approachful at 14 months.

It is difficult to interpret and integrate the results reported in the many studies of the relationship between heart rate variability (including RSA) and infant behaviors including cognition and temperament. Some of the reported differences in outcomes may result from subject population differences. For example, studies which reported significant predictions from heart rate variability to cognitive outcomes have included sick or at risk infants (Fox and Porges, 1985; Cusson and McCarthy, 1987) while those reporting no relationship (Richards and Cameron, 1989) included only healthy infants. It is possible that there are inherent differences in autonomic balance in infants who suffer illnesses early in life or that there are autonomic balance sequelae as a result of illness and early experiences for ill infants.

Apparent contradictions in results found between studies of the relationship between heart rate variability and behavioral response and temperament outcomes may

result from a number of factors. The laboratory situations used to elicit certain responses may not be effective, appropriate, or definitive. For example, behavioral response to removal of a pacifier was not related to heart rate variability measures while response to presumably more noxious stimuli such as passage of a gavage tube and circumcision were indeed related to heart rate variability measures (Stifter and Fox, 1990; DiPietro and Porges, 1988; Porter, Porges, and Marshall, 1988.) Another factor influencing outcomes (or their interpretation) is that infants at different developmental ages may react to stimuli or situations from different perspectives and/or capabilities. For instance, latency to approach a novel object may indicate fear at eight months and the ability to attend and assimilate information before approaching at 14 months.

Another issue is that the outcome measures chosen have often been global in nature (e.g., Bayley examinations and temperament questionnaires) so that there is difficulty in identifying the underlying mechanisms or physiological basis for the relationship between heart rate variability measures and the outcomes: For instance, what is the physiological linkage between better performance on cognitive examinations for infants with high amounts of RSA or why would infants with inhibited behaviors have higher heart rates and lower heart rate variability?

There have been different theoretical perspectives guiding the design of studies of heart rate variability and its predictive value. Gunnar (1990) summarized the current theories underlying much of the extant literature. Kagan and his colleagues, whose interest has been the sympathetic nervous system as a reflection of central nervous system arousal or overarousal, have focused on reactivity.. They believe that the behaviorally inhibited children in their studies have a higher tonic level of sympathetic activation and thus a lower threshold for response to the stress of unfamiliarity and task-related challenges. They have focused on changes in heart rate and global measures of heart rate variability primarily as a reflection of the extent to which sympathetic activation overrides

parasympathetic control. Until recently they have made no attempt to identify components of heart rate variability through time series analysis techniques. However, in a recent report, Snidman (1989) described her use of time series techniques to quantify power in two frequencies of the heart rate variability spectra to identify children as falling into one of three categories--sympathetically influenced, parasympathetically influenced, and sympathetic-parasympathetically influenced. She found that children who displayed inhibited behavior in the laboratory primarily fell into the sympathetically influenced category while those who were uninhibited fell primarily into the parasympathetically influenced category.

In contrast, Porges and his colleagues who have focused on parasympathetic activity have little interest in increases and decreases in heart rate (reactivity) in response to stimulation. Predictions based on RSA are made independent of heart rate and overall heart rate variability. Their measure focuses on time series quantification of RSA which they label vagal tone and which reflects parasympathetic influences on heart rate variability. These researchers believe that increased amounts of vagal tone (RSA) reflect greater maturity and organization of brainstem areas controlling the parasympathetic nervous system and thus is indicative of the individual's ability to self-regulate his behavior. Much of their work has focused on the relationship between vagal tone (RSA) and attention demonstrating that individuals with low RSA have difficulty sustaining attention and using attentional strategies to regulate behavior whereas those with high RSA do not have those difficulties. They theorize that poor attentional abilities could explain poor cognitive outcomes as well as emotional temperament differences. Children with low vagal tone (low RSA) exhibit poor attention regulation capabilities resulting in a lessened ability to regulate their emotional arousal which leads to overarousal and the inability to react appropriately to their environment. They expect children with high levels of RSA to be appropriately reactive with both positive and negative responses to mild and

moderate perturbations but not to become overaroused and incapable of functioning in the face of common stressful and/or challenging situations. Children with high RSA are expected to be more self-regulatory (perhaps a precursor to coping) in their interaction with the environment around them.

Justification for the Study

The research in this study was planned to address three areas which have received comparatively little attention in the literature to date:

1) Description of the patterns of heart rate variability (based on standard statistical measures of HRV and on spectral analysis decomposition of the phenomenon) in the newborn period and its stability over the first two months of life.

Basic studies of heart rate variability (Dykes, et al., 1986; Finley and Nugent, 1983; Giddens and Kitney, 1985; Hathorn, 1987) have pointed out that, in time series analyses data, infants and young animals have relatively low levels of heart rate variability in the high or respiratory frequency but have more variability in the lower frequencies. This fits with physiological studies (Assali, Brinkman, Woods, Dandavino, and Nuwayhid, 1978; Zugaib, Forsythe, Nuwayhid, Lieb, Tabsh, Erkkola, Ushioda, Murad, Brinkman, and Assali, 1980) which suggest that fetuses have more response to sympathetic influences than to parasympathetic, that sympathetic and parasympathetic are more balanced at birth, and that the parasympathetic influences continue to develop in the first year of life. There has been a concentration of interest in the component of heart rate variability in the high frequency range as a predictor of outcomes but little attention has been paid to the amount of variability in the lower frequency ranges, the ratio of low frequency and high frequency components and their change over time. It is not known if there are individual differences in the distribution of heart rate variability components and if these differences would be stable over time. It is possible that some individuals or groups of individuals may be

dominant in the lower frequencies which could be construed to be sympathetically influenced while others may be dominant in the high frequency region and thus parasympathetically influenced.

2) The relationship between heart rate variability and auditory evoked heart rate responses.

Many studies of heart rate variability as a predictor of outcomes in infants have selected global outcomes such as performance on Bayley Scales, performance on recognition memory tests, temperament ratings on parental report scales, or ratings of temperament and behavior in laboratory settings. It would seem important to determine the predictability of heart rate variability measures on more basic and discrete behavioral responses. A first step in demonstrating the validity of heart rate variability measures would be to predict cardiac responses to discrete stimuli. Cardiac responses to specific stimuli are also autonomically mediated. Martin, Sackett, Gunderson, and Goodlin-Jones (1988) identified two different patterns of auditory evoked heart rate responses in a study of pigtailed macaques (*Macaca nemestrina*). Infants raised in isolation showed only heart rate acceleration followed by a return to baseline within 10 to 11 seconds of stimulus onset while socially reared monkeys developed a pattern of a 10 to 11 second biphasic response of acceleration followed by deceleration with a subsequent return to baseline. These two patterns suggested a difference in reactivity and autonomic regulatory functions. The pattern of heart rate acceleration (which also showed little habituation) might be indicative of sympathetic arousal. The biphasic pattern, in turn, might be indicative of initial sympathetic arousal with a secondary parasympathetic regulatory function. There should be a relationship between baseline heart rate variability spectral patterns and cardiac response to auditory stimuli. Hypothetically one would assume that those individuals with a large high frequency (RSA) component in their heart rate variability pattern would be more likely to show a biphasic, parasympathetic regulatory

response to auditory stimuli while those with a large low frequency component and/or a small high frequency component would demonstrate a persistent acceleratory response.

3. The relationship of heart rate variability measures and performance on tests of recognition memory.

Linnemeyer and Porges (1986) have reported that infants with high vagal tone (high RSA) perform better on recognition memory tests. A linkage between other measures of heart rate variability and/or the total heart rate variability spectral pattern and recognition memory performance would support their results and provide further information on the mechanisms involved.

A primate model was chosen to explore the issues and questions posed in this study. There is evidence that pigtailed macaque monkeys (*Macaca nemestrina*) provide a valid model for the study of reproductive outcome and developmental risk in human infants. Developmental parallels between pigtailed macaque and human infants have been demonstrated for many aspects of perceptual-cognitive functioning including visual acuity (Teller, Regal, Bideen, and Pulos, 1978), general visual responsiveness (Boothe, Kiorpes, Regal, and Lee, 1982), habituation (Swartz, 1984), object permanence (Williams, 1979), and visual recognition memory (Gunderson and Sackett, 1982). In addition, low birth weight macaque monkey infants show developmental problems analogous to those found for their human counterparts (Gunderson, Grant-Webster, and Sackett, 1989).

Use of a primate model for this study was advantageous for several reasons. First, the necessary facilities and equipment for collection and analysis of data for heart rate variability, auditory evoked heart rate response, and recognition memory performance were in place and readily available in the infant primate laboratory. Second, standardized laboratory rearing conditions provided for more control over potentially confounding environmental factors. Third, although developmental characteristics and sequences of infant macaques parallel those of human infants, the rate of development is more rapid.

This difference in rate of development made it feasible to study longitudinal developmental changes in a shorter time period.

This study included both low birth weight infants and normal birth weight term infants. The predictability of measures of heart rate variability on overall cognitive outcomes has been most consistent with low birth weight or otherwise at risk infants. Consistent differences have also been found between low birth weight and term infants in cognitive outcomes such as Bayley examinations and visual recognition memory testing. It was hoped that use of both preterm and term infants would maximize the possibility of identifying different patterns of heart rate variability, auditory evoked heart rate responses, performance on recognition memory testing as well as determining relationships between those variables.

Specific Aims of the Study

This descriptive developmental study explored the relationship between heart rate variability, auditory evoked heart rate responses, and performance on recognition memory tests during the first two months of life in low birth weight and normal birth weight infant pigtailed-monkeys (*Macaca nemestrina*). The primary aims of the study were to:

1) describe heart rate variability in low birth weight and normal birth weight pig-tailed macaque infants over the first two months of life.

2) describe auditory evoked heart rate responses in infants at one month of age.

In addition, the following hypotheses were addressed:

1) low birth weight infants would have shorter heart periods (higher heart rates) and less heart rate variability than normal birth weight infants.

2) there would be stability of heart period and heart rate variability across time for individual infants.

3) low birth weight infants would have a more sustained acceleratory response during auditory evoked response testing while normal birth weight infants would have a biphasic response.

4) infants with higher heart rate variability during sleep would have a biphasic response to the auditory evoked response testing.

5) normal birth weight infants would perform better than low birth weight infants on problems of visual recognition memory.

6) heart rate variability measures would predict performance on problems of visual recognition memory; i.e., infants with higher heart rate variability would perform better on problems of visual recognition memory.

CHAPTER 2

METHODS

Design

A developmental design was used to explore heart rate variability and its stability in the first two months of life as well as the relationships between heart rate variability, an auditory-evoked heart rate response, and performance on problems of visual recognition memory.

Subjects

Subjects in this study were a convenience sample of twenty four infant pig-tailed monkeys (*Macaca nemestrina*) admitted to the nursery facility at the Infant Primate Research Laboratory (IPRL) of the University of Washington between May, 1992 and September, 1993. Infants were included in the study if they met the following criteria: a) no major congenital anomalies; b) no evidence of neurological or sensory deficits; c) no illness requiring veterinary intervention at the time of initial data collection; d) no involvement in another research project which would be incompatible procedurally.

Nine of the infants were low birth weight (defined as at or below the tenth percentile of the breeding colony birth weight distribution.) Fifteen of the subjects were normal birth weight. Twenty three of the subjects were admitted to the nursery facility as part of an "Infant Save" program that provides nursery rearing for animals who would die if left with their mothers at the breeding colony (nine for low birth weight, seven for inadequate mothering, four for maternal disorder, three for unrecorded reasons). One subject was a control subject in another study. All subjects were housed, cared for, and fed according to the standard protocols of the IPRL (IPRL, Ruppenthal and Sackett, 1992).

Measurement

Estimated Postconceptional Age

It was expected that developmental changes and/or attainment of milestones for the variables being studied were relative to postconceptional age (maturational) rather than postnatal age. Estimated postconceptional age was used to determine dates of testing. The animals in this study were not from time-mated pregnancies so their exact gestational ages were not known. Estimated postconceptional age (gestational age) was calculated using the mean of estimates based on five separate regression equations using birth weight, hand ossification centers, foot ossification centers, foot length, and crown-rump plus foot length. A description of the procedures for obtaining the anthropomorphic and bone ossification scores is described in Newell-Morris (1979). All of the measures were done by the investigator. The regression equations were based on colony data from timed matings and from normative growth values. Estimated ages from each of the regression equations are accurate to plus or minus 6 days. The expected conceptional age at birth for pig-tailed monkeys in this colony is 170 days.

Heart Rate Variability (HRV)

The ECG signal from a standard three electrode arrangement (right arm, left leg, and chest placement) was picked up and transmitted via a FM telemetry system to a cardiac rate meter that identified and timed R waves in the ECG. Data were simultaneously quantified and stored online via an IBM PC program that computed interbeat intervals (IBI) to the nearest ten thousandth of a second with an accuracy of plus or minus five ten thousandths of a second. At intermittent intervals during data collection a Graphtec strip chart recording was obtained for 10 second periods to monitor signal quality and heart rate.

The ECG data for heart rate variability was collected for a five minute period during an episode of sleep during test sessions at six different estimated postconceptional

days of age (each plus or minus two days): 175, 180, 190, 200, 210, and 230. The subject was placed in an incubator inside an acoustic sound chamber equipped with a video camera that displayed a picture on a monitor outside the chamber when lights were on in the chamber. Lights were turned out in the chamber for a minimum of ten minutes to give the infant an opportunity to settle into sleep. When the heart rate signal slowed, lights were turned on and the infant was observed for activity level. After a period of at least one minute of no visible activity, the five minute data collection was begun. The infant was determined to be asleep if little or no activity occurred and the heart rate remained lower than awake levels. No attempt was made to determine level or stage of sleep. If the infant appeared to awaken during data collection, lights were turned off and the process was restarted. The time from placement of the infant in the acoustic chamber to completion of the five minute data collection varied from approximately 20 minutes to two and a half hours.

The data files of interbeat intervals in ten thousandths of a second (four digits) were later transferred from the IBM PC to a mainframe computer via floppy disc for further analyses. Measures of heart rate variability were derived from the five minutes of IBI data for each infant at each age. These measures included both standard statistical measures of heart rate variability and spectral analysis based HRV scores.

Standard HRV Measures--A set of standard statistical measures selected from the literature on HRV during the perinatal period were derived from the raw IBI data. The data files consisting of five minutes of successive IBI's in ten thousandths of a second were initially subjected to a 0.05 alpha trim process to remove extreme outliers which were thought to be a result of artifact, error in the data collection process or ectopic beats. The average number of IBI intervals per file was 1101; the average number of IBI's eliminated by the alpha trimming process was 39. MEAN HEART PERIOD (the mean time interval between R waves in ten thousandths of a second) was calculated. Three measures

generally viewed as an indices of either total or long term variability were calculated: 1) the standard deviation (HP STDDEV) of the IBI's, 2) the interquartile range (HP IQR) of the IBI's, and 3) the median absolute deviation (HP MAD) of the IBI's. Two measures of short term variability were also determined: 1) the root mean square of successive differences (HP RMSSD), and 2) the interquartile range of successive differences (HP IQRSD). The ratio of the HP STDDEV divided by the HP RMSSD was also computed (SD/RMSSD). The measures of heart period and heart rate variability were transformed from ten thousandths of a second into milliseconds for purposes of reporting the results.

Spectral HRV Scores-- The data files consisting of five minutes of successive IBI's in ten thousandths of a second were initially processed in three stages in preparation for spectral analysis. In the first stage extreme IBI outliers, thought to be due to instrumental error, which were ± six MAD (Median Absolute Deviations) units from the median were corrected using interpolation from the surrounding segment. In the second stage, the modified series of IBI's were interpolated onto an evenly spaced grid to meet the requirements of spectral analysis procedures for evenly spaced intervals. The third stage of processing of the IBI data files utilized a method of "filter cleaning-filter smoothing" based on the method described by Martin and Thomson, (1983). An iterative process of fitting a low order model (a smooth curve), computing residuals, testing the residuals against a criteria of six MAD units, and deflating those residuals to the model was applied three times. The purpose of this process was to identify abnormal points in terms of their local context and deflate them to what the local model would have predicted. Using the smoothed, evenly spaced IBI data, a spectrum was computed using a smoothed Fourier periodogram model. The heart rate spectrum is typically divided into different regions for analysis. This study adopted Dykes, Ahmann, Baldzer, Carrigan, Kitney, and Giddens' (1986) division of the neonatal HRV spectrum into three portions--a low frequency (LF) region extending from 0.02 to .2 Hz, --a very low frequency (VLF)

region below the LF range to DC, and a high frequency (HF) region above LF to the Nyquist frequency of 2.5 Hz. Although these boundaries are somewhat arbitrary, they demarcate regions of variability commonly attributed to three recognized determinants of HRV--breathing (HF), the control of body temperature (VLF) and blood pressure (LF). The VLF and LF regions are influenced by both the sympathetic and parasympathetic branches of the autonomic nervous system while the HF range is considered to be primarily under parasympathetic control. Although the spectral curve is generated in a dB log base 10, for the purposes of this study it was transformed into natural units so that the band units composing the VLF, LF, and HF regions were expressed in milliseconds squared representing the variance accounted for by each of the regions of the HRV spectrum. The ratio of low frequency (LF) and the high frequency (HF) regions (LF/HF) was also calculated since this ratio or its change with development was expected to be of importance in predicting individual differences in infant auditory evoked heart rate responses and recognition memory test performance.

Auditory Evoked Heart Rate Response (AER)

Testing of the auditory evoked heart rate response was done in an Industrial Acoustics sound chamber on two consecutive days between 198 and 202 days of estimated postconceptional age (one postnatal month). During testing the ECG signal was picked up, transmitted, quantified, and stored as described above. The format of the file of IBI's demarcated stimulus and trial information. A test session consisted of a 29 second initial baseline period followed by 25 presentations of a 1-sec burst of 50- to 10,000-Hz white noise. Average sound intensity was 85 dB. The stimulus was presented at 30 second intervals . Electronic relays performed stimulus presentation with no special control of stimulus rise time.

Test sessions were initiated when the subject was quiescent in the cage and judged to be asleep. Because this was an habituation paradigm, once the test session was begun it

was continued through the 25 stimulus presentations even if the infant appeared to awaken. Activity level during testing was determined by observation utilizing a video camera mounted inside the acoustic sound chamber that displayed a picture of the infant in the chamber on a monitor located outside the sound chamber. At the time of each stimulus presentation, a five point scale was used to rate the activity level for the previous 30 second period: (0) for no visible activity; (1) for brief or slight movement (e.g. tail flick); (2) for brief generalized movement (body shift); (3) for more sustained movement; and, (4) for moving about incubator.

The files of IBI's with stimulus and trial demarcated were transferred by floppy disk to a mainframe computer for further analyses. Processing of the IBI files was done in three stages in preparation for statistical analysis: 1) the IBI's were converted to time base data by interpolation to one-tenth of a second; 2) in order to decrease the potential effect of extreme outliers, the data was further aggregated to a one second time period by using the median of the data segment; and 3) the data in heart period (IBI) was transposed into heart rate (beats per minute).

Responses to the stimulus were measured as differences from baseline during each of 29 seconds after stimulus onset, with second 0 being the time of stimulus presentation. Baseline heart rate was taken as the average rate in the 5 seconds preceding stimulus onset. There were 25 stimulus presentations for each day. Data was aggregated in trial blocks of five stimulus presentations using the means of responses from trials 1-5, 6-10, 11-15, 16-20, and 21-25 for each day for both low birth weight and normal birth weight groups. A repeated measures analysis of variance was performed with groups as the uncorrelated measure and the means of five second intervals within trials, trial blocks, and days as repeated measures.

In addition maximum heart rate change above baseline (MAXIMUM), maximum heart rate change below baseline (MINIMUM) and the range between the maximum above

and below baseline change (RANGE) was determined for each of the five trial blocks for both low birth weight and normal birth weight groups. A repeated measures analysis of variance with birth weight group as the uncorrelated measure and trial blocks and days as repeated measures was done for MAXIMUM, MINIMUM, and RANGE. Spearman Rank Correlations were used to test for relationships between activity level and MAXIMUM, MINIMUM, and RANGE for each trial block.

Heart Rate Variability and Auditory Evoked Heart Rate Response

The maximum change in heart rate above baseline (MAXIMUM), the maximum change below baseline (MINIMUM), and range between the changes above and below baseline (RANGE) from the auditory evoked reponse measures were correlated with the mean values for the heart rate variability measures at day 200 to test for relationships between heart rate variability and auditory evoked heart rate responses.

Performance on Visual Recognition Memory

The novelty paradigm used to test recognition memory in this study was the same as described in Gunderson, Grant-Webster, and Fagan (1987). The apparatus "consisted of a light gray display panel with two square rear-projection screens (9 cm on each side) placed 31 cm apart. Stimuli were back-projected onto the screens by two Kodak Ektograph slide projectors. The observer, hand-holding the animal, viewed the monkey's face on a 9-inch Panasonic monitor. A Panasonic WV-1850 camera was used, and the observer's view of the stimuli was blocked by an opaque screen. The subject's fixations to the right and left were recorded using timers operated by foot pedals. All testing was done in a darkened room. Illumination on the monkey's face was provided by two incandescent 60-watt lights on either side of the apparatus. The test lights were shielded by infrared filters. Additional illumination was provided by a 7-watt light placed in front of the opaque screen blocking the observer's view of the stimuli. Familiarization and test

periods, as well as intertrial intervals were controlled by a Commodore 64 computer" (Gunderson, Grant-Webster, and Fagan, 1987, p.672).

The subjects were administered a series of recognition problems at four postconception ages: 180 days, 190 days, 200 days and 210 days. The first age of testing was chosen as a test period when the infants were not expected to perform successfully and therefore as a contrast to later test periods. The last three ages are equivalent to maturational ages used in human infants and have been standardized for use with infant pig-tailed monkeys (Gunderson, et al.,1987; Gunderson, Grant-Webster, & Sackett, 1989). The stimuli consisted of ten high-contrast, abstract black and white pattern pairs in 35 mm slide form (see Appendix A for an example). Three problems (three pattern pairs) were administered at both the 180 and 190 ages and two problems (two pattern pairs) were administered at both the 200 and 210 ages.

The stimuli for the 180 day testing were selected from stimuli utilized in Gunderson and Sackett (1984) on the basis of simplicity and "easy" discriminability. The stimuli for the other three ages were from the Fagan Test of Infant Intelligence (Gunderson, et al., 1987). The elements in the patterns were large enough to be resolved by an animal with a minimal visual acuity of 20/800 Snellen. Sixteen of the subjects were administered a diagnostic test of visual acuity (details of this procedure may be found in Gunderson and Sackett, 1984).. All of the tested subjects passed at 20/800 before the 190 test age. Only one subject passed before the 180 test age. Six subjects (including 3 low birth weight) were tested on recognition memory before the visual acuity apparatus was available.

Each problem for each age period consisted of a familiarization period followed by a two-part test trial. During familiarization, two identical patterns were projected on the screen. The observer hand-held the animal 36 cm from the screen and recorded right and left fixations by a foot-operated timer until a predetermined amount of looking time had

been accumulated. The predetermined looking time ranged from 16 to 60 seconds depending on the problem. The familiarization period was timed from the subject's first fixation. For all problems the subject had a maximum of 180 seconds in which to accumulate the predetermined looking time. Three seconds following familiarization, the subject was given a two-part test trial. The familiar stimulus was paired with a novel stimulus on the screen. The observer again recorded right and left fixation times. In the first part of the test trial the left-right positions of the familiar and novel patterns was random across animals. The positions of the stimuli were reversed on the second part of the test trial to control for side preferences. The length of the test trial was dependent on the problem and ranged from 5 to 10 seconds. All of the recognition memory testing was done by the investigator who was not blind to the birth weight status of the infants but was blind to the positioning of the stimuli until all testing was completed for all subjects.

The computer program that controlled timing and presentation of the stimuli also automatically recorded study data including frequency of fixations to left and right, total duration of fixations to the left and right, and the duration of each fixation. Data were printed out and stored on floppy disk at the end of each test session. Electrodes were attached for recording heart rate data during recognition memory testing but the heart rate data were not analyzed for the purpose of this dissertation.

Data were missing for some problems within a test age for an occasional subject and for an entire test age for some subjects. Three normal birth weight subjects were admitted to the IPRL too late for the 180 age testing. One low birth weight infant at 180 and one normal birth weight infant at 190 were ill and could not be tested.The equipment was being repaired and not available for testing for one low birth weight infant and one normal birth weight infant at 190. One normal birth weight infant was untestable at age 210 because of fussiness. One low birth weight infants was scheduled and tested on the wrong dates and was eliminated for all testing ages. In a few instances infants failed to

accumulate 60 seconds of looking time during familiarization. Their data was included for analysis if they accumulated at least 50 seconds of looking time. Equipment malfunctions (e.g. failure of slides to advance or computer timing error) resulted in loss of data for one problem on 10 occasions for different infants at different ages. If two problem scores out of three were available, the infant was included on the 180 and 190 age periods. If one problem score out of two was available, the infant was included for the 200 and 210 analysis. There were seven possible scores for inclusion in the summary novelty preference score: an infant's summary score was included if four of the seven problems were available. The mean proportion of looking time at the novel stimulus for each stimulus was calculated for each of the problems for each age of testing for each infant. An infant's novelty preference score for each age was then calculated as the average of the problem scores available for that age period (three possible scores for 180 and 190; two possible scores for 200 and 210). An summary novelty score based on the testing at 190, 200, and 210 ages was also computed by averaging the proportion of looking time directed toward the novel stimulus for all available problem scores (seven possible scores.) The use of an summary score from the 190, 200, and 210 testing periods was congruent with the standardized testing done with human infants and with pig-tailed monkey infants in other studies. The 180 test period was included only as a contrast period for the purposes of this study and the infants were not expected to perform effectively and so was not included in the summary score.

One-tailed single sample t-tests and binomial tests were done to determine if the proportion of novelty scores were different from chance for both low birth weight and normal birth weight infants at each age and for the summary novelty score. Repeated measures analysis of variance with postnatal age as a covariate was used to test for differences between low birth weight and normal birth weight groups.

In addition, the amount of time required by infants to accumulate the predetermined familiarization time was computed for each problem and the mean familiarization time for each set of problems for the four ages of testing was determined. The familiarization times for each age were then analyzed using a repeated measures analysis of variance with postnatal age as a covariate to test for differences between low birth weight and normal birth weight groups.

Heart Rate Variability and Visual Recognition Memory

The mean values for the heart rate variability measures and the concurrent novelty preference scores for ages 180, 190, 200, and 210 were examined by Spearman Rank Correlations to test for relationships between heart rate variability measures and performance on tests of recognition memory.

CHAPTER 3

RESULTS

The purpose of this study was to explore heart rate variability and its stability in the first two months of life as well as the relationships between heart rate variability, an auditory-evoked heart rate response, and performance on problems of visual recognition memory.

Sample

The subjects in this study were nine low birth weight and fifteen normal birth weight pig-tailed infant monkeys (*Macaca nemestrina*). Table 1 presents information about subject characteristics. The low birth weight infants ranged in weight at birth from 330 grams to 400 grams with a mean birth weight of 363 grams (standard deviation [SD] 29.8). The normal birth weight infants had a birth weight range of 434 grams to 653 grams with a mean of 529 grams (SD=61.6). The difference in birth weight between the two groups was significant ($t = 8.87$, $p = 0.000$). The expected conceptional age at birth for pig-tailed macaques in this colony is 170 days. The mean estimated conceptional age at birth for the low birth weight group was 161.2 days (SD=4.02) with a range of 156 to 166 days. The normal birth weight group had a mean estimated conceptional age of 173.4 days (SD=3.27) and a range of 167 to 180 days. The estimated conceptional age difference between the two groups was significant ($t = 8.11$, $p = 0.000$). There were four females and five males in the low birth weight group. The normal birth weight group consisted of eight females and seven males. There was no significant difference between the two groups in the number of females and males. There was no significant difference in pre-pregnancy maternal weight or maternal parity for the two groups. The normal birth weight group had a mean postnatal age of 7.8 days (SD=3.3) at 180 days estimated conceptional age while the low birth weight group had a mean postnatal age of 19.1 (SD=5.6) at 180 days estimated conceptional age: This difference was significant at $p = 0.000$.

Although the low birth weight and normal birth weight group differed significantly on birth weight, birth weight percentile, and conceptual age, the low birth weight group is comprised of infants who are only mildly to moderately low birth weight and were essentially healthy except for their low birth weight status. The normal birth weight group was composed of infants from the "infant save" program who were not able to survive in the colony environment and thus may also contain infants with some risk factors. Both very low birth weight infants and infants with no risk factors were not well represented in the samples of infants for this study.

Description of Heart Rate Variability Over First Two Months

Standard Statistical Measures of Heart Rate Variability

Mean values for heart period and the heart rate variability measures trimmed at the 0.05 alpha level were derived from the five minutes of IBI's (Interbeat Intervals) collected during sleep for each of the infants at six different days of estimated post conceptional age--175, 180, 190, 200, 210, and 230. The sample size varies for different ages because of missing data. Three LBW and eight NBW infants were not admitted to the IPRL in time for the 175 day data collection. One NBW infant was ill and could not be tested at 180 days. One LBW infant was ill and could not be tested at 190 days. Equipment failure accounted for missing data for one NBW infant at 175 and 180 days and one NBW infant at 200 days. Appendix B contains the values for each infant at each age of testing. These values were then used for further descriptive and inferential analysis of the data. Because of the relatively small sample size, the non-normality of the distribution, and the occurrence of outliers in many of the variables at different ages, medians and interquartile ranges were determined to be the best descriptors for measures of central tendency and distribution for the heart rate measures. Nonparametric tests were used for measures of relationships and inferential statistics. Table 2 presents the medians and interquartile ranges for heart period and the standard statistical measures of heart rate variability during

sleep at the six different ages for both low birth weight and normal birth weight groups. There were no gender differences in any of the heart rate variability measures for either low birth weight or normal birth infants at any of the six ages. Figures 1 through 3 present boxplots showing the medians, interquartile ranges, minimum, maximum, and outliers for MEAN HEART PERIOD and the standard statistical heart rate variability measures of HP STDDEV (standard deviation) and HP RMSSD (root mean square of successive differences) across ages for both low birth weight and normal birth weight infants. Boxplots for the other heart rate variability measures are in Appendix C. One normal birth weight infant had values more than four standard deviations from the mean on most of the heart rate variability measures at estimated postconceptional ages 180 and 230. For the purpose of boxploting (to maintain scaling characteristics) his scores were modified so that they maintained rank order but were valued at one millisecond above the next highest infant values (Tabachnick and Fidell, 1989).

Normal Birth Weight Infants

The median heart period for normal birth weight infants ranged from a low of 251.0 (interquartile range[IQR]=25.9) at 190 days to a high of 313.2 (IQR=88.7) at 175 days of age. These median heart period values at 190 and 175 days are equivalent to heart rates of 192 and 239 beats per minute. Figure 1 shows the distribution for heart period across ages for both low birth weight and normal birthweight infants. A Friedman Anova across the five ages with adequate sample size (180 through 230) found a significant difference (Chi-Square 14.47, p=0.006) for median heart periods for normal birth weight infants. Subsequently, pairwise Wilcoxon Matched Pairs tests were done to identify the ages of the differences at a criterion p level ≤ 0.05. The median heart period at 180 days was significantly longer than those at 190, 200, and 210. The 190 day median heart period was significantly shorter than 210 and 230. The median heart period at 200 days was significantly shorter than the median heart period at 230.

HP STDDEV (standard deviation), HP IQR (interquartile range), and HP MAD (median absolute deviation) are standard statistical measures of long-term or total variability. These three measures were highly intercorrelated: Aggregated across all ages for normal birth weight infants, Spearman correlation coefficients for HP STDDEV with HP IQR, HP STDDEV with HP MAD, and HP IQR with HP MAD were highly intercorrelated with $r \geq 0.93$, $p=0.000$). (Appendix D contains the Spearman correlations for all heart rate variability measures aggregated across ages for both LBW and NBW groups.) Measures of total variability were quite small. HP STDDEV ranged in milliseconds from 5.0 (IQR=3.0) at 190 days to 9.2 (IQR=8.1) at 175 days. These values represent 10 and 11 beats per minute when converted to heart rate measures. HP IQR ranged from 7.2 (IQR=5.4) at 190 days to 10.5 (IQR=9.0) at 180 days. HP MAD ranged from 5.8 (IQR=3.6) at 190 days to 8.5 (IQR=5.4) at 175 days. Figure 2 shows the distribution for HP STDDEV across ages. A Friedman Anova to test for differences across ages 180 to 230 for normal birth weight infants was significant for HP STDDEV (Chi-Square 9.74, $p=0.045$). HP MAD and HP IQR appeared to have a similar trend (Appendix B) but were not significant. Wilcoxon Matched Pairs testing for HP STDDEV found 180 significantly greater than 190 and 200, and 190 less than 210 ($p \leq 0.05$).

HP RMSSD (root mean square of successive differences) and HP IQRSD (interquartile range of successive differences) were standard statistical measures of short-term heart rate variability. These two measures were also highly intercorrelated for scores aggregated across ages: Spearman correlation ($r=0.83$, $p=0.000$). HP RMSSD ranged from 1.6 milliseconds (IQR=1.1) at 190 days to 3.4 milliseconds (IQR=3.7) at 175 days (equivalent to 3 to 4 heart rate beats per minute). A Friedman Anova for differences across ages for normal birth weight infants was significant at $p=0.063$ (Figure 3). Wilcoxon Matched Pairs (criterion $p=\leq 0.05$) found 180 greater than 190 and 190 less than

230. HP IQRSD ranged from 1.8 (IQR=1.1) at 190 to 4.0 (IQR=5.3) at 175. The differences across ages 180 to 230 for HP IQRSD were not significant.

Low Birth Weight Infants.

The median heart period in milliseconds for low birth weight infants ranged from a low of 252.8 (IQR=27.5) at age 180 days to a high of 286.0 (IQR=45.2) at 230 days of age. These median heart period values at 180 and 230 days are equivalent to heart rates of 237 and 210 beats per minute. Although the pattern for change across ages for low birth weight infants (Figure 1) appeared similar to that for normal birth weight infants a Friedman Anova test found no significant differences between the median heart periods across the different ages in low birth weight infants.

HP STDDEV (standard deviation), HP IQR (interquartile range), and HP MAD (median absolute difference) were used as standard statistical measures of total or long-term heart rate variability. These three measures were highly intercorrelated: Aggregated across all ages for low birth weight infants Spearman correlation coefficients for HP STDDEV with HP IQR, HP STDDEV with HP MAD, and HP IQR with HP MAD were 0.98, 0.96, and 0.98 respectively (p=0.000). Measures of total variability were again quite small: The median HP STDDEV in milliseconds ranged from 4.8 (IQR=9.0) at 190 days of age to 11.0 (IQR=11.0) at 230 days of age; the median HP IQR ranged from 6.2 (IQR=8.9) at 190 days to 14.5 (IQR=13.4) at 230 days; the median HP MAD ranged from 5.0 (IQR=8.3) at 190 days to 11.5 (IQR=9.8) at 230 days. At a median heart period of 252.8 msec (heart rate 237) a HP STDDEV of 4.8 msec represents nine beats per minute. There were no significant differences between median values of HP STDDEV, HP IQR, or HP MAD across the six ages.

HP RMSSD and HP IQRSD were standard statistical measures of short-term heart rate variability. These two measures were also highly correlated for scores aggregated across ages: Spearman correlation 0.84 (p=0.000). HP RMSSD median values in

milliseconds ranged from 1.6 (IQR=2.7) at 190 days to 5.9 (IQR=6.6) at 230 days. The range of median values for HP IQRSD was 1.1 (IQR=2.5) at 190 days to 4.0 (IQR=4.3) at 230 days. There were no significant differences between median values of either HP RMSSD or HP IQRSD across ages.

Comparison of LBW and NBW Infants.

There were significant differences in the median heart periods at estimated conceptional ages 175 and 180 between low birth weight and normal birth weight infants. Normal birth weight infants had longer heart periods (slower heart rates) at those ages (Mann-Whitney U, $p \leq 0.03$) than low birth weight infants. There were no significant differences between LBW and NBW infants for any of the measures of total or short-term variability at any of the estimated postconceptional ages.

In order to determine if postnatal age (rather than estimated postconceptional age) would result in differences between the low birth weight and normal birth weight groups, Mann-Whitney U tests were performed between groups using mean postnatal age at times of testing based on estimated postconceptional age.. The mean postnatal age of low birth weight infants at the 180 day estimated postconceptional age test was 19 days while the mean postnatal age for normal birth weight infants at the 190 day estimated postconceptional age test was 17 days. At this similar postnatal age (19 for LBW and 17 for NBW) the low birth weight group was significantly higher for HP RMSSD (opposite from what was predicted). The mean postnatal age of low birth weight infants at the 190 test was 29 days while the mean postnatal age for normal birth weight intants at the 200 test was 27 days. There were no significant differences in heart period or heart rate variability measures between groups at this similar postnatal age. Comparison of low birth weight infants at the 200 testing (mean postnatal age 38 days) and normal birth weight infants at the 210 testing (mean postnatal age 36 days) was also non significant for all heart rate variables. MEAN HEART PERIOD was significantly shorter for low birth

weight infants at 49 days (210 test) than normal birth weight infants at 55 days (230 test) with $p \leq 0.01$.

Since the only significant difference between low birth weight and normal birth weight groups for same estimated postconceptional age testing was for MEAN HEART PERIOD at 180, the groups were combined to test for the significance in the changes across time for each of the standard statistical measures of heart period and heart rate variability. Friedman Anova found significant differences across the different ages from 180 through 230 for MEAN HEART PERIOD (Chi Square=11.08, p=0.026), HP STDDEV (Chi Square=10.39, p=0.034), and HP RMSSD (Chi Square=12.59, p=0.014). HP MAD, HP IQR, and HP IQRSD were not significant with p=0.148, p=0.135 and p=0.124 respectively. Subsequent Wilcoxon Matched Pairs testing (at a significance level of ≤ 0.05) found MEAN HEART PERIOD at 180 greater than 190, 200, and 210; 190 less than 210 and 230; and 200 less than 230. HP STDDEV at 180 was significantly greater than 190 and 200 while 190 was less than 210. For HP RMSSD 180 was greater than 190 and 190 was less than 230.

Spectral Measures of Heart Rate Variability

Figure 4 shows the distribution of variance in the three frequency bands: VLF (very low frequency), LF (low frequency), and HF (high frequency) of the spectral curve across ages for low birth weight and normal birth weight infants. The high frequency band accounts for very little of the total variance at any of the ages for either LBW or NBW infants. The low frequency band is predominant for LBW infants at all ages except 210. The VLF and LF bands are equivalent for NBW infants at each age. The values for the medians and interquartile ranges of the spectral measures for both low birth weight and normal birth weight infants at different estimated postconceptional ages are presented in Table 3.

There were no significant differences between the low birth weight and normal birth weight group for any of the spectral measures at any of the estimated postconceptional ages of testing or when compared at similar postnatal ages.

Appendix C contains comparison boxplots for LBW and NBW infants for spectral total variance (TVAR), VLF, LF, and HF. The interquartile ranges depicted in the boxplots generally demonstrate a wider dispersion of values in the low birth weight group for all of the spectral measures at all ages although there were more outliers in the normal birth weight group. As in the standard statistical measures of heart rate variability, the medians of the spectral frequency measures showed no differences across ages for low birth weight infants. There were significant differences in the medians for normal birth weight infants in TVAR and LF (Friedman Anova $p \leq 0.05$). For TVAR, age 180 was greater than 190, 200, and 210 ($p \leq 0.05$). For LF, age 180 was greater than 190 and 200 ($p \leq 0.05$) and 190 was less than 200 and 230 ($p \leq 0.05$). When the groups were combined to test for differences across ages, there were no differences for any of the spectral measures.

Derived Measures of Heart Rate Variability

The ratios of SD / RMSSD (standard deviation divided by root mean square standard deviation) and LF / HF (spectral low frequency divided by spectral high frequency) were derived for all infants at all ages to determine the relative proportions of long-term variability to short-term variability which theoretically represents the relative proportion of more sympathetically controlled variability versus parasympathetically controlled variability. Appendix B contains boxplots showing the distribution of these variables across ages for both LBW and NBW infants. There were no differences across ages for either SD / RMSSD or LF / HF for either group of infants. There were also no differences between LBW and NBW groups at any age for these measures.

Stability of Heart Rate Variability Measures Across Ages for Individuals.

Spearman Rank Correlations were performed to test for stability of heart period and heart rate variability measures across ages for individual infants. Comparisons were made across the six estimated postconceptional ages for each of the twelve heart rate variables for the low birth weight group, the normal birth weight group, and the groups combined. Appendix E contains tables showing the correlations across ages for heart rate variability measures for low birth weight infants, normal birth weight infants and the combined groups. For low birth weight infants there were only 15 correlations significant at $p \leq 0.05$ for all of the comparisons for an average of 1.25 significant correlations for each heart rate variable. For normal birth weight infants there were a total of only 11 correlations significant at $p \leq 0.05$ for an average of 0.9 significant correlations for each variable. The number of significant correlations for each group does not differ from what would be expected by chance alone. When the groups were combined, a total of 33 correlations significant at $p \leq 0.05$ were found for an average of 2.2 significant correlations for each variable. Although this number is greater than for groups analyzed separately, it also does not differ significantly from chance. In addition, there is no consistent discernible pattern to the significant correlations; e.g., they are not grouped at younger ages, older ages, or at adjacent ages.

Auditory Evoked Heart Rate Response

Data from fifteen normal birth weight and seven low birth weight infants were used in the analysis. Computer error resulted in the loss of data for one low birth weight infant and one low birth weight infant completed the study after analysis had been completed on the AER data. There was no difference between groups in the mean heart rate in the initial baseline period before the first auditory stimulus. The mean heart rate for low birth weight infants in the initial baseline period was 223.9 (SD=25.5). The mean heart rate for normal birth weight infants in the initial baseline period was 224.9 (SD=15.7). Figure 5

shows the pattern of response to auditory stimuli on day one in trial blocks of five (trials 1-5, 6-10, 11-15, 16-20, and 21-25) for both low birth weight and normal birth weight infants. In the first trial block both groups of infants had an initial increase in heart rate above baseline within the first five seconds, showed a maximum deceleration below baseline by ten to eleven seconds, and returned to baseline between twenty and twenty-five seconds. The low birth weight infants demonstrated slightly more acceleration above baseline, decelerated further, and took longer to return to baseline. In the second trial block, normal birth weight infants had very little acceleration (approximately 3 beats/minute) or deceleration (approximately 1 beat/minute) while low birth weight infants accelerated approximately 7 beats/minute and decelerated approximately 4 beats/minute. Both groups had stabilized at baseline by twenty seconds. The normal birth weight group maintained a similar pattern for the last three trial blocks. By trial block four, the low birth weight group had diminished both their acceleratory and deceleratory responses. A repeated measures ANOVA was done to examine statistical significance for these apparent patterns. In order to reduce the number of data points for the repeated measures design, the mean value for five second intervals from stimulus onset for each trial (resulting in six means for seconds from stimulus onset 1-5, 6-10, 11-15, 16-20, 21-25, and 26-29) was calculated. The repeated measures ANOVA then used groups (LBW and NBW) as the uncorrelated measure with means of seconds from stimulus, trial blocks, and days as repeated measures. The means of seconds was the only significant main effect ($p=0.000$) validating the acceleratory and deceleratory responses. The decrement in response across trial blocks was confirmed by a highly significant ($p=0.000$) interaction of means of seconds from stimulus and trial blocks. The three way interaction of group by means of seconds from stimulus by trial block was significant at $p=.042$ thus confirming that the normal birth weight group decreased its response more rapidly over time. Figure 6 shows the pattern of response on day one with means of seconds used instead of all seconds from

stimulus onset. This represents the data as analyzed in the repeated measures ANOVA. There was also a significant three way interaction of day by trial block by means of seconds from stimulus (p=0.042). On day two, both groups of infants had a moderate acceleratory response in trial block one and then showed minimal response in subsequent trial blocks (Figure 7).

In addition, maximum heart rate change above baseline (MAXIMUM), maximum heart rate change below baseline (MINIMUM) and the range between the maximum above and below baseline change (RANGE) was determined for each stimulus trial for both low birth weight and normal birth weight groups. Figures 8, 9, and 10 show the distributions of MAXIMUM, MINIMUM, and RANGE across trial blocks for both days and for both groups of infants. A repeated measures analysis of variance with birth weight group as the uncorrelated measure and trial blocks (trials aggregated-1-5, 6-10, 11-15, 16-20, and 21-25) and days as repeated measures was done for MAXIMUM, MINIMUM, and RANGE. The trial block main effect was significant for MAXIMUM (p=0.009), MINIMUM (p=0.003), and RANGE (p=0.001). There was no significant main effect for either group or days on the three measures. The interaction effect of trial block by days was significant for RANGE (p=0.044). The interaction effect of group by trial block for all three of the measures was non-significant: MAXIMUM (p=0.29), MINIMUM (p=0.15) and RANGE (p=0.12).

In order to determine if activity level influenced the heart rate changes during the auditory evoked response trials, mean activity level during each trial block was calculated for each infant and tested against MAXIMUM, MINIMUM, and RANGE for the corresponding trial blocks using Spearman Rank Correlations. Activity level was not correlated with heart rate changes for trial blocks one, two, three, or five. There was a positive correlation between activity level and all three measures of heart rate change in

trial block four: for MAXIMUM, r=0.50 (p=0.017); for MINIMUM, r=.48 (p=0.023); and for RANGE, r=.66 (p=0.001)

Relationships Between Heart Rate Variability and Auditory Evoked Response

Spearman Rank Correlations were done to identify relationships between Heart Rate Variability measures obtained during sleep at age 200 and the MAXIMUM, MINIMUM, and RANGE values by trial blocks obtained on the Auditory Evoked Response testing for Day One which were done between ages 198 and 202. Tables 4, 5, and 6 present those results. Initally, the correlations were done with the low birth weight and normal birth weight groups combined. There were a few significant correlations between heart rate variability measures and MAXIMUM for the groups combined. Most of the heart rate variability measures were significantly related to both the MINIMUM and RANGE values of the auditory evoked response measures for Trial Blocks One through Three with correlations ranging from r=0.43 to r=0.65 when the groups were combined. The relationships between total or long term heart rate variability measures and RANGE were usually significant at p=0.01 or greater.

When the groups were analyzed separately, the normal birth weight group had the same pattern of significantly related results between heart rate variability measures and MAXIMUM, MINIMUM, and RANGE for Trial Blocks One through Three as found for the groups combined. Examination of the results for low birth weight infants alone, indicated that the correlation values were as high and had apparently the same distribution but did not reach significance. The lack of significance for the low birth weight infants may have been due to the small sample size.

Performance on Recognition Memory Testing

The proportion of looking time directed toward the novel stimulus was calculated for each of the recognition problems for each estimated postconceptional age of testing for each infant. An infant's novelty preference score for each age was then calculated as the

average of the problem scores available for that age period (three possible scores for 180 and 190; two possible scores for 200 and 210). An summary novelty score based on the testing at 190, 200, and 210 ages was also computed by averaging the proportion of looking time directed toward the novel stimulus for all available problem scores (seven possible scores). A description of missing data and its treatment is on p. 26 in Chapter 2.

The mean proportion of looking time at the novel stimulus for each age and for the summary novelty score for the low birth weight and normal birth weight groups is presented in Table 7. At ages 180 low birth weight infants directed 56% of their looking time at the novel stimulus. This percentage differs from a chance looking time of 50% (t_6=2.61, p<0.025, one-tailed). Six of seven looked at the novel stimulus longer, p=0.062, one-tailed binomial. At age 190 for low birth weight infants a novelty score of 54% was significant with a one-tailed t_5=2.5, p<0.05. Again six of seven looked longer at the novel stimulus, p=0.11, one-tailed binomial. The proportion of time looking at the novel stimulus at ages 200 and 210 or for the summary novelty score was not significantly different from chance for the low birth weight infants.

Normal birth weight infants directed a mean of 56% of their looking time at the novel stimulus at the 190 age testing. This differs from chance, t_{13}=3.16, one-tailed, p< 0.005. Twelve of fourteen infants looked longer at the novel stimulus, p<0.006, one-tailed binomial. The summary novelty score for normal birth weight infants was 55%, t_{14}=2.78, one-tailed, p<0.01. Twelve of fifteen looked longer at the novelty stimulus, p=0.017, one-tailed binomial. The proportion of time looking at the novel stimulus was not significant for normal birth weight infants at the 180, 200, or 210 ages.

An analysis of variance for repeated measures with estimated postconceptional age as the repeated measure, low birth weight and normal birth weight groups as the nonrelated measure and postnatal age as a covariate was done to examine differences between groups and across ages. There were no significant findings for the main effects of

groups (low birth weight vs normal birth weight) or estimated postconceptional age of testing. Postnatal age as a covariate was also not significant.

A repeated measures analysis of variance was also performed using the amount of time infants required to reach predetermined familiarization time for problems at each of the ages. There was no significant difference between the low birth weight and normal birth weight groups and no effect for the covariate of postnatal age. There was a significant effect for ages of testing but this was expected because the predetermined familiarization times were age and problem specific.

Correlations were done to examine the consistency of novelty preference scores across ages and with the summary novelty score for both low birth weight and normal birth weight infants. There was no consistency across ages 180, 190, 200, and 210 for either group of infants. There was a predictable relationship between the 210 testing and the summary novelty score: For low birth weight infants $r=0.69$, $p=0.038$ and for normal birth weight infants $r=0.81$, $p=0.000$.

Relationships between Heart Rate Variability and Recognition Memory Testing

Spearman Rank Correlations were done to test for relationships between concurrent standard statistical and spectral measures of heart rate variability and performance on tests of recognition memory at the 180, 190, 200, and 210 ages of testing. For normal birth weight infants LF was negatively correlated, $r=-0.61$ at age 180 with novelty preference scores. For low birth weight infants at age 180, novelty preference on recognition memory testing was correlated with HP IQRSD ($r=0.91$, $p=0.005$) and VLF ($r=0.86$, $p=0.014$). There were no other significant relationships between heart rate variability measures and recognition memory scores for either group of infant at any other ages. With the groups combined there were only three relationships significant at $p\leq 0.05$ between heart rate variables and novelty preference scores across all ages: MEAN HEART PERIOD at 180, LF at 200 and VLF at 210. There were no significant

relationships between time to accumulate familiarization time and heart rate variability measures for either group at any age.

Table 1. Subject Information: Eartag identification, lab number, sex, estimated conceptional age at birth, birthweight in grams, birthweight percentile, postnatal age in days at ECA 180, pre-pregnancy maternal weight, and maternal parity.

NORMAL BIRTH WEIGHT INFANTS

ET	Lab No	S	ECA	BW	%ile	PNA180	MatWt	P
WZ	J92239	F	167	434	51	12	5.7	3
YR	F92289	F	173	536	95	8	7.0	15
CL	J92399	F	173	500	89	8	5.3	4
EP	J92469	F	177	545	97	3	8.5	8
FA	F92480	F	176	525	94	4	7.0	13
GN	F92533	F	180	653	100	2	8.8	11
IR	K93049	F	176	560	97	6	6.3	6
JC	T93064	F	173	545	96	8	7.1	2
XO	F92257	M	171	475	49	11	8.6	7
DG	K92427	M	172	455	38	12	6.4	1
EZ	J92479	M	174	539	84	8	11.0	9
HE	J93007	M	174	590	99	6	5.6	2
JA	T93060	M	174	608	98	7	7.8	7
JJ	J93072	M	173	538	96	9	7.2	4
LM	K93136	M	168	440	26	13	4.9	2
Mean			173	530	82	8	7.1	6.3
S.D.			3.3	62	26	6	1.6	4.3

LOW BIRTH WEIGHT INFANTS

ET	Lab No	S	ECA	BW	%ile	PNA180	MatWt	P
XR	J92259	F	157	347	6	23	3.9	1
ZH	K92307	F	156	331	4	29	4.2	1
MF	J93157	F	157	330	4	25	5.6	5
PN	F93251	F	166	350	6	14	8.1	8
XZ	F92268	M	166	400	10	14	6.5	4
YV	K92293	M	162	385	4	16	5.0	3
CH	J92395	M	164	392	9	14	10.3	4
CT	J92407	M	164	397	10	16	5.1	5
SJ	M93311	M	159	336	1	21	4.7	2
Mean			161	363	6	19	5.9	3.7
S.D.			4	30	3	6	2.1	2.2

Table 2. Median and IQR for Standard Heart Rate Variability Measures in Milliseconds for Low Birth Weight and Normal Birth Weight Infants at Different Estimated Postconceptional Ages.

	AGE	175	180	190	200	210	230
VARIABLE	GROUP						
HEART PERIOD	LBW	268.8 (43.3)	252.8 (27.5)	254.4 (26.4)	263.9 (50.9)	263.1 (28.6)	286.0 (45.2)
	NBW	313.2 (88.7)	290.6 (49.7)	251.0 (25.9)	263.5 (33.2)	269.7 (37.8)	289.5 (76.3)
HP STDDEV	LBW	6.3 (6.2)	8.7 (7.3)	4.8 (9.0)	8.1 (7.4)	9.3 (10.2)	11.0 (11.0)
	NBW	9.2 (8.1)	8.7 (3.4)	5.0 (3.0)	6.2 (3.1)	7.2 (5.0)	7.7 (8.8)
HP IQR	LBW	8.0 (12.1)	11.5 (7.6)	6.2 (8.9)	9.5 (7.7)	11.7 (13.5)	14.5 (13.4)
	NBW	10.2 (6.5)	10.5 (9.0)	7.2 (5.4)	8.5 (4.3)	8.3 (7.5)	10.0 (8.5)
HP MAD	LBW	5.6 (8.8)	6.7 (6.0)	5.0 (8.3)	7.4 (6.9)	6.7 (9.0)	11.5 (9.8)
	NBW	8.5 (5.4)	8.2 (5.9)	5.8 (3.6)	6.7 (3.6)	6.3 (5.2)	6.7 (7.7)
HP RMSSD	LBW	2.6 (2.1)	2.5 (2.9)	1.6 (2.7)	2.6 (7.1)	3.2 (5.4)	5.9 (6.6)
	NBW	3.4 (3.7)	2.4 (1.5)	1.6 (1.1)	1.9 (2.1)	2.0 (1.4)	2.7 (3.6)
HP IQRSD	LBW	2.2 (1.9)	1.5 (1.4)	1.1 (2.5)	1.5 (4.9)	3.5 (2.4)	4.0 (4.3)
	NBW	4.0 (5.3)	2.5 (1.5)	1.8 (1.1)	1.8 (2.5)	2.0 (1.3)	2.5 (3.5)

Note: Subject number varied by age and group LBW 175 n=6, 180 n=9, 190 n=8, 200, 210, 230 n=9. NBW 175 n=6, 180 n=13, 190 n=15, 200 n=14, 210, 230 n=15 Standard Deviation (HP STDDEV) Interquartile Range (HP IQR) Median Absolute Deviation (HP MAD) Root Mean Square of Successive Differences (HP RMSSD) Interquartile Range of Successive Differences (HP IQRSD)

Table 3. Median and IQR for Spectral and Derived Heart Rate Variability Measures for Low Birth Weight and Normal Birth Weight Infants at Different Estimated Postconceptional Ages.

	AGE	175	180	190	200	210	230
VARIABLE	GROUP						
SPECTRAL TVAR	LBW	41.71 (114.45)	57.24 (106.25	36.77 (170.47)	68.45 (122.51)	76.80 (165.10)	125.40 (228.73)
	NBW	101.50 (218.99)	81.63 (62.75)	29.12 (26.52)	45.69 (38.74)	51.65 (75.32)	53.44 (146.55)
SPECTRAL VLF	LBW	19.30 (55.39)	20.16 (32.37)	27.20 (55.91)	26.57 (50.30)	52.97 (69.84)	36.76 (70.13)
	NBW	51.38 (83.01)	45.03 (53.51)	12.90 (24.37)	19.29 (21.29)	18.28 (35.80)	18.08 (65.27)
SPECTRAL LF	LBW	25.81 (58.02)	38.47 (58.26)	9.18 (89.28)	42.06 (67.80	20.23 (102.30)	59.83 (130.94)
	NBW	30.04 (121.11)	33.88 (47.21)	14.70 (11.67)	23.90 (18.30)	20.83 (40.11)	28.97 (64.31)
SPECTRAL HF	LBW	2.55 (4.97)	1.94 (2.10	1.02 (5.15)	1.84 (11.69)	2.90 (5.26)	4.50 (15.54)
	NBW	3.78 (8.53)	1.85 (2.64)	1.11 (0.93)	1.28 (2.74)	0.96 (1.36)	2.27 (4.71)
LF / HF	LBW	12.64 (17.04	20.72 (15.99)	16.11 (18.19)	13.32 (15.51)	14.66 (7.56)	10.04 (6.16)
	NBW	14.43 (37.23)	16.14 (23.46)	13.96 (13.88)	11.49 (42.47)	14.55 (27.02)	13.24 (15.34)
SD / RMSSD	LBW	3.11 (1.18)	2.39 (0.98)	3.36 (1.87)	2.89 (1.20)	2.09 (1.72)	2.04 (1.09)
	NBW	2.74 (2.67)	3.15 (1.65)	3.82 (2.57)	3.73 (2.65)	3.43 (2.03)	2.50 (1.77)

Note: Subject number varied by age and group LBW 175 n=6,180 n=9 190 n=8, 200, 210, 230 n=9. NBW 175 n=6, 180 n=13, 190 n=15, 200 n=14, 210, 230 n=15. Total Variance (TVAR) Very Low Frequency VLF) Low Frequency (LF) High Frequency (HF) Low Frequency divided by High Frequency (LF/HF) Standard Deviation divided by Root Mean Square of Successive Differences (SD/RMSSD)

Table 4. Spearman Correlations Between Heart Rate Variability Measures and Heart Rate Changes from Baseline On Auditory Evoked Response for Low Birth Weight and Normal Birth Weight Infants (n=22)

	HP STDDEV	HP RMSSD	TOTAL VARIANCE	VLF	LF	HF
MAXIMUM						
Trial Block						
One	.28	.39	.30	.27	.25	.33
Two	.43*	.43*	.46*	.35	.50*	.49*
Three	.35	.54**	.39	.21	.39	.45*
Four	.24	.37	.29	.09	.39	.34
Five	.69***	.50*	.68***	.72***	.64**	.49*
MINIMUM						
Trial Block						
One	.50*	.43*	.55**	.48*	.43*	.37
Two	.54**	.39	.62**	.49*	.58**	.41
Three	.61**	.51*	.65***	.47*	.61**	.47*
Four	.42	.40	.51*	.28	.52*	.39
Five	.35	.32	.33	.30	.29	.24
RANGE						
Trial Block						
One	.51*	.54**	.57**	.45*	.47*	.47*
Two	.60**	.46*	.67***	.54**	.64**	.42
Three	.61**	.57**	.68***	.44*	.67***	.52*
Four	.40	.50*	.48	.24	.52*	.44*
Five	.50*	.45*	.52*	.46*	.48*	.40

Note: *p ≤0.05 two-tailed **p ≤0.01 two-tailed ***p ≤0.001 two-tailed

Standard Deviation (HP STDDEV) Root Mean Square of Successive Differences (HP RMSSD) Spectral Total Variance (TOTAL VARIANCE) Spectral Very Low Frequency (VLF) Spectral Low Frequency (LF) Spectral High Frequency (HF) Maximum increase above baseline (MAXIMUM) Maximum decrease below baseline (MINIMUM) Maximum increase above baseline minus maximum decrease below baseline (RANGE)

Table 5. Spearman Correlations Between Heart Rate Variability Measures and Heart Rate Changes from Baseline On Auditory Evoked Response for Normal Birth Weight Infants (n=15)

	HP STDDEV	HP RMSSD	TOTAL VARIANCE	VLF	LF	HF
MAXIMUM						
Trial Block						
One	.30	.38	.25	.27	.05	.31
Two	.61*	.40	.55*	.43	.43	.57*
Three	.36	.53*	.45	.08	.42	.44
Four	.38	.44	.41	.06	.50	.40
Five	.79***	.35	.77***	.81***	.60*	.36
MINIMUM						
Trial Block						
One	.57*	.57*	.60*	.55*	.34	.44
Two	.45	.34	.46	.45	.28	.28
Three	.69**	.56*	.67**	.50	.52	.47
Four	.30	.25	.35	.10	.32	.14
Five	.46	.40	.45	.38	.38	.35
RANGE						
Trial Block						
One	.53*	.58*	.54*	.45	.30	.39
Two	.86***	.54*	.84***	.75**	.62*	.49
Three	.70**	.53*	.75**	.39	.70**	.46
Four	.46	.49	.53*	.17	.55*	.40
Five	.70**	.51	.73**	.63*	.55*	.47

Note: *p ≤0.05 two-tailed **p ≤0.01 two-tailed ***p ≤0.001 two-tailed

Standard Deviation (HP STDDEV) Root Mean Square of Successive Differences (HP RMSSD) Spectral Total Variance (TOTAL VARIANCE) Spectral Very Low Frequency (VLF) Spectral Low Frequency (LF) Spectral High Frequency (HF) Maximum increase above baseline (MAXIMUM) Maximum decrease below baseline (MINIMUM) Maximum increase above baseline minus maximum decrease below baseline (RANGE)

Table 6. Spearman Correlations Between Heart Rate Variability Measures and Heart Rate Changes from Baseline On Auditory Evoked Response for Low Birth Weight Infants (n=7).

	HP STDDEV	HP RMSSD	TOTAL VARIANCE	VLF	LF	HF
MAXIMUM						
Trial Block						
One	.29	.50	.36	.29	.50	.43
Two	.18	.43	.21	.18	.43	.25
Three	.29	.54	.25	.29	.43	.32
Four	.14	.46	.21	.14	.39	.36
Five	.82*	.93**	.86**	.82**	.89**	.93**
MINIMUM						
Trial Block						
One	.46	.54	.50	.46	.64	.43
Two	.46	.50	.61	.46	.68	.57
Three	.43	.43	.54	.43	.64	.43
Four	.54	.61	.64	.54	.68	.68
Five	.07	.43	.04	.07	.21	.21
RANGE						
Trial Block						
One	.64	.82*	.68	.64	.79*	.75*
Two	.25	.39	.29	.25	.46	.25
Three	.64	.71	.68	.64	.79*	.64
Four	.29	.57	.36	.29	.50	.50
Five	.29	.57	.36	.29	.50	.50

Note: *p ≤0.05 two-tailed **p ≤0.01 two-tailed ***p ≤0.001 two-tailed

Standard Deviation (HP STDDEV) Root Mean Square of Successive Differences (HP RMSSD) Spectral Total Variance (TOTAL VARIANCE) Spectral Very Low Frequency (VLF) Spectral Low Frequency (LF) Spectral High Frequency (HF) Maximum increase above baseline (MAXIMUM) Maximum decrease below baseline (MINIMUM) Maximum increase above baseline minus maximum decrease below baseline (RANGE)

Table 7. Means and Standard Deviations for Recognition Memory Novelty Preference Scores for Low Birth Weight and Normal Birth Weight Infants at Different Estimated Postconceptional Ages.

AGE	180	190	200	210	Summary
GROUP					
LBW	0.56 (0.06) * n=7	0.54 (0.04) * n=6	0.50(0.16). n=8	0.51 (0.19) n=8	0.52 (0.05) n=8
NBW	0.47 (0.07) n=11	0.56 (0.07) * n=14	0.52(0.15) n=15	0.56 (0.20) n=14	0.55 (0.07) * n=15

Note: * Different from chance at $p \leq 0.025$
Difference between groups significant at age 180 only, $p=0.006$

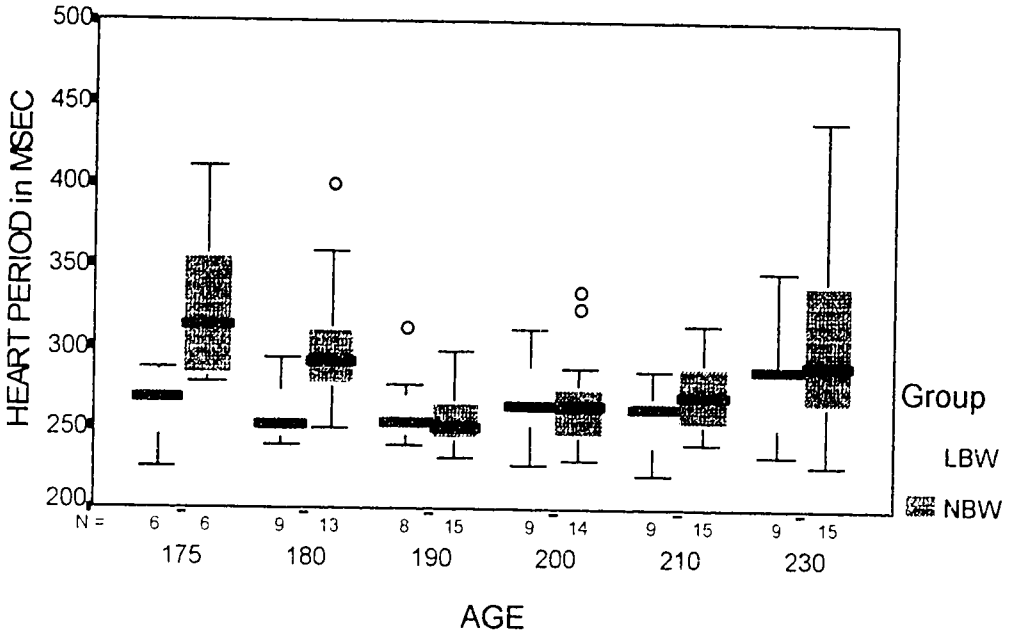

Figure 1. Mean Heart Period across estimated postconceptional ages for both low birth weight and normal birth weight infants.

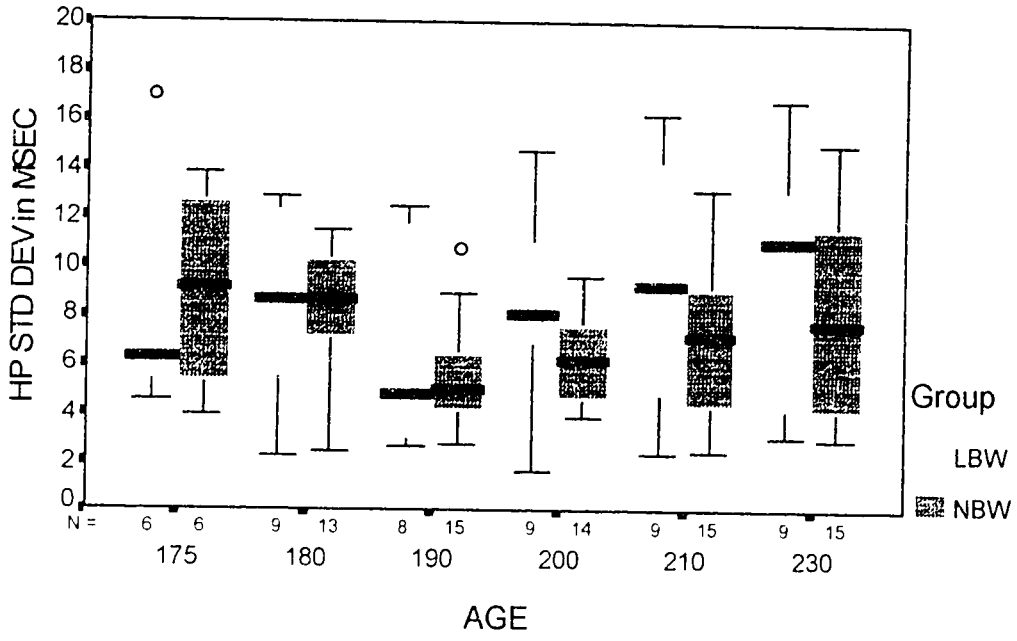

Figure 2. HP Standard Deviation across estimated postconceptional ages for both low birth weight and normal birth weight infants.

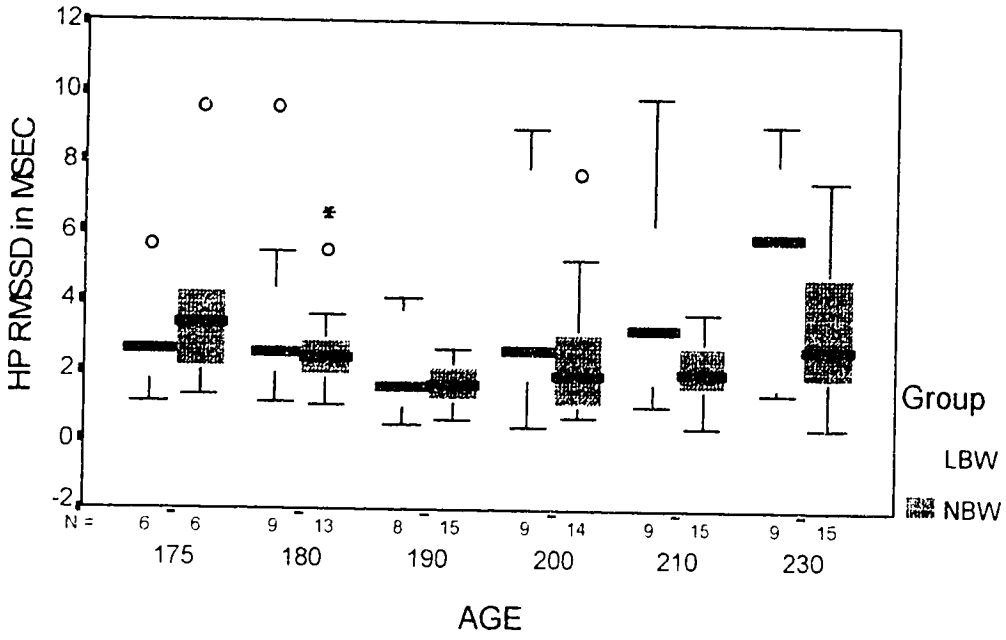

Figure 3. HP Root Mean Square of Successive Differences across estimated postconceptional ages for both low birth weight and normal birth weight infants.

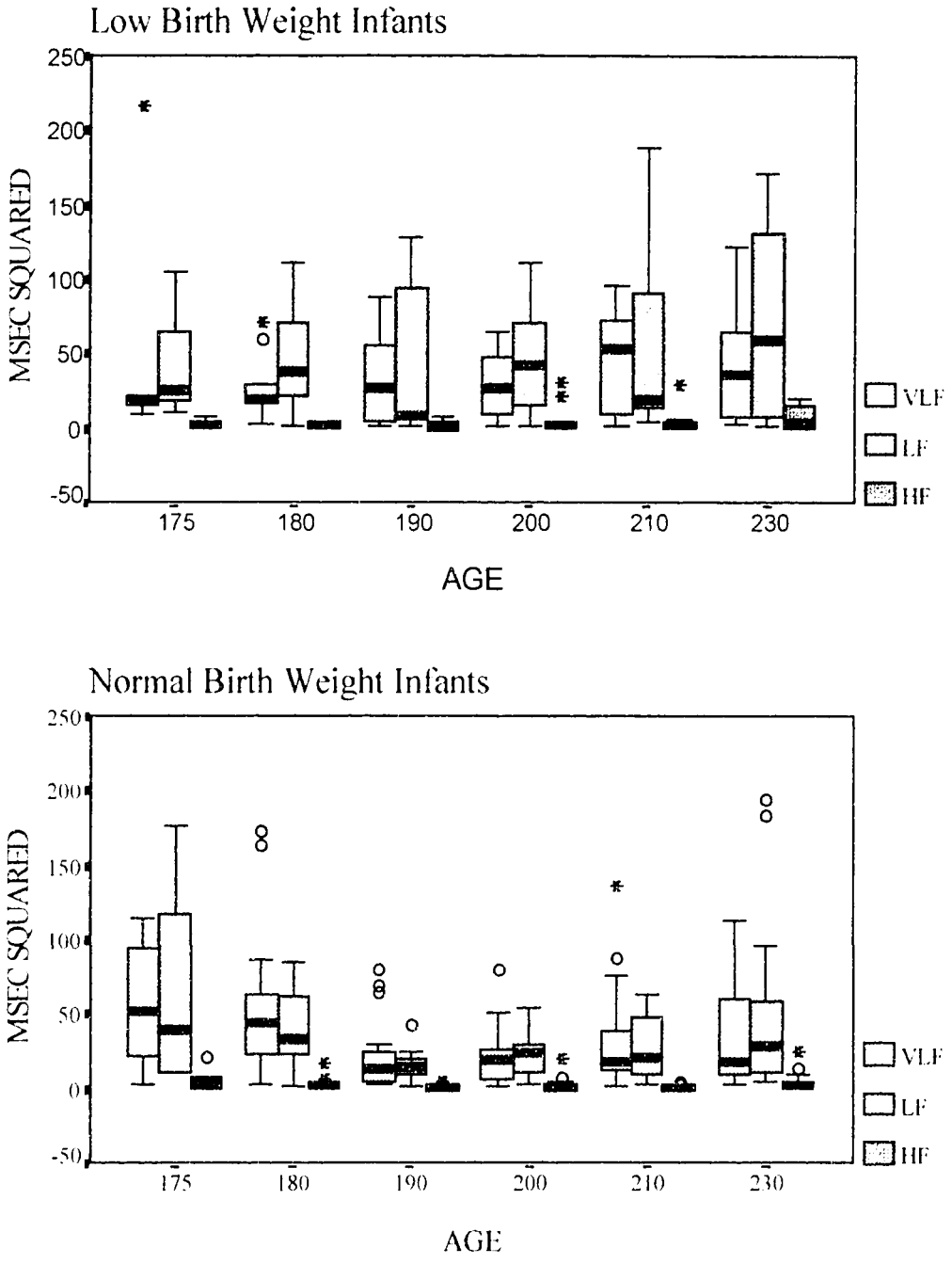

Figure 4. Comparison of the distribution of very low frequency (VLF), low frequency (LF), and high frequency (HF) components of spectral heart rate variability in milliseconds squared across estimated postconceptional ages for low birth weight and normal birthweight infants.

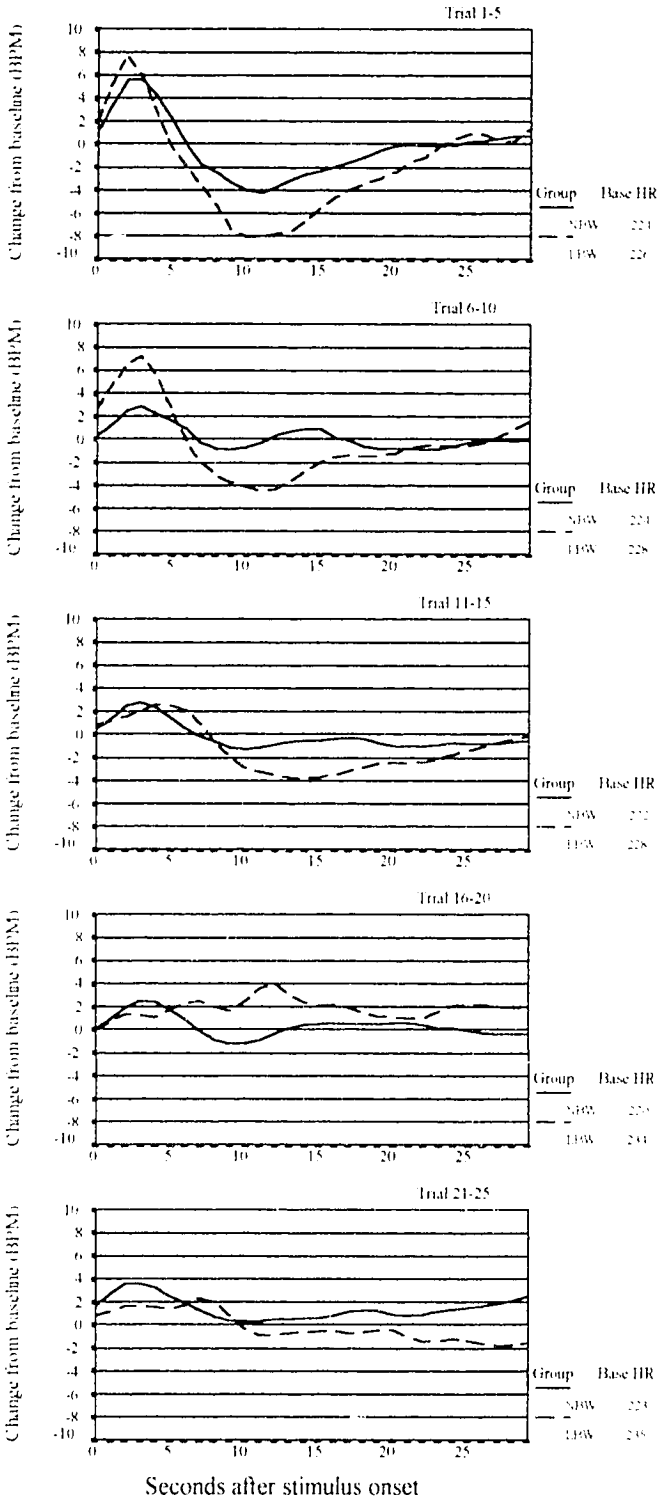

Figure 5. Heart rate response to auditory stimulus by trial block on day one.

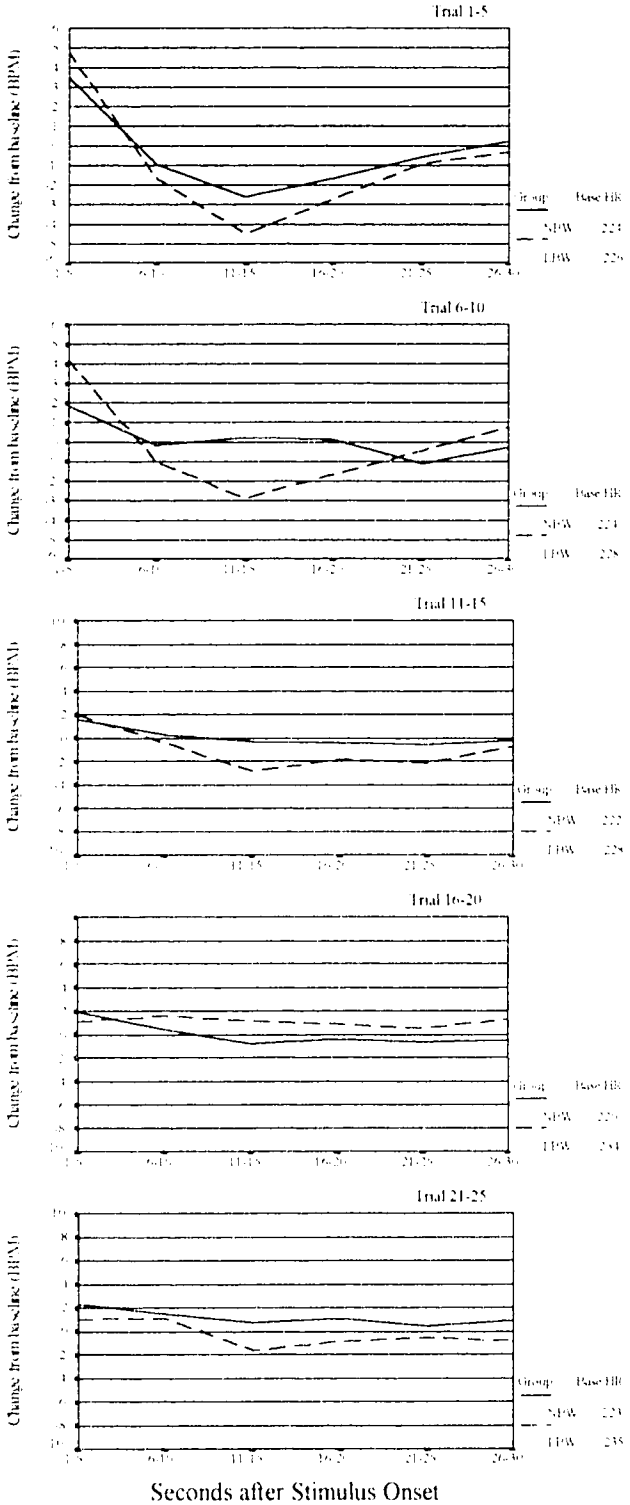

Figure 6. Heart rate response to auditory stimulus using means of five second intervals over trial blocks on day one.

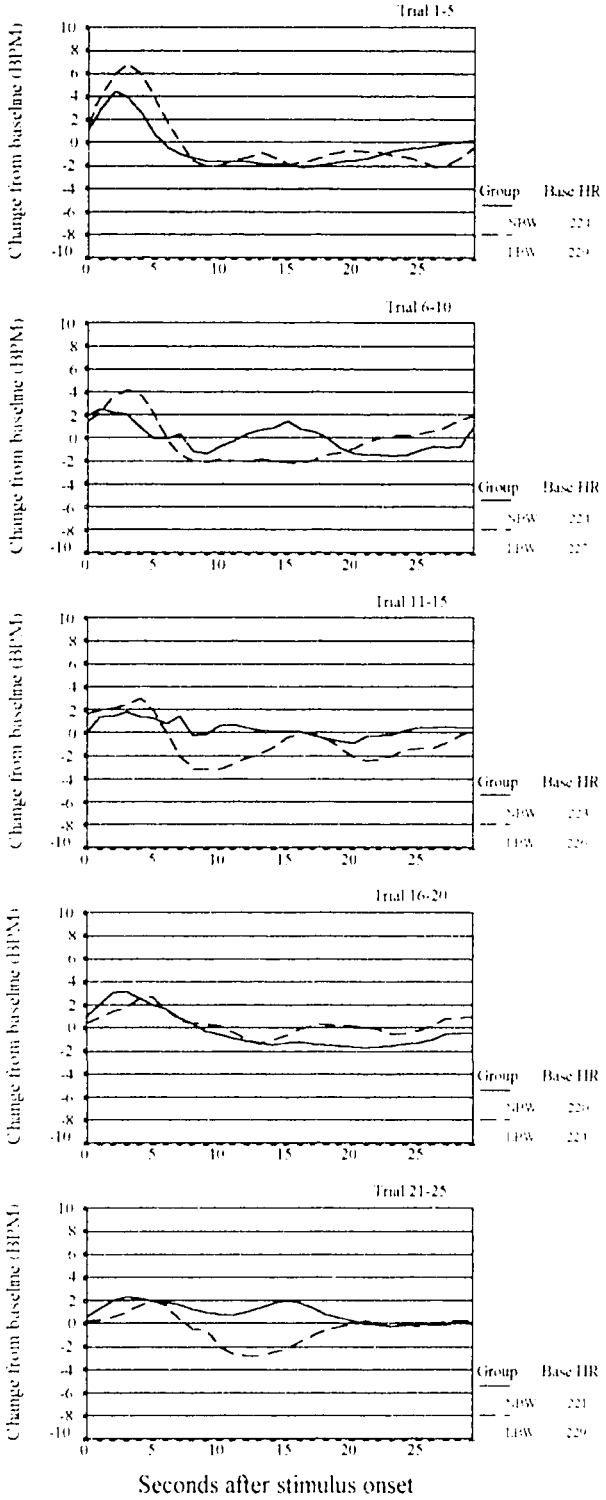

Figure 7. Heart rate response to auditory stimulus by trial block on day two.

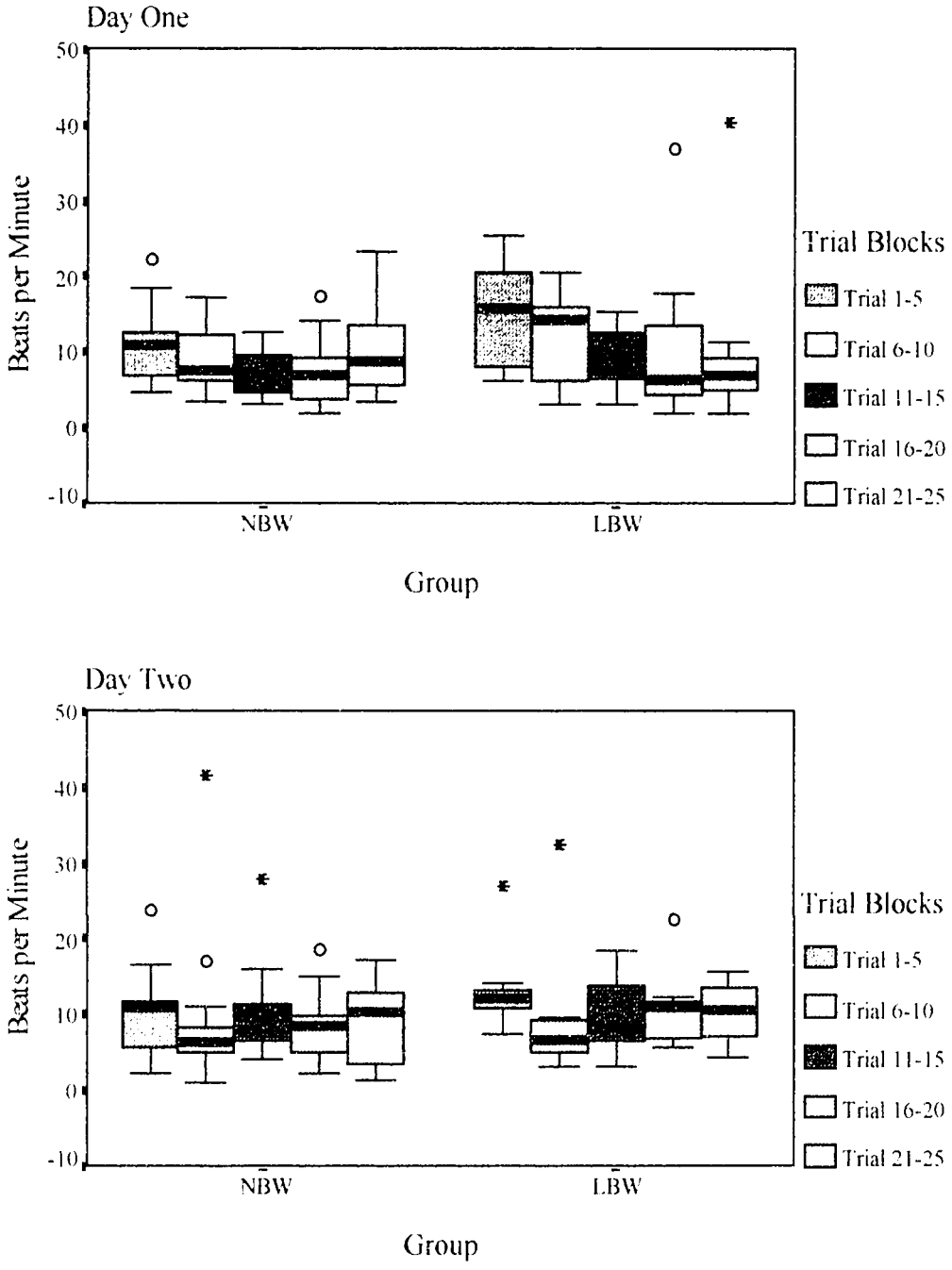

Figure 8. Distribution of MAXIMUM--Change in heart rate above baseline in response to auditory stimuli across trial blocks on days one and two for both low birth weight (LBW) and normal birth weight (NBW) infants.

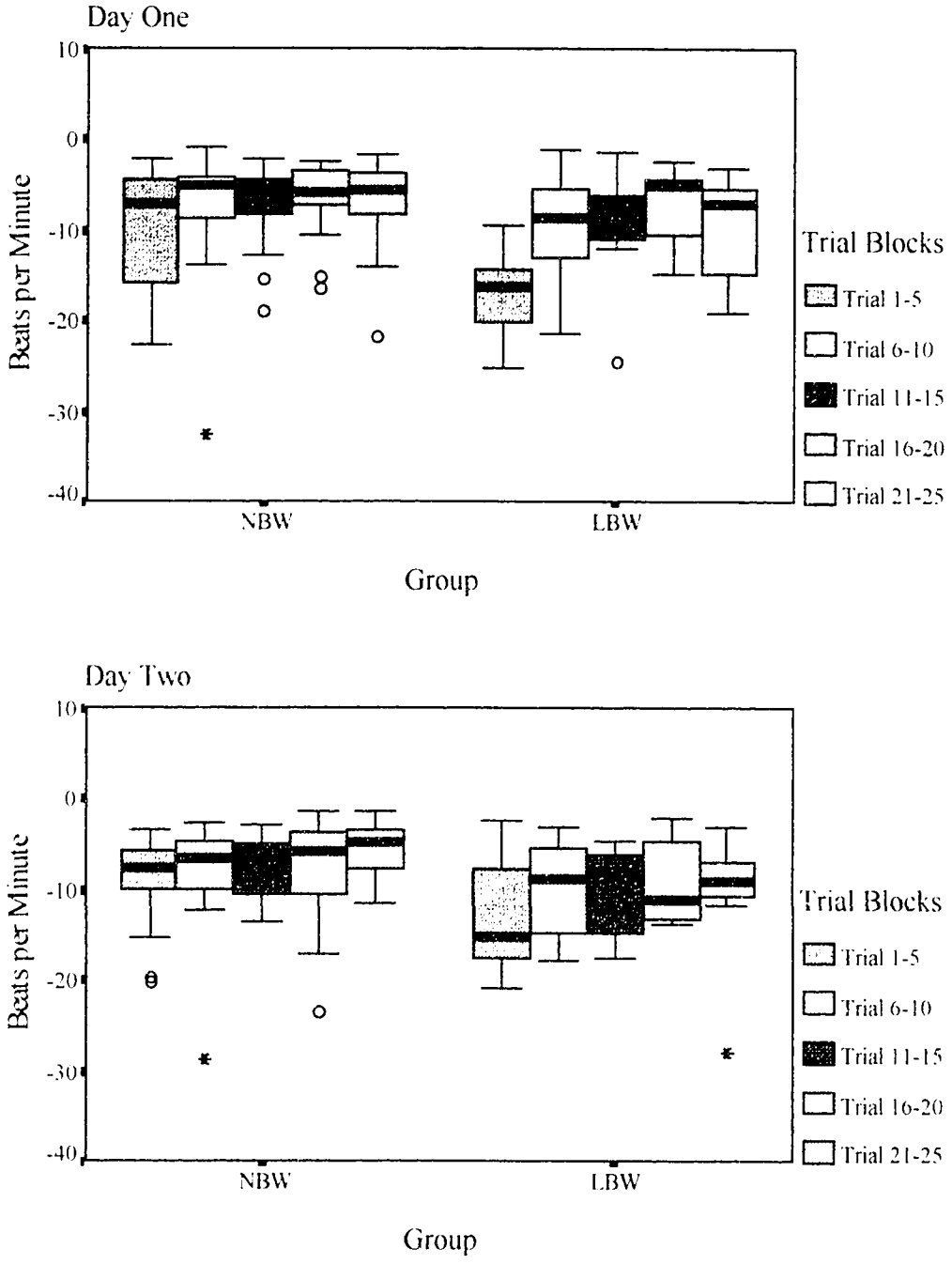

Figure 9. Distribution of MINIMUM--Change in heart rate below baseline in response to auditory stimuli across trial blocks on days one and two for both low birth weight (LBW) and normal birth weight (NBW) infants.

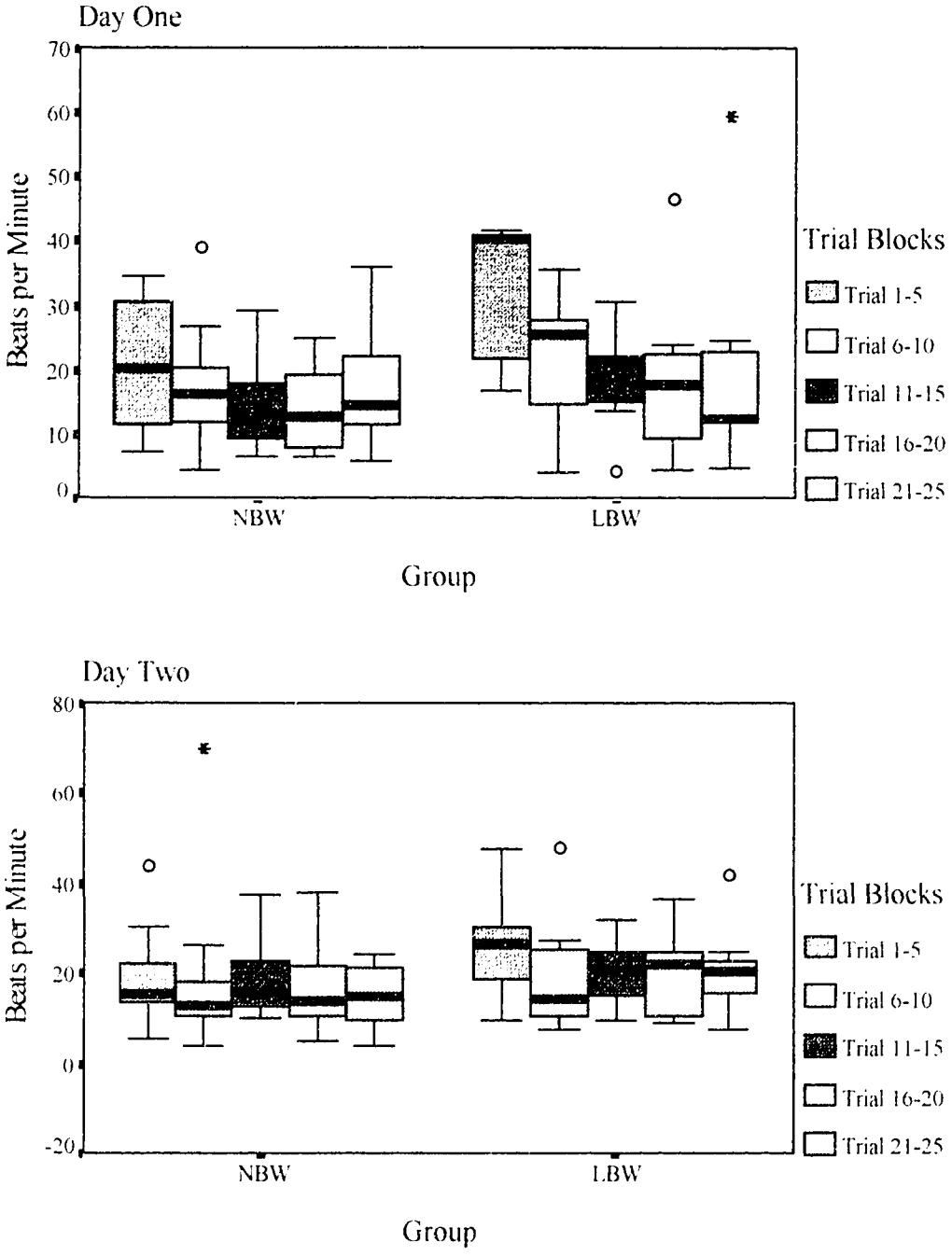

Figure 10. Distribution of RANGE--Change in heart rate (MAXIMUM minus MINIMUM) in response to auditory stimuli across trial blocks on days one and two for both low birth weight (LBW) and normal birth weight (NBW) infants.

CHAPTER 4

DISCUSSION

The purpose of this study was based on the belief that some of the long term development problems of infants born prematurely are a result of the interaction between a neurologically immature organism and the developmentally nonsupportive characteristics of the Neonatal Intensive Care Unit environment. Some infants seem especially unable to maintain stability and self-regulation in the face of perturbing stimulation and react with autonomically based signs such as apnea, bradycardia, gagging, emesis, and temperature instability. Identification of a reliable and valid indicator of autonomically based self-regulatory ability that would reflect individual differences in vulnerability to environmental events and/or be useful in studies to determine what aspects of the environment infants were apt to respond to adversely would be useful. A review of the literature on heart rate variability suggested that it might be such an indicator. The purpose of this study, using an infant primate model, was to explore heart rate variability measures and their predictive usefulness in the early months of life for low birth weight and normal birth weight infants. The specific aims of this study were to:

1) describe heart rate variability in low birth weight and normal birth weight pig-tailed macaque infants over the first two months of life.
2) describe auditory evoked heart rate responses in infants at one month of age.

In addition, the following hypotheses were addressed:

1) low birth weight infants would have shorter heart periods (higher heart rates) and less heart rate variability than normal birth weight infants.
2) there would be individual differences in heart period and heart period variability which would be stable across time.

3) low birth weight infants would havea more sustained acceleratory response during auditory evoked response testing while normal birth weight infants would have a biphasic response.

4) infants with higher heart rate variability during sleep would have a biphasic response to the auditory evoked response testing.

5) normal birth weight infants would perform better than low birth weight infants on problems of visual recognition memory.

6) heart rate variability measures would predict performance on problems of visual recognition memory; i.e., infants with higher heart rate variability would perform better on problems of visual recognition memory.

Description of Heart Rate Variability Over First Two Months

The median heart period in milliseconds for low birth weight infants ranged from a low of 252.8 (interquartile range [IQR=27.5] at a conceptual age 180 days to a high of 286.0 (IQR=45.2) at 230 days of conceptual age. These median heart period values at 180 and 230 days are equivalent to heart rates of 237 and 210 beats per minute. The median heart period for normal birth weight infants ranged from a low of 251.0 (IQR=25.9) at 190 days to a high of 313.2 (IQR=88.7) at 180 days of age. The equivalent heart rates in beats per minutes were 239 and 191 respectively. These values are consistent with those reported by Sackett, Fahrenbruch, and Ruppenthal (1979) for macaques infants (*Macaca nemestrina*) in the first month of life.

Measures of total or long term variability were quite small. For example, the median HP STDDEV for low birth weight infants ranged from 4.8 milliseconds (IQR=9.0) at 190 days to 11.0 (IQR=11.0) at 230 days. For normal birth weight infants, the range in milliseconds was 5.0 (IQR=3.0) at 190 days to 9.2 (IQR=8.1) at 175 days. These values are equivalent to approximately 5 to 12 beats per minute when converted to heart rate. Short term variability was very small. The median HP RMSSD ranged from a low of 1.6

milliseconds (IQR=1.1) in normal birth weight infants at 190 days to a high of 5.9 milliseconds (IQR=6.6) in low birth weight infants at 230 days. These values in milliseconds are approximately 2 to 9 beats per minute for heart rate. No reports were found in the literature for measures of heart rate variability for comparably aged infant macaques.

The values for heart period and heart rate variability measures found for this sample of low birth weight and normal birth weight infants macaques (although generally not verifiable from other literature sources) are consistent with what would be expected from reports in the literature that smaller animal species and the infants within species tend to have shorter heart periods (faster heart rates) and less heart rate variability (both long term and short term) than do larger and older animals (Assali, et al., 1978; Giddens and Kitney, R.,1985; Haddad, et al., 1984; and Woodson, 1988.)

Hypothesis One

Hypothesis One stated that low birth weight infants would have shorter heart periods (higher heart rates) and less heart rate variabililty than normal birth weight infants. The findings in this study do not generally support this hypothesis. Of all the heart rate variables, only mean heart period at the estimated postconceptional ages of 175 and 180 days was found to be significantly different between low birth weight and normal birth weight infants with low birth weight infants having shorter heart periods. Mean heart period at the 190 through 230 estimated postconceptional ages and all heart rate variabililty measures at all estimated postconceptional ages showed no differences between groups. When groups were compared at similar postnatal ages there were also no differences except for mean heart period when low birth weight infants at a mean age of 49 days were compared with normal birth weight infants at a mean age of 55 days. For that comparison, low birth weight infants again had shorter heart periods. Considering the

number of comparisons made (six estimated postconceptional ages and four postnatal ages for twelve heart rate variables) these findings could have been due to chance alone.

It also is possible that at early postnatal ages low birth weight infants have shorter heart periods and less heart rate variability but become more like normal birth weight infants by the time they reach term conceptional age. This study did not examine heart period or heart rate variabililty in low birth weight infants in the early postnatal time period: The first data collection on these measures occurred after the infants had reached term postconceptional ages. Siassi, Hodgman, Cabal, and Hon (1979) report decreasing heart rates (increasing heart periods) and increases in heart rate variability measures in their cross-sectional study of human premature infants from 27 to 40 weeks conceptional age.

Developmental Pattern for Heart Period and Heart Rate Variability

The normal birth weight group had a developmental pattern for MEAN HEART PERIOD, HP STDDEV (a measure of total variability), and HP RMSSD (a measure of short term variability) which started out higher at the early ages of 175 and 180 days postconception, dropped to a low level at 190 days and began to rise again between 200 and 230 days of postconception age. The other standard statistical and spectral measures of heart rate variability appeared to have a similar pattern although the values did not reach statistical significance. The low birth weight group also appeared to have a similar pattern in the boxplots although their differences across ages also did not reach significance. The failure to reach levels of significance for the low birth weight group may be explained by the small sample size and the wider dispersion of values.

This pattern of development shown for the normal birthweight infant macaques and suggested for low birth weight infants is consistent with several reports found in the literature for human infants. A study by Haddad, Epstein, Epstein, Leistner, and Mellins (1980) followed eighteen normal human infants through the first four months of life.

Although their interest was in describing differences in heart period and variability measures during quiet versus rapid eye movement sleep, their results showed that heart period, long term variability, and short term variability started higher in the first two weeks of life, reached a low at one month of age and began rising again from that point on through the fourth month in both sleep states. Katona, Frasz, and Egbert (1980) studied 13 full-term and 8 pre-term infants during sleep at home in the first year of life. Timing of their data collection was based on postnatal age rather than conceptual age. In their population, heart period decreased during the first weeks of life attaining a minimum at 4-6 weeks in full-term infants and at 8-10 weeks in preterm infants. Over-all heart rate variability (measured as the standard deviation of heart period) and short term heart rate variability (measured as variability associated with respiration) followed a similar pattern. Harper (1985) reported finding a comparable pattern for heart rate changes in the first four months of life for term infants but found similar changes in heart rate variability only during quiet sleep. Schechtman, Harper, and Kluge (1989) used a time-domain technique to assess maturational changes in heart rate variability in low, mid, and high frequency bands during sleep-waking states in normal infants from one week to six months of age. They found the same pattern of a decrease in variability at one month and a subsequent rise through four months in all three frequency bands in quiet sleep, REM sleep and awake. Variability leveled out or decreased slightly after four months. Although their methods of quantification and analysis differed from this current study, their frequency bands are roughly comparable to the very low, low, and high frequency bands examined in this study. While changes in variability in the frequency bands across time in this study did not reach levels of significance, examinations of the boxplots suggest a similar pattern.

The results of this study support the conclusions of others that the postnatal development of heart period and heart rate variability does not occur in a simple linear manner but may be divided into three distinct periods: neonatal, early infancy, and later

infancy (Haddad, 1980; Harper, 1985; Schechtman, Harper, & Kluge, 1989). The physiological mechanisms responsible for changes in heart period and variability over time are not discernible from the results of the current study. Katona, Frasz, and Egbert (1980) suggested that there are alterations in the intrinsic rate of the denervated heart, in the level of sympathetic control, and in the level of parasympathetic control. The finding from the current study that the patterns of changes are apparent in very low, low, and high frequency bands would seem to support this view. Schechtman, Harper, and Kluge (1989) suggested a decrease in parasympathetic tone as a possible mechanism for the decrease in heart period and all types of heart rate variability from the neonatal to the age of one month. Harper (1985) emphasized that many factors including sleep state, circadian and ultradian rhythms, thermoregulatory responses, and respiratory patterns influence heart rate and heart rate variability and that these factors are themselves undergoing maturational processes in the early months of life. Much remains to be studied about the developmental patterns of all of these factors and their interrelatedness.

One of the conclusions to be drawn from the results of this study describing the pattern of development of heart period and heart rate variability in the normal birth weight infant macaques is that infant macaques may be useful as an animal model for studying heart rate phenomena. Further study of larger numbers of both low birth weight and normal birth weight macaque infants collecting data on a postnatal as well as conceptual age basis is needed. Inclusion of data concerning sleep state, thermoregulatory status, and respiratory activity associated with heart rate variability measures is also warranted. Data collected more frequently and over a longer age period would be helpful in determining the age ratio for comparing macaque and human infant developmental phenomena.

Stability of Heart Rate Variability Measures Across Ages for Individuals

Hypothesis Two

Hypothesis Two stated that there would be stability of heart period and heart rate variability across time for individual infants. The findings in this study do not support the conclusion that there are individual differences in heart period and heart rate variability which are stable across time. Comparisons were made across the six estimated postconceptional ages for each of the twelve heart rate variables for the low birth weight group, the normal birth weight group, and the groups combined using Spearman Rank Correlation tests. For low birth weight infants there were only 15 correlations significant at $p \leq 0.05$ for all of the comparisons for an average of 1.25 significant correlations for each heart rate variable. For normal birth weight infants there were a total of only 11 correlations significant at $p \leq 0.05$ for an average of 0.9 significant correlations for each variable. The number of significant correlations for each group does not differ from what would be expected by chance alone. When the groups were combined, a total of 33 correlations significant at $p \leq 0.05$ were found for an average of 2.2 significant correlations for each variable. Although this number is greater than for groups analyzed separately, it also does not differ significantly from chance. In addition, there is no consistent discernible pattern to the significant correlations; e.g., they are not grouped at younger ages, older ages, or at adjacent ages.

The failure to find stability over time seems logical in the light of evidence that there are nonmonotonic developmental changes occurring in heart rate and heart rate variability across these ages. Few studies were found in the literature which examined the issue of stability of heart period and heart rate variability over time. Arendt, Halpern, Maclean, and Youngquist (1991) examined the stability of vagal tone (a measure related to spectral high frequency variability) in human newborns on two consecutive days in the first week of life and found no correlation in either sleep or awake states. Lewis, et al.

(1970) studied heart rate and a measure of total variability from fetal periods through the first year of life in human infants. They reported some stability for heart rate (inverse of heart period) in the last half of the first year of life but not for their measure of heart rate variability.

Auditory Evoked Heart Rate Responses

Heart rate responses to the auditory stimulus were measured as differences from baseline during each of 29 seconds after stimulus onset, with second 0 being the time of stimulus presentation. Baseline heart rate was taken as the average rate in the 5 seconds preceding stimulus onset. There were 25 stimulus presentations for each day. Data was aggregated in trial blocks of five stimulus presentations using the means of responses from trials 1-5, 6-10, 11-15, 16-20, and 21-25 for each day for both low birth weight and normal birth weight groups. There were no differences in baseline heart rate between the two groups prior to onset of the first auditory stimulus. In the first trial block both groups of infants had an initial increase in heart rate above baseline within the first five seconds, showed a maximum deceleration below baseline by ten to eleven seconds, and returned to baseline between twenty and twenty-five seconds. The low birth weight infants demonstrated slightly more acceleration above baseline, decelerated further, and took longer to return to baseline. In the second trial block, normal birth weight infants had very little acceleration (approximately 3 beats/minute) or deceleration (approximately 1 beat/minute) while low birth weight infants accelerated approximately 7 beats/minute and decelerated approximately 4 beats/minute. Both groups had stabilized at baseline by twenty seconds. The normal birth weight group maintained a similar pattern for the last three trial blocks. By trial block four, the low birth weight group had diminished both their acceleratory and deceleratory responses. (See Figure 5 in Chapter 2.)

Hypothesis Three

Hypothesis Three stated that low birth weight infants would have a more sustained acceleratory response during auditory evoked response testing while normal birth weight infants would have a biphasic response. This expectation was based on findings by Martin, Sackett, Gunderson, and Goodlin-Jones (1988) which identified two different patterns of auditory evoked heart rate responses in a study of older pigtailed macaques (*Macaca nemestrina*). Infants raised in isolation showed only heart rate acceleration followed by a return to baseline within 10 to 11 seconds of stimulus onset while socially reared monkeys developed a pattern of a 10 to 11 second biphasic response of acceleration followed by deceleration with a subsequent return to baseline. These two patterns suggested a difference in reactivity and autonomic regulatory functions. It was thought that the pattern of heart rate acceleration (which also showed little habituation) might be indicative of sympathetic arousal. The biphasic pattern, in turn, might be indicative of initial sympathetic arousal with a secondary parasympathetic regulatory function.

Therefore, it was expected that the low risk normal birth weight infants in the current study would show the biphasic response and the higher risk low birth weight infants would show the sustained acceleratory response indicative of sympathetic arousal. This hypothesis was not supported by the results of the study. Plotting of the response patterns and analysis of the data using the MAXIMUM (increase above baseline), MINIMUM (decrease below baseline) and RANGE (difference between MAXIMUM and MINIMUM) indicated both groups of infants had an initial biphasic response. The low birth weight infants appeared to have a stronger biphasic response than the normal birth weight infants although the difference between the two groups was not statistically significant. Analysis of variance for repeated measures found that the low birth weight group was slower to habituate their response pattern.

The explanation for the biphasic response patterns is not entirely clear but a further search of the literature yielded one possibility. Graham and Jackson (1970) state that the diphasic acceleratory-decelerative heart rate response has often been found when the auditory stimulus is between 60 and 90 db with no control of rise time. They characterize this response as a startle response. The conditions for presentation of the auditory stimulus in this study were a stimulus of 85 db with no control of rise time. It seems likely that infants at the 200 postconceptional age would have a startle response and that the response would be greater in low birth weight than normal birth weight infants. The older infants in the Martin, Sackett, Gunderson, and Goodlin-Jones (1988) study may have had a different basis for their response. The heart rate regulatory basis for the response is not determinable from this study although it may still be related to a parasympathetic deceleratory response to an initial sympathetic arousal.

The finding that the low birth weight infants were slower to habituate to the auditory stimulus is consistent with the literature which reports that low birth weight infants have difficulty decreasing their level of arousal once aroused (Als, Lester, and Brazelton, 1979). It is also interesting to note that heart rate response to the auditory stimulus was not related to level of observed behavioral activity for either group of infants. For low birth weight infants especially this reinforces the need to provide protection from environmental perturbations which may result in sustained physiological demands which are not apparent from simple observation.

Hypothesis Four

Hypothesis Four stated that infants with higher heart rate variability during sleep would have a biphasic response to auditory evoked response testing. There was some support for this hypothesis in the findings. Spearman Rank Correlations were done to identify relationships between Heart Rate Variability measures obtained during sleep at age 200 and the MAXIMUM, MINIMUM, and RANGE values by trial blocks obtained

on the Auditory Evoked Response testing for Day One which were done between ages 198 and 202. There were a few significant correlations between heart rate variability measures and MAXIMUM for the groups combined. Most of the heart rate variability measures were significantly related to both the MINIMUM and RANGE values of the auditory evoked response measures for Trial Blocks One through Three with correlations ranging from r=0.43 to r=0.65 when the groups were combined. The relationships between total or long term heart rate variability measures and RANGE were usually significant at p=0.01 or greater.

When the groups were analyzed separately, the normal birth weight group had the same pattern of significantly related results between heart rate variability measures and MAXIMUM, MINIMUM, and RANGE for Trial Blocks One through Three as found for the groups combined. Examination of the results for low birth weight infants alone, indicated that the correlation values were as high and had apparently the same distribution but did not reach significance. The lack of significance for the low birth weight infants may have been due to the small sample size. Since the biphasic response was associated with greater MINIMUM and RANGE values, it follows that higher heart rate variability during sleep was associated with the biphasic auditory evoked heart rate response pattern. This is further supported by the fact that the significant correlations occurred in the first three trial blocks before the biphasic response had been habituated. Theoretically, one would anticipate that the biphasic response would be most strongly associated with measures of short term variability since slowing of heart rate (greater excursion below baseline) and short term variability are parasympathetically mediated. However, this does not appear to be the case in this data. The sleep measures of total or long term variability (HP STDDEV, TOTAL VARIANCE, VLF, and LF) have stronger and more consistent correlations with MINIMUM and RANGE than do the measures of short term variability (HP RMSSD and HF). There was also no relationship between the values for MINIMUM

and RANGE for auditory evoked heart rate response with the sleep heart rate variables of SD / RMSSD and LF / HF which were supposed to be indicators of the relative influence of sympathetic versus parasympathetic influences on heart rate variability. The most parsimonious explanation for the findings of the relationship between the auditory evoked heart rate response and sleep heart rate variability is that infants with high variability during sleep also have high variability in response to stimulation. There is also some support for the notion that infants with high variability in sleep are slower to habituate to the stimulus. There was no relationship between sleep heart rate variability measures and activity levels during the auditory evoked heart rate response testing. Whether there might be clinical implications for these findings is unclear. There appears to be some relationship between higher heart rate variabililty during sleep and cardiac reactivity (both initial and continuing) to external stimulation but there is not enough information to determine if it is indicative of better self-regulation or might be indicative of better outcomes for infants. More study is needed of the relationships between heart rate variability measures and different stimuli in different environmental contexts as well as infant outcomes measures.

Performance on Visual Recognition Memory

Hypothesis Five

Hypothese Five stated that normal birth weight infants would perform better than low birth weight infants on problems of visual recognition memory. The repeated measures of analysis of variance tests for differences between low birth weight and normal birth weight groups with estimated postconceptional age of testing as the repeated measure and postnatal age as the covariate found no differences between the low birth weight and normal birth weight groups for visual recognition memory performance. These findings of no difference between groups were true for both novelty preference and amount of time necessary to accrue predetermined familiarizations times for the stimuli.

Other studies of infant monkeys have found that low birth weight infants and other risk groups have performed more poorly than normal birth weight infants (Gunderson, Grant-Webster, and Fagan, 1987; Gunderson, Grant-Webster, and Sackett, 1989). However, these studies used different measures of analysis: These studies (and most studies involving visual recognition memory testing in human and macaque infants) used the summary score for all problems across ages to test for both differences between groups and differences from chance preferences for novelty. Gunderson, Grant-Webster, and Fagan (1987) found significnt differences between high and low risk groups in the summary novelty preference score and found that the low risk group differed from chance while the high risk group did not differ from chance. Gunderson, Grant-Webster, and Sackett (1989) found no difference between groups of normal and low birth weight infants (t-test) but found that the normal birth weight group performed better than chance while the low birth weight group did not. Results of the same method of analysis for infants in this current study found no significant difference between low birth weight and normal birth weight infants but did find that normal birth weight infants performed better than chance while low birth weight infants did not. These results are consistent with the literature. It would seem that the differences between groups are not very large and that the small sample size (especially for low birth weight infants) influenced the ability to find significant results.

Relationship between Heart Rate Variabililty and Recognition Memory

Hypothesis Six

Hypothesis Six stated that heart rate variability measures would predict performance on problems of visual recognition memory: i.e., infants with higher heart rate variability would perform better on problems of visual recognition memory. Spearman Rank Correlations were done to test for relationships between concurrent measures of heart rate variability and performance on recognition memory testing at the 180, 190, 200,

and 210 estimated postconceptional ages. There were very few correlations significant at the $p \leq 0.05$ level for novelty preference scores. There were fewer than what would have been expected by chance alone for the number of comparisons made and also showed no explanatory pattern. There were no significant correlations between heart rate variability measures and accumulation of familiarization time for the problems. The conclusion from the findings of this study is that there is no relationship between heart rate variability during sleep baseline conditions and performance on visual recognition memory. Linnemeyer and Porges (1986) reported that infants with high vagal tone (a measure of short term variability similar to spectral HF in this study) looked longer at the novel stimulus (had higher novelty preference scores) than infants with low vagal tone. There are two obvious factors which might have contributed to the difference in findings between their study and the current one: (1) Their measure of vagal tone is perhaps a more precise measure of short term variability associated with respiratory sinus arrhythmia using fewer bands of the high frequency spectrum; and (2) their baseline measure of vagal tone were assessed while the infants were in an awake state just prior to initiation of the recognition memory testing.

Conclusions and Recommendations

The pattern of change in heart rate variabililty measures across estimated postconceptional ages for both normal birth weight and low birth weight infants and the failure to find differences related to postnatal age suggest that development of heart rate variablity is more dependent on maturational than experiential factors. Further study is needed with larger numbers of infants and more planned comparisons for both postconceptional and postnatal ages in order to substantiate and further elucidate this conclusion.

Another conclusion to be drawn from the results of this study describing the pattern of development of heart period and heart rate variability in the normal birth weight

infant macaques is that infant macaques may be useful as an animal model for studying heart rate phenomena. Further study of larger numbers of both low birth weight and normal birth weight macaque infants collecting data on a postnatal as well as postconceptional age basis is needed. Data collected more frequently and over a longer age period would be helpful in determining the age ratio for comparing macaque and human infant developmental phenomena. Inclusion of data concerning sleep state, circadian rhythms, thermoregulatory status, and respiratory activity associated with heart rate variability measures is also warranted.

The failure to find differences in baseline (during sleep) heart rate variability measures between the low birth weight and normal birth weight infants or to find individual differences which were stable across ages mitigates against concluding that heart rate variability is indicative of inherent autonomically based self-regulatory abilities. The failure to find a relationship between baseline heart rate variability measures and performance on visual recognition testing suggests that baseline heart rate variability measures have little value as predictive measures for cognitive outcomes. Because of limitations based on the characteristics of the sample populations in this study, it is necessary to be cautious of generalizing these results. Very low birth weight infants were not well represented in the low birth weight group. The normal birth weight group consisted of infants who could not survive in the normal colony environment and may not represent an entirely normal population. Characteristics of the sample and the relatively small sample size may have influenced the ability to find group differences and stability across time for heart rate variability measures.

The positive relationship between heart rate variability measures and the auditory evoked heart rate response does suggest that heart rate variability may provide some predictability for physiological responses to environmental stimuli. Further studies are needed to determine the predictability of heart rate variability for different types of stimuli

(e.g., visual, touch), and different environmental contexts. Studies of the relationship between heart rate variability measures and behavioral responses to environmental stimuli occurring at the same time (rather than baseline measures) are also indicated.

Monitoring equipment in most NICU's for human infants is not currently equipped to provide heart rate variability information in a form which would be useful for collecting data for research purposes or predicting responses to environmental stimuli in the clinical setting. One of the reasons for conducting this study with a population of infant macaques where such instrumentation was available was to determine if the usefulness of heart rate variability measures would warrant modification of NICU monitoring equipment. The results of this study would suggest that further study of heart rate variability should be done where instrumentation is already available before there is an attempt to make it available in a clinical setting.

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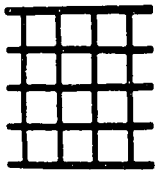
APPENDIX A

Examples of Visual Recognition Memory Patterns

Problem One at 190 Days Postconceptional Age
Familiarization time of 60 seconds
Test time of 10 seconds



FAMILIAR

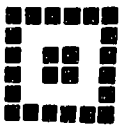
NOVEL

Problem One at 200 Days Postconceptional Age
Familiarization time of 16 Seconds
Test time of 5 Seconds

FAMILIAR

NOVEL

Problem One at 210 Days Postconceptional Age
Familiarization time of 30 Seconds
Test time of 5 Seconds



FAMILIAR

NOVEL

APPENDIX B
Mean Values of Heart Rate Variables During Sleep At Each Estimated Postconceptional Age

Values of Heart Rate Variables During Sleep at Each Estimated Postconceptional Age: Normal Birth Weight Infants.

ID	AGE	G	C	BW	ECA	HP	SD	RMSSD	IQR	IQRSD	MAD	TVAR	VLF	LF	HF	LF/HF	SD/RMD
wz	175	1	1	434	167	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
wz	180					9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
wz	190					2769	065	017	110	010	074	43.42	21.49	20.46	1.481	13.81	03.82
wz	200					2657	040	018	045	015	044	11.54	6.833	4.017	0.690	05.82	02.22
wz	210					2468	043	012	070	010	052	20.22	12.99	6.413	0.821	07.81	03.58
wz	230					2789	052	028	075	025	059	24.03	12.89	8.413	2.734	03.08	01.86
xo	175	0	1	475	171	3566	127	043	108	065	096	239.5	114.1	117.8	7.590	15.52	02.95
xo	180					2620	079	019	075	010	059	72.30	58.45	12.64	1.200	10.53	04.16
xo	190					2609	035	012	045	010	045	16.90	4.708	11.13	1.058	10.52	02.92
xo	200					2751	060	024	075	020	059	31.01	10.63	17.86	2.506	07.13	02.50
xo	210					2777	024	016	035	013	015	7.493	2.013	4.754	0.726	06.55	01.50
xo	230					3607	104	043	135	030	115	96.28	48.48	44.53	3.269	13.62	02.42
yr	175	1	1	536	173	3149	039	025	070	025	052	16.61	2.741	10.95	2.920	03.75	01.56
yr	180					3026	082	024	150	020	111	64.25	23.25	33.88	7.116	04.76	03.42
yr	190					2476	048	022	075	020	059	22.52	3.824	14.70	4.001	03.67	02.18
yr	200					2602	073	020	115	020	074	60.74	26.80	31.66	2.274	13.92	03.65
yr	210					2600	060	017	080	010	059	51.65	26.09	23.91	1.657	14.43	03.53
yr	230					2666	060	024	075	010	059	48.06	18.08	27.88	2.105	13.24	02.50
cl	175	1	1	500	173	2826	100	096	130	100	104	100.8	24.33	54.75	21.72	02.52	01.04
cl	180					2800	087	036	115	025	089	81.63	10.13	69.65	1.847	37.71	02.42
cl	190					2432	064	011	096	012	067	37.49	16.77	19.75	0.963	20.51	05.82
cl	200					2526	095	024	099	015	080	116.0	80.06	35.33	0.587	60.19	03.96
cl	210					2408	043	013	060	012	045	18.09	14.24	3.600	0.252	14.29	03.31
cl	230					2276	040	004	072	006	053	16.30	3.452	12.54	0.307	40.85	10.00
dg	175	0	1	455	172	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
dg	180					2494	024	010	030	009	022	5.453	2.809	2.382	0.262	09.09	02.40
dg	190					2691	049	015	072	021	053	28.73	7.034	20.64	1.056	19.55	03.27
dg	200					2613	072	017	114	027	085	46.86	22.83	22.50	1.531	14.70	04.24
dg	210					2875	072	021	083	020	063	33.31	12.03	20.83	0.447	46.60	03.43
dg	230					2895	141	065	195	030	141	188.3	87.47	96.45	4.361	22.12	02.17
ep	175	1	1	545	177	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
ep	180					9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
ep	190					2763	108	021	150	020	111	110.6	65.46	43.93	1.230	35.72	05.14
ep	200					2678	096	016	155	016	119	106.9	52.03	53.87	1.019	52.87	06.00
ep	210					3066	094	020	135	030	104	185.4	136.1	48.13	1.167	41.24	04.70
ep	230					3217	087	019	130	025	104	119.0	42.21	74.56	2.274	32.79	04.58
ez	175	0	1	539	174	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
ez	180					2640	063	020	070	025	045	47.09	21.01	24.00	2.076	11.56	03.15
ez	190					2625	089	022	115	020	089	107.4	80.69	24.93	1.735	14.37	04.05
ez	200					2302	046	010	068	010	045	25.68	19.87	5.132	0.673	07.63	04.60
ez	210					2494	093	014	110	015	076	94.38	76.37	17.00	1.008	16.87	06.64
ez	230					2301	042	013	060	015	045	12.55	7.350	4.781	0.422	11.33	03.23
fa	175	1	1	525	176	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
fa	180					3116	104	028	175	035	133	102.4	45.03	52.35	5.009	10.45	03.71
fa	190					2363	058	013	042	018	031	39.16	29.08	8.971	1.110	08.08	04.46
fa	200					2415	044	008	050	010	037	18.49	6.854	11.37	0.270	42.11	05.50
fa	210					2713	090	020	135	020	104	96.31	30.52	63.02	2.772	22.73	04.50
fa	230					2863	035	017	050	015	037	16.45	4.466	11.35	0.631	17.99	02.06

ID	AGE	G	C	BW	ECA	HP	SD	RMSSD	IQR	IQRSD	MAD	TVAR	VLF	LF	HF	LF/HF	SD/RMD
gn	175	1	1	653	180	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
gn	180					4014	556	531	486	234	360	1105.	397.0	598.2	109.7	05.45	01.05
gn	190					2975	059	023	085	025	067	42.02	11.08	25.34	5.598	04.53	02.57
gn	200					2872	076	031	080	035	059	61.01	32.14	26.00	2.872	09.05	02.45
gn	210					3108	132	032	225	025	126	154.3	88.84	61.22	4.208	14.55	04.13
gn	230					4968	523	797	478	685	304	2102.	72.62	933.7	1096.	00.85	00.66
he	175	0	1	590	174	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
he	180					2906	105	017	175	025	111	116.2	87.57	27.64	1.002	27.58	06.18
he	190					2505	050	016	072	021	058	29.12	12.90	14.91	1.314	11.35	03.13
he	200					2736	064	031	090	035	074	48.71	18.87	25.29	4.545	05.56	02.06
he	210					2887	080	028	095	035	126	84.08	31.37	48.73	3.985	12.23	02.86
he	230					3633	141	053	175	060	141	309.8	110.9	184.6	14.25	12.95	02.66
ir	175	1	1	560	176	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
ir	180					3291	090	017	095	030	082	106.0	63.71	41.56	0.739	56.24	05.29
ir	190					2510	027	026	036	036	027	9.052	2.882	4.326	1.844	02.35	01.04
ir	200					3243	078	077	105	075	082	67.47	19.71	28.02	19.74	01.42	01.01
ir	210					2509	050	027	065	020	052	27.17	13.00	13.24	0.928	14.27	01.85
ir	230					2644	039	027	040	020	030	23.02	11.26	10.25	1.512	06.78	01.44
ja	175	0	1	607	174	3114	053	021	075	040	059	34.15	21.77	11.51	0.863	13.34	02.52
ja	180					2817	071	029	105	030	082	41.82	26.55	14.38	0.891	16.14	02.45
ja	190					2546	029	016	030	010	022	6.703	4.476	2.130	0.097	21.96	01.81
ja	200					9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
ja	210					2542	089	036	125	035	089	67.13	18.28	46.85	1.998	23.45	02.47
ja	230					3407	077	064	100	045	082	53.44	15.28	28.97	9.190	03.15	01.20
jc	175	1	1	545	173	2788	084	013	095	010	074	102.2	78.42	23.32	0.479	48.68	06.46
jc	180					2773	069	024	050	015	045	56.12	32.01	23.11	1.007	22.95	02.88
jc	190					2317	047	007	072	006	058	26.66	15.99	10.51	0.162	64.88	06.71
jc	200					2455	038	010	055	010	037	16.44	4.708	11.48	0.246	46.67	03.80
jc	210					2697	036	024	042	018	031	14.99	6.339	8.022	0.634	12.65	01.50
jc	230					2553	029	008	042	006	031	8.102	3.116	4.743	0.244	19.44	03.63
jj	175	0	1	538	173	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
jj	180					3583	095	024	120	035	096	241.0	163.5	75.58	1.959	38.58	03.96
jj	190					2420	030	006	036	006	031	13.07	5.809	7.147	0.115	62.15	05.00
jj	200					2433	059	007	100	010	074	44.52	14.97	29.12	0.430	67.72	08.43
jj	210					2676	043	004	054	006	053	19.06	7.834	10.95	0.276	39.67	10.75
jj	230					3389	128	043	145	045	122	163.0	113.1	44.53	5.341	08.34	02.98
lm	175	0	1	440	168	4115	139	042	165	040	133	276.5	95.33	176.5	4.645	38.00	03.31
lm	180					2942	103	055	105	020	082	112.5	48.11	62.26	2.166	28.74	01.87
lm	190					2448	066	006	080	010	067	82.30	70.29	11.21	0.803	13.96	11.00
lm	200					3352	058	052	074	055	059	33.14	2.499	22.11	8.528	02.59	01.12
lm	210					3135	104	037	151	020	111	90.21	47.83	41.42	0.957	43.28	02.81
lm	230					3097	081	019	105	010	067	59.49	25.39	33.37	0.721	46.28	04.26

Note: G=gender (0=female,1=male) C=Group (0=LBW, 1=NBW) BW=birthweight at birth
ECA=estimated conceptual age at birth HP=heart period SD=standard deviation

The values in this table are in ten thousandths of a second instead of msec.
Missing values are 999,9999,99999.

Values of Heart Rate Variables During Sleep at Each Estimated PostconceptionalAge: Low Birth Weight Infants.

ID	AGE	G	C	BW	ECA	HP	SD	RMSSD	IQR	IQRSD	MAD	TVAR	VLF	LF	HF	LF/HF	SD/RMD
xr	175	1	0	347	157	2698	064	018	085	015	059	43.73	15.43	27.19	1.113	24.43	03.56
xr	180					2718	087	031	115	015	067	71.67	21.23	48.50	1.940	25.00	02.81
xr	190					2447	027	017	040	010	022	7.517	2.299	4.464	0.753	05.93	01.59
xr	200					2639	069	018	085	010	059	69.69	8.820	58.21	2.652	21.95	03.83
xr	210					2631	052	017	075	015	059	23.90	7.991	14.90	1.012	14.72	03.06
xr	230					2731	031	014	045	015	045	9.252	3.313	5.356	0.583	09.19	02.21
xz	175	0	0	400	166	2878	061	022	075	020	052	36.47	9.228	24.43	2.815	08.68	02.77
xz	180					2528	047	020	055	015	059	31.84	8.169	21.55	2.122	10.16	02.35
xz	190					2611	026	012	040	010	015	8.198	4.895	2.036	1.267	01.61	02.17
xz	200					2871	081	024	095	015	074	49.98	32.32	15.82	1.844	08.58	03.38
xz	210					2861	143	073	190	040	126	145.5	73.14	65.91	6.464	10.20	01.96
xz	230					3466	110	079	155	085	115	141.6	36.76	84.30	20.56	04.10	01.39
yv	175	0	0	385	162	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
yv	180					2453	124	043	160	025	133	154.9	71.04	79.83	3.984	20.04	02.88
yv	190					2512	120	036	130	020	082	161.4	63.07	95.18	3.182	29.91	03.33
yv	200					2561	087	026	115	020	104	122.8	48.36	71.08	3.381	21.02	03.35
yv	210					2344	023	011	027	012	027	9.990	2.490	7.021	0.479	14.66	02.09
yv	230					2974	162	091	197	055	147	223.0	65.65	142.3	15.10	09.42	01.78
zh	175	1	0	331	156	2470	095	030	155	024	119	89.59	19.20	65.13	5.262	12.38	03.17
zh	180					2434	064	019	085	015	067	57.24	16.91	38.47	1.857	20.72	03.37
zh	190					2763	113	041	125	050	115	185.7	50.21	129.0	6.505	19.83	02.76
zh	200					3116	123	078	165	090	123	176.6	63.92	82.10	30.58	02.68	01.58
zh	210					2676	124	032	132	027	102	222.4	84.07	135.4	2.895	46.77	03.88
zh	230					2860	131	059	171	066	138	264.6	122.0	132.4	10.15	13.04	02.22
ch	175	0	0	392	164	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
ch	180					2398	055	024	078	027	058	34.27	20.16	12.82	1.291	09.93	02.29
ch	190					2502	033	009	039	012	031	15.74	7.605	7.828	0.305	25.67	03.67
ch	200					2269	017	004	027	006	018	4.410	2.868	1.395	0.146	09.55	04.25
ch	210					2216	047	010	036	018	027	29.40	24.86	4.115	0.421	09.77	04.70
ch	230					2512	042	014	055	020	045	31.64	7.247	23.66	0.728	32.50	03.00
ct	175	0	0	397	164	2839	045	011	055	010	045	39.70	19.40	19.53	0.764	25.56	04.09
ct	180					2493	022	011	024	012	018	4.768	3.366	1.132	0.270	04.19	02.00
ct	190					2575	034	005	054	006	040	12.01	3.633	7.602	0.778	09.77	06.80
ct	200					2319	016	007	021	012	018	3.251	1.373	1.737	0.141	12.32	02.29
ct	210					2445	093	059	117	039	067	76.80	52.97	20.23	3.599	05.62	01.58
ct	230					2452	048	016	060	015	045	20.89	12.80	7.470	0.619	12.07	03.00
mf	175	1	0	330	157	9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
mf	180					2719	129	054	175	035	141	144.2	29.04	110.9	4.301	25.78	02.39
mf	190					9999	999	999	999	999	999	99999	99999	99999	99999	99999	99999
mf	200					2839	078	027	110	015	089	68.45	24.83	42.06	1.554	27.07	02.89
mf	210					2864	156	062	221	070	156	313.3	95.98	188.5	28.89	06.52	02.52
mf	230					2876	169	083	230	050	189	275.0	85.16	172.6	17.19	10.04	02.04

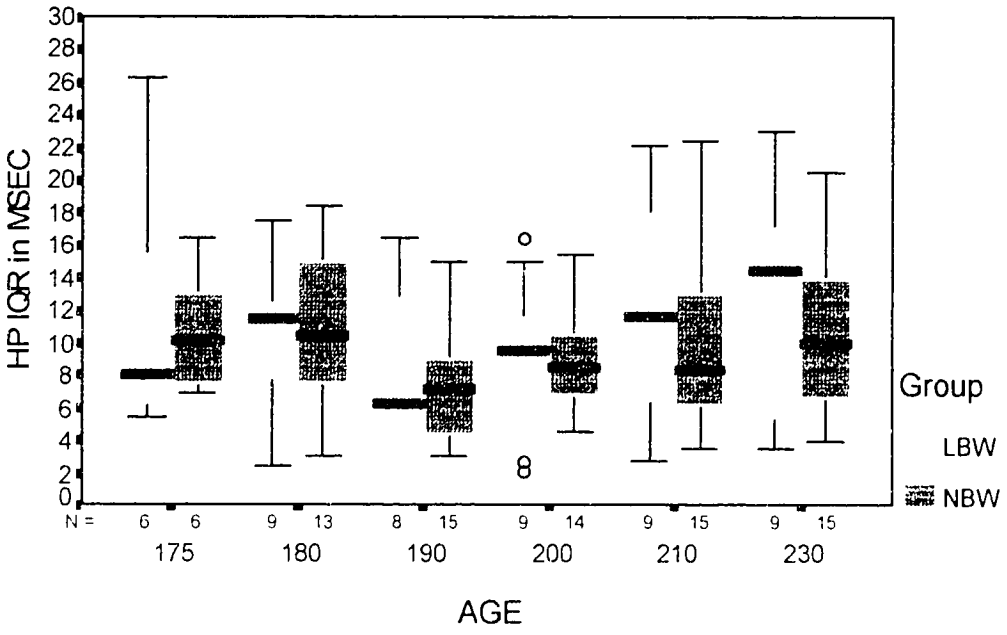
ID	AGE	G	C	BW	ECA	HP	SD	RMSSD	IQR	IQRSD	MAD	TVAR	VLF	LF	HF	LF/HF	SD/RMD
pn	175	1	0	350	166	2678	171	056	264	042	173	331.2	217.1	105.9	8.213	12.89	03.05
pn	180					2938	099	025	125	030	104	134.4	60.59	71.06	2.703	26.29	03.96
pn	190					3124	125	037	165	040	126	188.3	88.22	92.59	7.479	12.38	03.38
pn	200					2998	148	090	150	110	111	197.8	65.58	111.0	21.16	05.25	01.64
pn	210					2401	048	026	065	035	052	30.17	9.543	19.34	1.289	15.00	01.85
pn	230					2894	117	071	145	040	119	125.4	61.10	59.83	4.501	13.29	01.65
sj	175	0	0	336	159	2254	054	031	064	030	044	32.78	19.89	10.61	2.286	04.64	01.74
sj	180					2676	123	096	125	015	104	56.11	16.72	38.19	1.200	31.83	01.28
sj	190					2388	061	014	070	010	059	57.80	46.80	10.54	0.452	23.32	04.36
sj	200					2532	110	088	095	030	070	50.79	26.57	23.12	1.010	22.89	01.25
sj	210					2641	163	099	180	040	133	161.1	64.47	91.13	5.553	16.41	01.65
sj	230					2334	030	043	035	020	026	5.479	2.935	2.108	0.436	04.83	00.70

Note: G=gender (0=female,1=male) C=Group (0=LBW, 1=NBW) BW=birthweight at birth
ECA=estimated conceptual age at birth HP=heart period SD=standard deviation

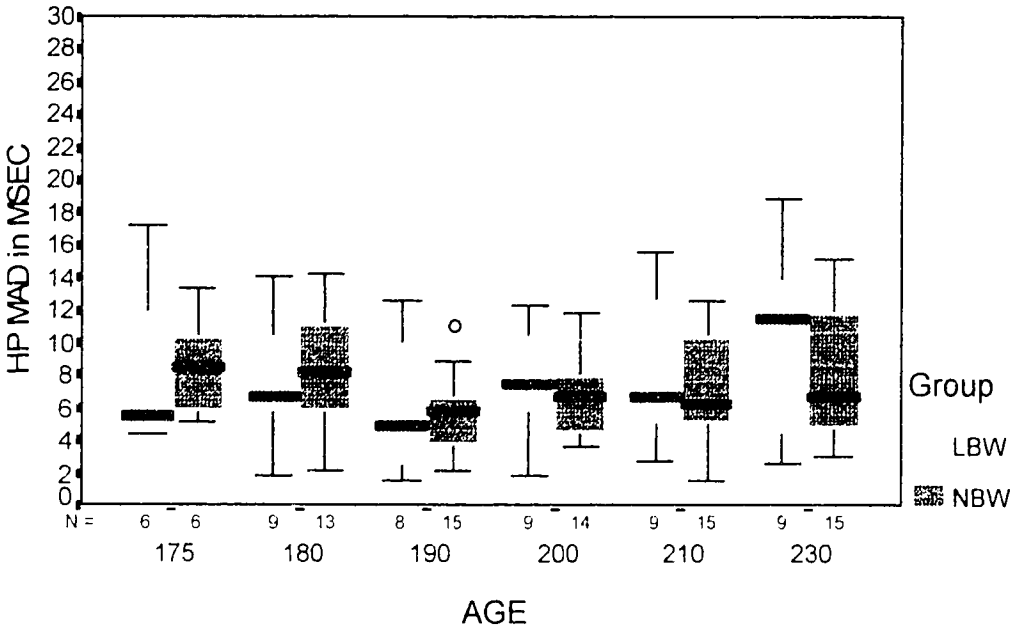
The values in this table are in ten thousandths of a second instead of msec.
Missing values are 999,9999,99999.

APPENDIX C

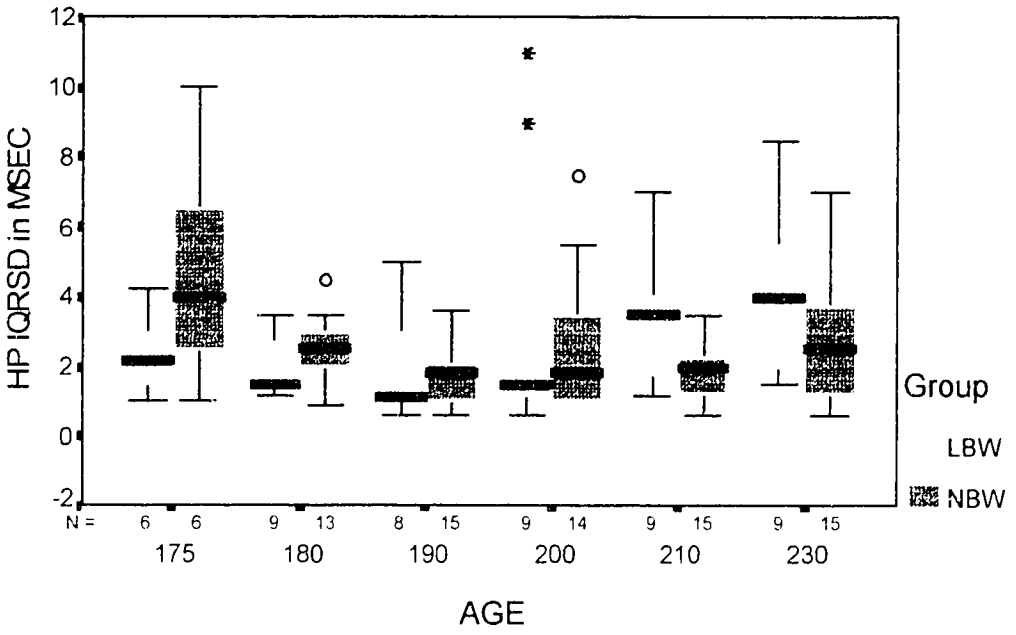
Boxplots of Heart Rate Variables Across Estimated Postconceptional Ages for Both LBW and NBW Infants



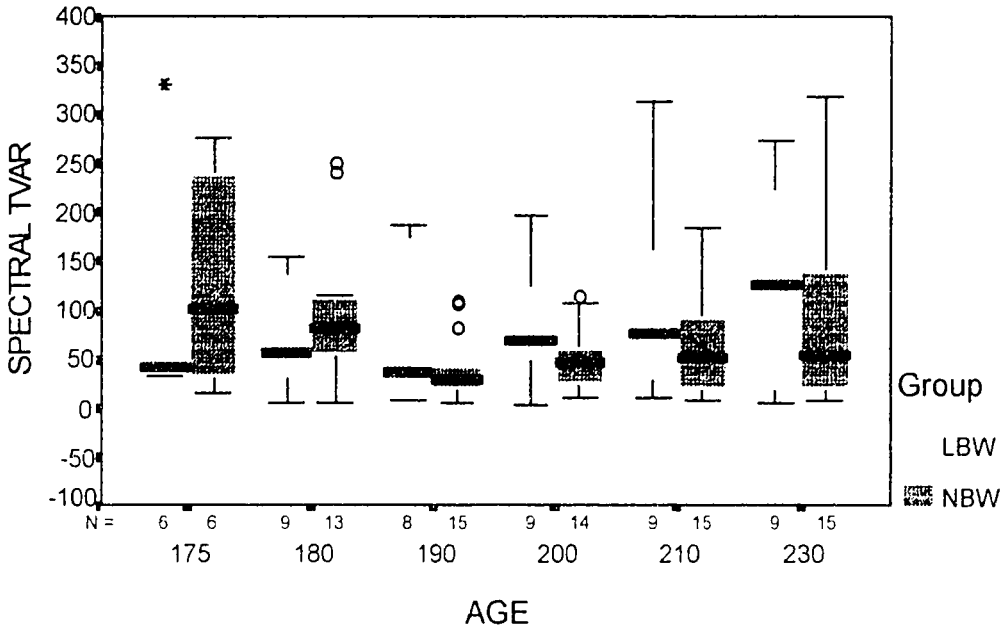
HP IQR Across Estimated Postconceptional Ages for Both LBW and NBW Infants



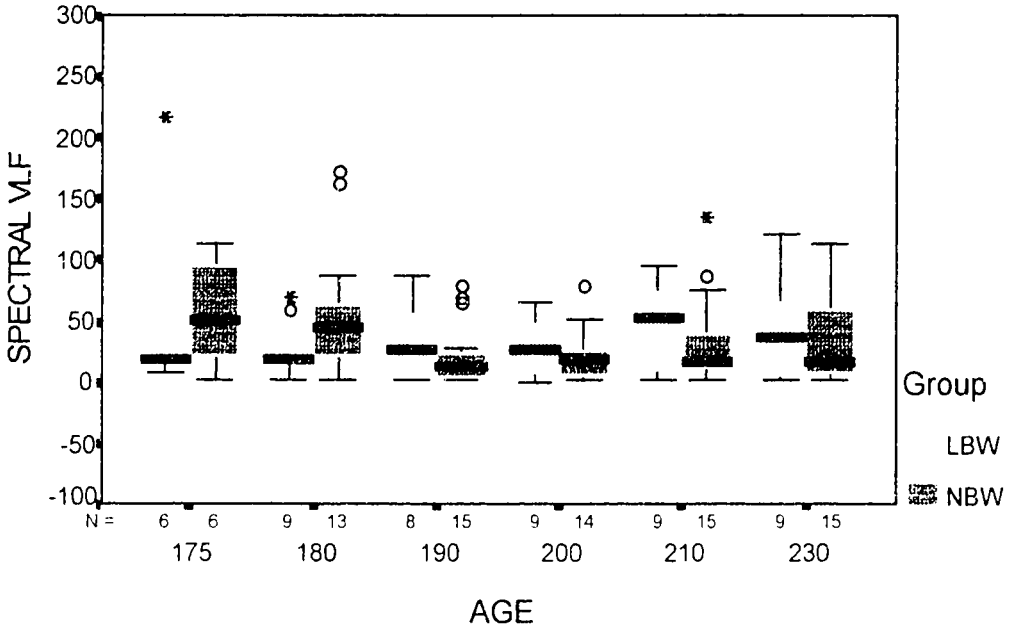
HP MAD Across Estimated Postconceptional Ages for Both LBW and NBW Infants



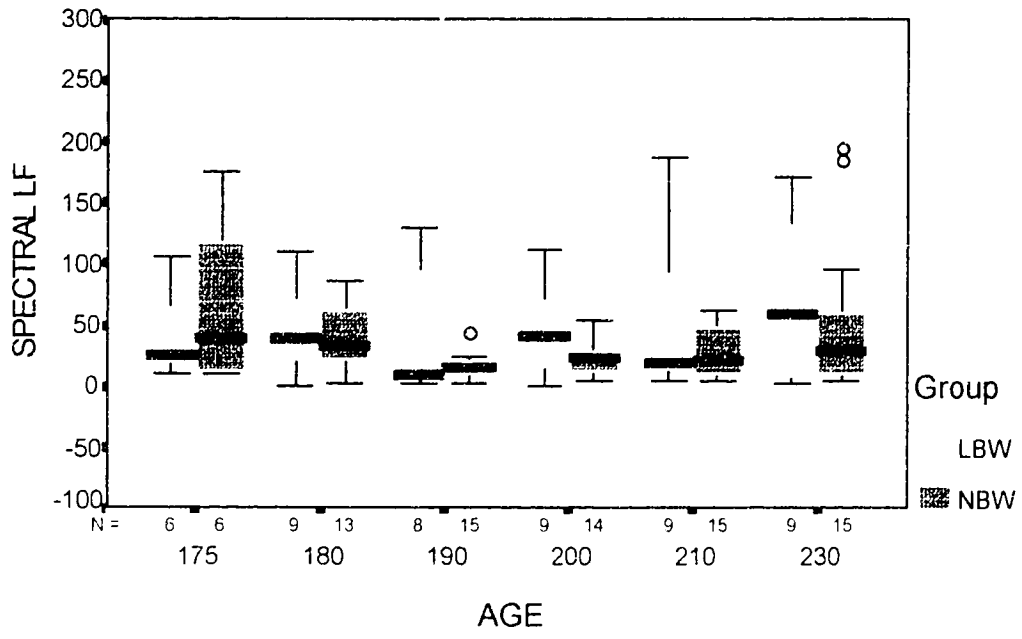
HP IQRSD Across Estimated Postconceptional Ages for Both LBW and NBW Infants



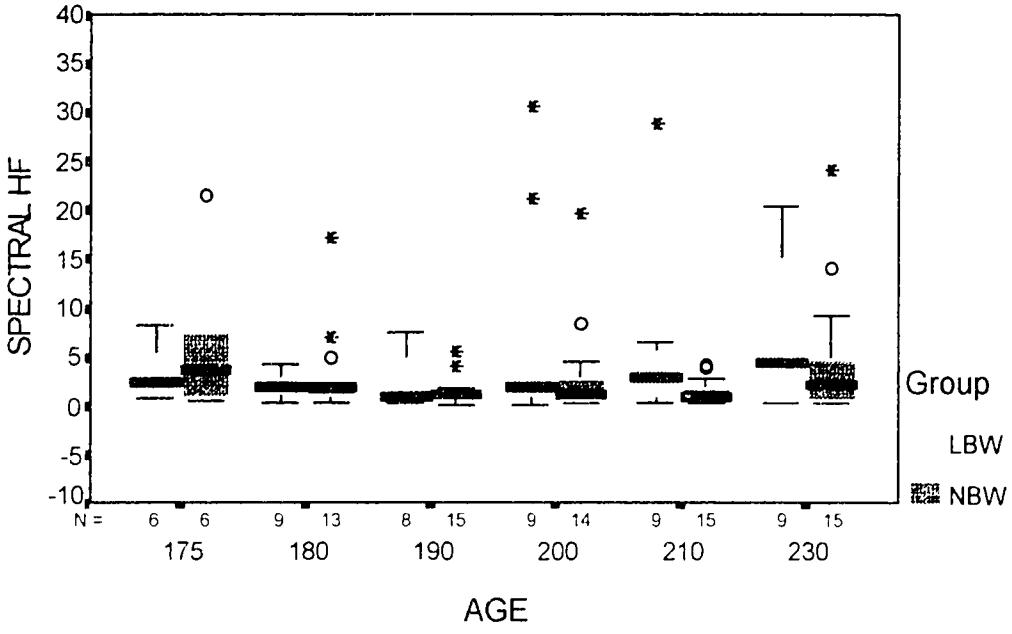
Spectral Total Variance (msec squared) Across Estimated Postconceptional Ages for Both LBW and NBW Infants



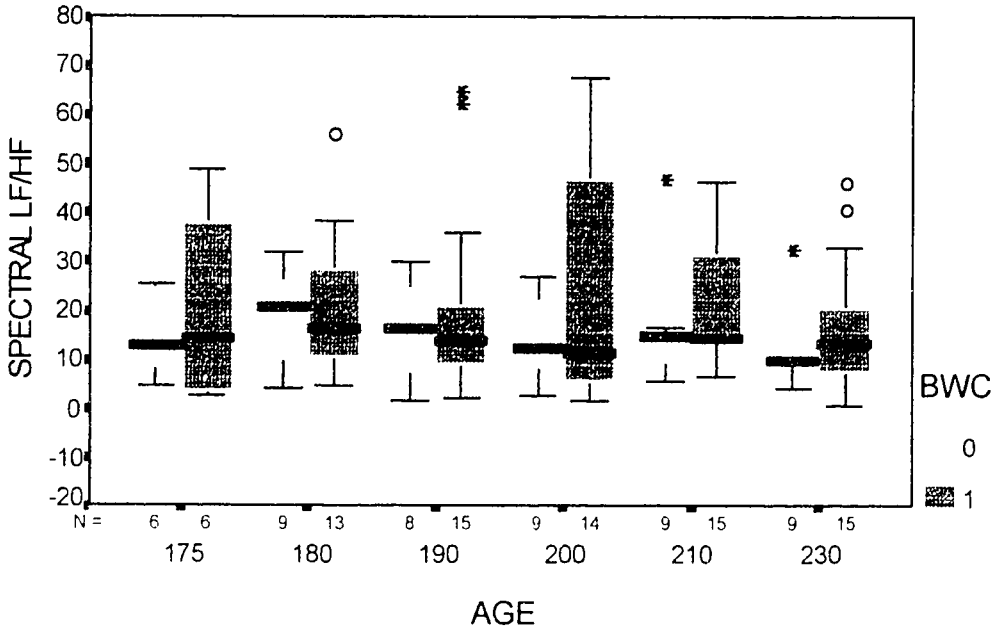
Spectral Very Low Frequency (msec squared) Across Estimated Postconceptional Ages for Both LBW and NBW Infants



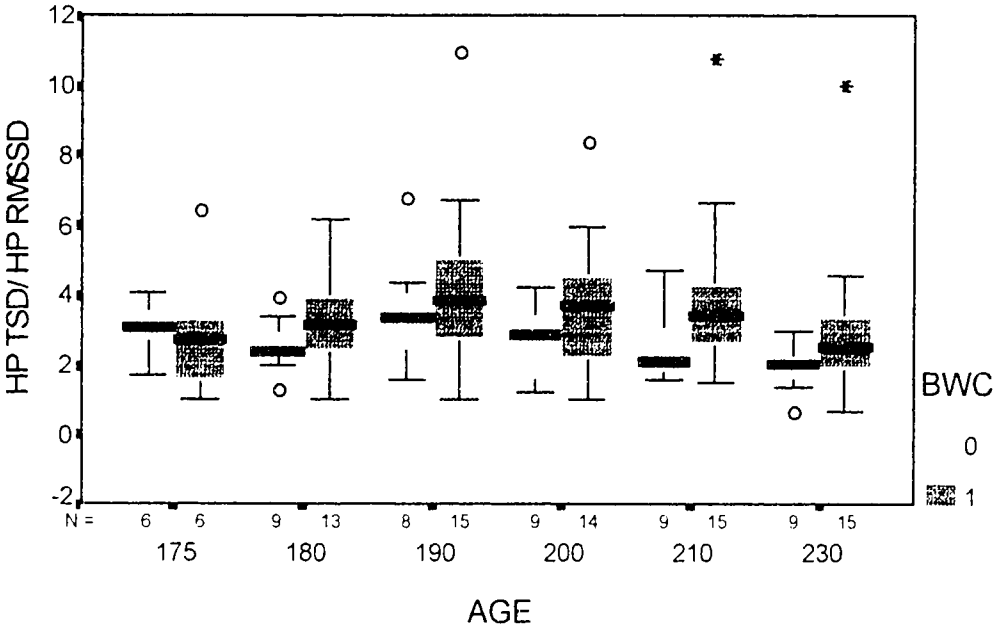
Spectral Low Frequency (msec squared) Across Estimated Postconceptional Ages for Both LBW and NBW Infants



Spectral High Frequency (msec squared)Across Estimated Postconceptional Ages for Both LBW and NBW Infants



Ratio of Spectral Low Frequency / Spectral High Frequency Across Estimated Postconceptional Ages for Both LBW and NBW Infants



Ratio of HP STD DEV / HP RMSSD Across Estimated Postconceptional Ages for Both LBW and NBW Infants

APPENDIX D
Spearman Correlations Among All Heart Rate Variables
Aggregated Across Ages
LBW and NBW Separately

Spearman Correlations for Heart Rate Variability Measures Aggregated Across All Estimated Postconceptional Ages for LBW Infants (n=51)

	HEART PERIOD	STD DEV	RMSSD	IQR	IQRSD	MAD	TVAR	VLF	LF	HF	LF/HF
STD DEV	.62**										
RMSSD	.53**	.87**									
IQR	.65**	.98**	.84**								
IQRSD	.52**	.79**	.84**	.78**							
MAD	.65**	.96**	.82**	.98**	.77**						
TVAR	.63**	.96**	.78**	.95**	.77**	.94**					
VLF	.55**	.92**	.74**	.89**	.78**	.88**	.94**				
LF	.67**	.92**	.76**	.93**	.76**	.92**	.96**	.84**			
HF	.67**	.87**	.80**	.91**	.83**	.88**	.90**	.82**	.90**		
LF/HF	-.02	.18	-.03	.15	-.16	.20	.20	.12	.27	-.11	
SD/RMSSD	-.11	-.16	-.59**	-.16	-.45*	-.13	-.05	-.04	-.06	-.25	.45

**p=0.000 *p≤0.01

Spearman Correlations for Heart Rate Variability Measures Aggregated Across All Estimated Postconceptional Ages for NBW Infants (n=78)

	HEART PERIOD	STD DEV	RMSSD	IQR	IQRSD	MAD	TVAR	VLF	LF	HF	LF/HF
STD DEV	.63**										
RMSSD	.73**	.60**									
IQR	.60**	.93**	.54**								
IQRSD	.72**	.58**	.83**	.56**							
MAD	.64**	.94**	.58**	.98**	.60**						
TVAR	.62**	.97**	.55**	.89**	.56**	.90**					
VLF	.46**	.89**	.38*	.78**	.41**	.78**	.93**				
LF	.67**	.91**	.63**	.88**	.61**	.90**	.91**	.73**			
HF	.65**	.59**	.81**	.60**	.79**	.63**	.59**	.39**	.66**		
LF/HF	-.15	.17	-.39**	.14	-.38*	.11	.18	.22	.18	-.56**	
SD/RMSSD	-.36*	.11	-.68**	.13	-.50**	.09	.15	.29*	.01	-.45**	.66**

**p=0.000 *p≤0.01

APPENDIX E
Spearman Correlations for Heart Rate Variabiity Measures
Across Estimated Postconceptional Ages

Spearman Correlations of Mean Heart Period Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	-.09 (n=6)				
190	.14 (n=6)	.02 (n=8)			
200	-.20 (n=6)	.37 (n=9)	.67 (n=8)		
210	.09 (n=6)	.37 (n=9)	.14 (n=8)	.53 (n=9)	
230	.49 (n=6)	.17 (n=9)	.60 (n=8)	.62 (n=9)	.17 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Standard Deviation Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	.37 (n=6)				
190	.54 (n=6)	.62 (n=8)			
200	.77 (n=6)	.43 (n=9)	.69 (n=8)		
210	-.54 (n=6)	.08 (n=9)	-.33 (n=8)	.12 (n=9)	
230	.66 (n=6)	.40 (n=9)	.55 (n=8)	.28 (n=9)	-.12 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of IQR Across Ages of Testing for LBWSubjects

	175	180	190	200	210
180	.49 (n=6)				
190	.52 (n=6)	.65 (n=8)			
200	.75 (n=6)	.56 (n=9)	.75* (n=8)		
210	-.49 (n=6)	.00 (n=9)	-.19 (n=8)	-.04 (n=9)	
230	.49 (n=6)	.37 (n=9)	.48 (n=8)	.59 (n=9)	-.17 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of MAD Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	.26 (n=6)				
190	.49 (n=6)	.58 (n=8)			
200	.66 (n=6)	.62 (n=9)	.66 (n=8)		
210	-.71 (n=6)	.23 (n=9)	-.17 (n=8)	.11 (n=9)	
230	.84* (n=6)	.59 (n=9)	.49 (n=8)	.73* (n=9)	.04 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of RMSSD Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	.49 (n=6)				
190	.60 (n=6)	.26 (n=8)			
200	1.0** (n=6)	.42 (n=9)	.74* (n=8)		
210	.09 (n=6)	.13 (n=9)	-.14 (n=8)	.40 (n=9)	
230	.54 (n=6)	.28 (n=9)	.44 (n=8)	.49 (n=9)	.23 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

. Spearman Correlations of IQRSD Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	.85* (n=6)				
190	.70 (n=6)	.66 (n=8)			
200	.89* (n=6)	.15 (n=9)	.59 (n=8)		
210	.14 (n=6)	.04 (n=9)	-.42 (n=8)	.16 (n=9)	
230	.46 (n=6)	.25 (n=9)	.57 (n=8)	.49 (n=9)	.16 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral Total Variance Across Ages for LBW Subjects

	175	180	190	200	210
180	.71 (n=6)				
190	.49 (n=6)	.52 (n=8)			
200	.77 (n=6)	.77* (n=9)	.69 (n=8)		
210	-.31 (n=6)	-.17 (n=9)	.19 (n=8)	-.07 (n=9)	
230	.49 (n=6)	.47 (n=9)	.48 (n=8)	.38 (n=9)	.35 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral VLF Across Ages for LBW Subjects

	175	180	190	200	210
180	.31 (n=6)				
190	.60 (n=6)	.55 (n=8)			
200	.26 (n=6)	.43 (n=9)	.81* (n=8)		
210	-.26 (n=6)	-.47 (n=9)	-.10 (n=8)	.00 (n=9)	
230	-.03 (n=6)	.37 (n=9)	.60 (n=8)	.55 (n=9)	.35 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral LF Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	.77 (n=6)				
190	.43 (n=6)	.52 (n=8)			
200	.83* (n=6)	.73* (n=9)	.64 (n=8)		
210	-.26 (n=6)	.18 (n=9)	.14 (n=8)	.15 (n=9)	
230	.60 (n=6)	.58 (n=9)	.48 (n=8)	.35 (n=9)	.27 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral HF Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	.71 (n=6)				
190	.77* (n=6)	.62 (n=8)			
200	.77* (n=6)	.53 (n=9)	.78* (n=8)		
210	-.08 (n=6)	.10 (n=9)	.12 (n=8)	-.18 (n=9)	
230	.54 (n=6)	.72 (n=9)	.62 (n=8)	.35 (n=9)	.30 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of LF / HF Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	-.49 (n=6)				
190	-.37 (n=6)	.07 (n=8)			
200	-.09 (n=6)	.32 (n=9)	.17 (n=8)		
210	-.54 (n=6)	.62 (n=9)	.14 (n=8)	-.32 (n=9)	
230	.49 (n=6)	-.20 (n=9)	.43 (n=8)	-.45 (n=9)	-.08 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of SD / RMSSD Across Ages of Testing for LBW Subjects

	175	180	190	200	210
180	.20 (n=6)				
190	.03 (n=6)	-.55 (n=8)			
200	.49 (n=6)	-.05 (n=9)	-.36 (n=8)		
210	.03 (n=6)	.33 (n=9)	-.52 (n=8)	.52 (n=9)	
230	.94** (n=6)	-.03 (n=9)	.19 (n=8)	.34 (n=9)	.45 (n=9)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Mean Heart Period Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.31 (n=6)				
190	.60 (n=6)	-.21 (n=13)			
200	1.0** (n=5)	.16 (n=12)	.42 (n=14)		
210	.66 (n=6)	.12 (n=13)	.13 (n=15)	.53* (n=14)	
230	.66 (n=6)	.27 (n=13)	.34 (n=15)	.49 (n=14)	.68** (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Standard Deviation Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.49 (n=6)				
190	.43 (n=6)	.18 (n=13)			
200	-.20 (n=5)	.15 (n=12)	.02 (n=14)		
210	-.03 (n=6)	.36 (n=13)	.53* (n=15)	.23 (n=14)	
230	.49 (n=6)	.26 (n=13)	.03 (n=15)	.34 (n=14)	.29 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of IQR Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	-.20 (n=6)				
190	.54 (n=6)	.03 (n=13)			
200	-.30 (n=5)	.02 (n=12)	-.04 (n=14)		
210	.09 (n=6)	.44 (n=13)	.29 (n=15)	-.01 (n=14)	
230	.26 (n=6)	.27 (n=13)	.05 (n=15)	.32 (n=14)	.25 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of MAD Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	-.20 (n=6)				
190	.58 (n=6)	.01 (n=13)			
200	.10 (n=5)	-.09 (n=12)	-.03 (n=14)		
210	.09 (n=6)	.49 (n=13)	.19 (n=15)	.07 (n=14)	
230	.03 (n=6)	.22 (n=13)	.05 (n=15)	.32 (n=14)	.44 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of RMSSD Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.20 (n=6)				
190	-.09 (n=6)	-.23 (n=13)			
200	.67 (n=5)	.01 (n=12)	.29 (n=14)		
210	-.60 (n=6)	.23 (n=13)	.12 (n=15)	.58* (n=14)	
230	-.26 (n=6)	-.18 (n=13)	.24 (n=15)	.29 (n=14)	.31 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of IQRSD Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.22 (n=6)				
190	.34 (n=6)	.18 (n=13)			
200	.21 (n=5)	-.05 (n=12)	.60* (n=14)		
210	-.12 (n=6)	.23 (n=13)	.45 (n=15)	.51 (n=14)	
230	.13 (n=6)	.43 (n=13)	.25 (n=15)	.30 (n=14)	.40 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral Total Variance Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.60 (n=6)				
190	.49 (n=6)	.18 (n=13)			
200	-.50 (n=5)	.35 (n=12)	-.09 (n=14)		
210	-.09 (n=6)	.25 (n=13)	.59* (n=15)	.22 (n=14)	
230	.43 (n=6)	.45 (n=13)	-.03 (n=15)	.35 (n=14)	.28 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral Very Low Frequency Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.83* (n=6)				
190	.60 (n=6)	-.20 (n=13)			
200	-.60 (n=5)	-.23 (n=12)	-16 (n=14)		
210	-.43 (n=6)	.10 (n=13)	.49 (n=15)	.40 (n=14)	
230	.43 (n=6)	.48 (n=13)	-.28 (n=15)	.12 (n=14)	.05 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral LF Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.14 (n=6)				
190	.14 (n=6)	.09 (n=13)			
200	-.10 (n=5)	.50 (n=12)	.09 (n=14)		
210	-.26 (n=6)	.16 (n=13)	.13 (n=15)	.07 (n=14)	
230	.49 (n=6)	.11 (n=13)	.31 (n=15)	.48 (n=14)	.45 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral HF Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.43 (n=6)				
190	.54 (n=6)	.38 (n=13)			
200	.30 (n=5)	-.10 (n=12)	.46 (n=14)		
210	-.43 (n=6)	.38 (n=13)	.49 (n=15)	.38 (n=14)	
230	.03 (n=6)	-.08 (n=13)	.09 (n=15)	.44 (n=14)	.36 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of LF / HF Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.03 (n=6)				
190	.37 (n=6)	.32 (n=13)			
200	-.40 (n=5)	-.08 (n=12)	.64* (n=14)		
210	-.09 (n=6)	-.10 (n=13)	.35 (n=15)	.34 (n=14)	
230	.26 (n=6)	.04 (n=13)	.33 (n=15)	.31 (n=14)	.33 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of SD / RMSSD Across Ages of Testing for NBW Subjects

	175	180	190	200	210
180	.03 (n=6)				
190	.54 (n=6)	-.30 (n=13)			
200	-.40 (n=5)	-.07 (n=12)	.39 (n=14)		
210	-.72 (n=6)	-.11 (n=13)	.20 (n=15)	.67** (n=14)	
230	-.09 (n=6)	-.06 (n=13)	.80** (n=15)	.36 (n=14)	.09 (n=15)

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Mean Heart Period Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.36 n=12				
190	.07 n=12	-.14 n=24			
200	.17 n=12	.29 n=24	.46* n=24		
210	.34 n=12	.30 n=24	.06 n=24	.43* n=24	
230	.50 n=12	.27 n=24	.34 n=24	.56** n=24	.62** n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Standard Deviation Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.39 n=12				
190	.57 n=12	.43* n=24			
200	.21 n=12	.24 n=24	.34 n=24		
210	-.38 n=12	.02 n=24	.09 n=24	.22 n=24	
230	.38 n=12	.27 n=24	.27 n=24	.28 n=24	.08 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of IQR Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.48 n=12				
190	.50 n=12	.22 n=24			
200	.55 n=12	-.03 n=24	.58** n=24		
210	-.28 n=12	-.18 n=24	.14 n=24	.42* n=24	
230	.03 n=12	.24 n=24	.36 n=24	.40* n=24	.29 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of MAD Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.13 n=12				
190	.65* n=12	.28 n=24			
200	.34 n=12	.23 n=24	.34 n=24		
210	-.37 n=12	.27 n=24	.02 n=24	.07 n=24	
230	.58* n=12	.37 n=24	.29 n=24	.45* n=24	

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of RMSSD Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.36 n=12				
190	.20 n=12	.11 n=24			
200	.68* n=12	.20 n=24	.49* n=24		
210	-.31 n=12	.00 n=24	-.02 n=24	.51** n=24	
230	.15 n=12	.11 n=24	.44* n=24	.50** n=24	.32 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of IQRSD Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.48 n=12				
190	.50 n=12	.22 n=24			
200	.55 n=12	-.03 n=24	.58** n=24		
210	-.28 n=12	-.18 n=24	.14 n=24	.41* n=24	
230	.03 n=12	.24 n=24	.36 n=24	.40* n=24	.29 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral Lf Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.41 n=12				
190	.43 n=12	.46* n=24			
200	.23 n=12	.52** n=24	.37 n=24		
210	-.31 n=12	.01 n=24	.08 n=24	.13 n=24	
230	.58* n=12	.32 n=24	.48* n=24	.39 n=24	.32 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of Spectral HF Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.54 n=12				
190	.74** n=12	.52** n=24			
200	.44 n=12	.06 n=24	.52** n=24		
210	-.31 n=12	.14 n=24	.29 n=24	.26 n=24	
230	.25 n=12	.26 n=24	.47* n=24	.51** n=24	.30 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of LF / HF Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	-.13 n=12				
190	.12 n=12	.29 n=24			
200	-.22 n=12	.03 n=24	.51** n=24		
210	-.10 n=12	.24 n=24	.36 n=24	.19 n=24	
230	.21 n=12	.00 n=24	.28 n=24	.11 n=24	.17 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

Spearman Correlations of SD / RMSSD Across Ages of Testing for Both LBW and NBW Subjects

	175	180	190	200	210
180	.02 n=12				
190	.29 n=12	-.23 n=24			
200	-.15 n=12	.05 n=24	.22 n=24		
210	-.36 n=12	.07 n=24	.08 n=24	.58** n=24	
230	.23 n=12	.10 n=24	.62** n=24	.41* n=24	.25 n=24

*p≤ 0.05 two-tailed **p≤ 0.01 two-tailed

CURRICULUM VITA

NAME: Dorothy M. Patteson

PLACE OF BIRTH: Springfield, Illinois

DATE OF BIRTH: February 13, 1942

EDUCATION:

University of Washington Seattle, Washington	1994	Ph.D.
University of Wisconsin-Madison Madison, Wisconsin	1969	M.S. in Pediatric Nursing
University of Illinois Urbana/Chicago, Illinois	1967	B.S.N
Barnes Hospital School of Nursing St. Louis, Missouri	1963	Diploma

PUBLICATIONS:

Schneider, J.M., Ziegel, E., & Patteson, D.M. (1975) Education of the perinatal nurse clinician: Program and Philosophy. Nursing Clinics of North America, 10(2), 285-91.

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