The Effects of Vestibular Stimulation Rate and Magnitude of Acceleration on Central Pattern Generation for Chest-Wall Kinematics in Preterm Infants.

by

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ABSTRACT

The vestibular system of the fetus is responsive to accelerations *in utero* by 25 weeks gestational age (Hooker, 1969). However, the restrictive environment of the crib/isolette in the neonatal intensive care unit (NICU) and decreased positional changes limits vestibular experience and associated neural activity among preterm infants.

This project was developed to test a set of hypotheses concerning the role of vestibular inputs on respiratory and oromotor systems during suck and early feeding development in preterm infants. Linear acceleration of the vestibular otoliths was achieved using a customized glider chair, the VestibuGlide System**,** developed in the Communication Neuroscience Laboratories at the University of Kansas. The VestibuGlide system features an integrated position-servo motor and a digital controller to generate physiologically appropriate sinusoidal displacements of the glider chair in the horizontal plane at specified rates (.5, .65, .8, .95 Hz) and accelerations (.21, .36, and .51 m/s^2). It was hypothesized that providing this type of input to the vestibular apparatus will modify the central patterning of chest wall motion, and secondarily may alter suck and feed development during a critical period of brain development.

Twelve preterm infants (7F/5M, birth GA 32; 6, BW 1927g) were recruited from the NICU at Stormont-Vail Regional Hospital in Topeka. Each infant received the 15 minute gliding protocol starting at 32 wks PMA, 3x/day before a scheduled feed for 10 days. Infants were fitted with two soft cloth Respitrace™ inductance bands around the rib cage and abdomen to measure respiratory rate. The gliding protocol alternates between baseline and stimulus conditions every minute. During baseline conditions, the glider chair was stationary. Respiration, suck dynamics, and pulse-oximetry were recorded and monitored throughout the study.

On average, infants received 24 VestibuGlide sessions. Stimulus condition had a significant effect for the in rib cage [$F(7, 77) = 25.53$, $p < 0.01$] and abdominal [$F(7, 77) = 23.60$, $p < 0.01$] breaths per minute (BPM). In general, infants increased their respiratory rate in response to the VestibuGlide stimulus. Stimulus number 7 provided the highest acceleration to the infant and induced significantly higher BPM than stimuli 1, 4, and 5 for the rib cage and stimuli 1 and 4 for the abdomen. It is clear that acceleration has the largest influence over the respiratory central pattern generator (rCPG) and is capable of inducing significant changes in chest wall kinematics.

In spite of the increases in BPM during vestibular stimulation, infants maintained stable oxygen saturation (SpO_2) and pulse rate throughout the VestibuGlide study. In fact, stimulus condition had a significant effect on SpO_2, $F(7, 77) = 2.57$, $p < .05$. Infants had higher SpO_2 during stimulus conditions 3, 4, and 6 compared to baseline conditions; however, after a Bonferroni-correction these differences could not reach statistical significance. Infants are able to modify their respiratory rate in response to vestibular stimulus while maintaining their $SpO_2$and pulse. All infants were offered a Soothie™ pacifier during each VestibuGlide session. Vestibular stimulation had no effect on NNS development.

Oral feeds were measured in days to achieve ≥90% oral feed for two consecutive days. A daily oral feed percentage was calculated across the eight daily feeds for all infants in the study and was compared to a cohort of 12 untreated preterm infants matched for birth GA (n=12, 7F/5M, GA 33; 2, BW 1950g) from an ongoing NIH trial underway in the mentor's laboratory (NIH R01 DC003311, Barlow-PI) recruited from Stormont-Vail Healthcare NICU in Topeka, KS and Overland Park Regional Medical Center NICU in Overland Park, KS. ANOVA revealed no difference in the oral feed growth slopes between the VestibuGlide treated infants and the

control infants: F (1, 22) = .25, p =.625. On average, VestibuGlide infants advanced their oral feeds at 8.17% per day; whereas, control infants advanced their oral feeds at 9.47% per day.

The length of stay in the NICU was measured from the admission date (birth date) to the discharge date for all infants in the VestibuGlide study and 17 untreated preterm control infants. ANOVA revealed a significant difference between the two groups F (1, 28) = 6.71, p=.015. The VestibuGlide group discharged from the hospital 12 days sooner than the control infants resulting in a substantial reduction in hospitalization costs (~$42,000/infant).

Overall, vestibular stimulation delivered to the preterm infant between 32 and 34 weeks PMA effectively modulates respiratory rate and resets the rCPG.

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45 minutes of gliding per day over ten days. I watched these infants develop, grow, and depart the NICU, and I will remember all of you individually and wish you all the best in your future.

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ABBREVIATION KEY

BPD……. Bronchopulmonary dysplagia

BPM……Breaths per minute

BW.……Birth weight

CLD…….Chronic lung disease

CN…….....Cranial nerve

CNS…….....Central nervous system

cpm…… Cycles per minute

Est…… Estimated

FBMs……... Fetal breathing movements

GA……Gestational age

NICU……Neonatal intensive care unit

NNS…….....Non-nutritive suck

NNS STI…….…. Non-nutritive suck spatiotemporal index

PMA…… Post-menstrual age

rCPG…….... Respiratory central pattern generator

RDS…….….Respiratory distress syndrome

sCPG…….....Suck central pattern generator

SE…….……....Standard Error

SpO_2…….....Oxygen saturation

CHAPTER ONE: INTRODUCTION

The proposed experiments evaluated the effect of vestibular inputs on respiratory and oromotor systems during suck and early feeding development in preterm infants. Bi-directional linear acceleration of the vestibular otoliths was achieved by using a new apparatus designed and developed in the Communication Neuroscience Laboratories at the University of Kansas, known as the VestibuGlide System (Barlow, Kieweg, & Zimmerman, 2011, see Figure 1). This system features an integrated position-servo motor and digital controller to generate physiologically appropriate linear displacements in the horizontal plane at programmed rates and accelerations.

Figure 1: VestibuGlide Chair.

Specific Aim #1

To examine the role of vestibular stimulus rate on chest wall motor patterning (movement) in preterm infants. Vestibular stimulation was initiated at 32 weeks post-menstrual age (PMA) using a servo-controlled linear glider chair at sinusoidal rates of 30, 39, 48, 57 cycles per minute (cpm) with displacements corresponding to 88.90, 53.34, 34.04, and 24.64 mm. These stimulus parameters yielded a peak acceleration of 0.36 meters per second squared

(m/s^2) at each rate. The selected frequencies lie within the expected range for chest wall motion during infant's respiration (40-60 breaths per minute (BPM)). It was hypothesized that vestibular stimulation at the selected rates with peak acceleration held constant will modify chest wall movements associated with breathing among preterm infants.

Specific Aim #2

To test the effect of vestibular stimulus acceleration on chest wall motor patterning (movement) in preterm infants. Vestibular stimulation was initiated at 32 weeks PMA using a servo-controlled linear glider chair with a constant sinusoidal frequency of 39 cpm with displacements ranging from 27.94-75.44 mm. These stimulus parameters yielded peak accelerations of .21, .36, and .51m/s^2, respectively. It was hypothesized that the degree of chest wall modulation will vary as a function of vestibular acceleration among preterm infants.

Specific Aim #3

To examine the efficacy of vestibular stimulation on the attainment of oral feeding proficiency in preterm infants. The gliding protocol, presented at the various rates and accelerations in a counterbalanced format, occurred approximately 15 minutes before the infants' daily feedings. The transition time to full oral feeds was measured for all infants in the study and was compared to a cohort of untreated preterm infants matched for birth GA (N=12). It was hypothesized that preterm infants exposed to daily regimens of vestibular stimulation at the prescribed rates and accelerations will manifest a significant decrease in the time (days) to attain 90% oral feed compared to a group of control infants, who did not receive vestibular stimulus.

Specific Aim #4

To examine the efficacy of vestibular stimulation on non-nutritive suck (NNS) development in preterm infants. A pacifier was offered to the infant during the VestibuGlide procedure. The following suck variables were analyzed total oral compressions per minute, burst cycles per minute, non-NNS compressions per minute (extraneous mouthing movements), NNS bursts per minute, mean NNS cycles per burst, mean amplitude of NNS cycles per minute, mean NNS intraburst cycle period, mean period between NNS bursts, NNS cycles as a percent of the total oral compressions, and the NNS spatiotemporal index (NNS STI). It was hypothesized that vestibular stimulation will accelerate the development of NNS in preterm infants.

BACKGROUND, SIGNIFICANCE, AND RATIONALE

Respiratory complications are one of the most common and immediate problems facing premature infants. These complications range from a mild oxygen need to an immense oxygen dependency that can result in the scarring of lung tissue. Respiratory complications not only prolong the time spent in the neonatal intensive care unit (NICU), but can also hinder lung and brain development (Inder, Warfield, Wang, Huppi, & Volpe, 2005; Perlman & Volpe, 1989). Therapies designed to reduce respiratory needs and increase the ability for premature infants to breathe independently are vital for this fragile population.

FUNDAMENTALS OF BREATHING AND THE NEONATE

The development of the mammalian respiratory system is extremely unique in that prenatal breathing does not involve gas exchange, while the goal of postnatal breathing is to attain adequate gas exchange as a function of task dynamics. The transition from breathing

amniotic fluid to breathing air normally occurs immediately after birth—where the infant, who has had no previous experience with gas exchange, can breathe independently. In order to fully understand infant breathing the following sections will be considered: fetal breathing, breathing at birth, chest wall structural changes, and chest wall compliance.

Fetal Breathing

Breathing movements begin in the womb and mature in character and frequency throughout development. Fetal breathing patterns were first observed in the mid-1970s with the advent of high-speed ultrasound. Fetal breathing movements (FBMs) are considered a precursor to postnatal breathing. Much like neonatal respirations, FBMs are mainly diaphragmatic and are presumably controlled by the medullary respiratory pattern generator (Kaplan, 1983). Although there are some similarities between postnatal and prenatal breathing, FBMs have many unique characteristics.

When considering fetal breathing, it is important to remember that the fetal thoracic cavity is entirely occupied by fluid and tissue (Dawes, 1974). Therefore, fetal breathing does not involve gaseous exchange or alveolar expansion. Continuous recordings of breathing over several weeks in near-term fetuses revealed two types of FBMs: gasps and sighs, occurring at frequencies ranging from 1 to 4 Hz and irregular breathing movements at frequencies up to 4 Hz that vary in both rate and depth (Dawes, 1974). FBMs are not continuous, which increases the likelihood for long periods apnea to occur in fetuses at a lower gestation age (GA) (Natale, Nasello-Paterson, & Connors, 1988). Apnea is the cessation of breathing for 10 seconds or longer characterized by no movement of respiratory muscles and an unchanged volume in the lungs.

There are several methodologies that can be used to assess FBMs, including Doppler sonography and ultrasound techniques. Doppler sonography is a non-invasive measure of blood flow used in the third trimester of pregnancy. Studies in fetal lambs revealed that FBMs induce intra-tracheal pressure deflection with small tidal movements of fluid that reflect fetal respiratory efforts (Dawes, Fox, Leduc, Liggins, & Richards, 1972; Maloney, et al., 1975). Doppler sonography can assess tracheal fluid flow velocity as early as 20 weeks GA (Kalache, et al., 2000). Another method for detecting FBMs incorporates a thin beam of ultrasound directed from a transducer to the mother's abdomen to attain echoes from the fetal heart. Ultrasound technologies have demonstrated FBMs to occur at an average frequency of 40-70 per minute and are present approximately 70% of the time during the latter half of gestation (Boddy & Mantell, 1972; Dawes, 1974).

Fetal breathing can be influenced by a variety of pharmacological and physiological factors present in the mother (Kaplan, 1983; Thompson & Hunt, 2005). Maternal blood glucose levels have a direct effect on FBMs. In fact, there is an increase in FBMs two-to-three hours after the mother consumes a meal due to a rise in maternal glucose levels (Patrick, Natale, & Richardson, 1978). Alcohol ingestion can depress FBMs. This is evidenced by a controlled study where women near-term ingested 30ml of vodka diluted ginger ale resulting in an onset of fetal apnea 10-30 minutes post-ingestion that lasted for approximately 50 minutes (Fox, et al., 1978). In one study, vigorous maternal exercise led to fewer apneic periods and an increase in irregular breathing patterns (Marsal, Lofgren, & Gennser, 1979). Fetal breathing increases three-fold when the mother inhales 5% CO_2 for 15 minutes (Ritchie & Lakhani, 1980).

Although FBMs provide an immense amount of insight into the breathing mechanism *in utero*, it remains unclear whether they reflect overall fetal health. However, fetal breathing along

with other measures of fetal well-being has been advantageous in guiding doctors on the need for an urgent delivery (Manning & Platt, 1979; Trudinger, Lewis, & Petit, 1979).

Breathing at Birth

The development and initiation of breathing likely stem from a complex interaction of chemoreceptors, thermoreceptors, hormones, and sensory stimuli from both central and peripheral inputs (Thompson & Hunt, 2005). It is commonly thought that mild fetal asphyxia during labor stimulates peripheral chemoreceptors leading to the first breath, which is then maintained by other sensory stimuli like cold and touch (Thompson & Hunt, 2005). This view has been challenged by animal studies revealing that denervation of the carotid and aortic chemoreceptors do not alter fetal breathing or the initiation of the first breath (Jansen, Ioffe, Russell, & Chernick, 1981). Postnatal studies also support the importance of cooling for establishing a regular respiratory pattern and the role of CO_2 in maintaining that pattern (Gluckman, Gunn, & Johnston, 1983; Thompson & Hunt, 2005). One study explored perinatal adrenaline release and found that it plays an important role in respiratory initiation and adaptation to extra-uterine life (Richet, Davicco, & Barlet, 1985). Failure to achieve adequate gas exchange at birth represents a major cause of perinatal morbidity and mortality.

The Breathing Apparatus and Neonates: Structural Change in the Chest Wall

The breathing apparatus has a long developmental course contingent on neural and musculoskeletal development (Boliek, Hixon, Watson, & Morgan, 1996). Normal function of the immature chest wall is impeded by its distinctive shape, deformity, and increased compliance requiring adaptation of the respiratory central pattern generator (rCPG) for the maintenance of

optimal respiratory function (Hershenson, 1992). Therefore, an intact rCPG is essential for optimal respiration during the neonatal period.

Throughout development the thorax changes considerably. For example, at birth the ribs are horizontal at rest (Devlieger, 1987; Openshaw, Edwards, & Helms, 1984). The horizontal rib placement evident in the neonate constrains the thoracic cross-sectional area making it more circular and horizontal compared to the adult thorax (Takahashi & Atsumi, 1955). These anatomical differences result in a deficient respiratory system. Because the rib cage is already at a horizontal plane in the young neonate, there is reduced involvement of the rib cage in producing tidal volumes (Hershenson, Colin, Wohl, & Stark, 1990; Hershenson, Stark, & Mead, 1989), leading to the common observation that young infants are predominately abdominal (diaphragmatic) breathers (Hershenson, 1992).

The Breathing Apparatus and Healthy Neonates: Compliance of the Chest Wall

Healthy term newborns have an extremely compliant chest wall characterized by thin cartilage, incomplete bone mineralization, and a relatively high cartilage to bone ratio (Bryan & Wohl, 1986). Poor mineralization of the ribs at term birth can reduce the outward recoil of the chest wall in newborns thereby reducing rib cage volume and the inward movements of the rib cage during diaphragmatic breathing (Gerhardt & Bancalari, 1980). Paradoxical breathing, or chest distortion, can occur where there is an inward movement of the rib cage and an outward displacement of the abdomen during inspiration (Davi, Sankaran, Maccallum, Cates, & Rigatto, 1979; Knill, Andrews, Brayan, & Brayan, 1976). Paradoxical breathing is a less efficient method of breathing as the muscular effort necessary for a total tidal volume during this type of breathing is four times greater than during normal respiratory movements (Grassino, 1974).

Throughout development, there is a progressive mineralization of the ribs and an increase in the ratio of bone to cartilage (Bryan & Wohl, 1986). As the infant grows, the effects of gravity and the change to an upright posture pulls the rib cage downward. The principal changes in rib cage shape occur by two years of age (Openshaw, et al., 1984). Total respiratory compliance continues to decrease from 5 to 16 years of life (Sharp, Druz, Balagot, Bandelin, & Danon, 1970).

The previous sections highlight some of the major anatomical differences between the newborn and adult breathing apparatus. Additional changes occur after the newborn period throughout the first year of life that subserves the breathing mechanism, including changes in structure and mechanics, functional behavior, ventilation, perfusion, gas exchange, and the nervous system. (Table 1) (Boliek, et al., 1996). Knowledge of how the chest wall develops is critical to disease and illness prevention, especially with the preterm infant population.

Table 1: Changes in breathing in the first year of life adapted from Boliek (1996).

Evolution of the breathing apparatus during the first year of life
Changes in structure
• Alveoli increase in number • Alveoli increase in size • Alveolar ducts increase in number • Alveolar surface area increases • Lung size and weight increases • Airways increase in radius and length
Changes in mechanics
• Thoracic cavity enlarges and changes in shape • Inclination of ribs increases with upright posture • Chest wall compliance decreases with upright posture • Rib cage muscle bulk increases • Airway resistance decreases • Pleural pressure becomes more subatmospheric
Changes in functional behavior
• Tidal volume increases • Expiratory reserve volume increases • Inspiratory capacity increases • Vital capacity increases • Progression from dynamic to passive end-expiratory level • Resting tidal breathing variability decreases • Respiratory rate decreases • Minute ventilation increases • Maximal inspiratory and expiratory pressures increase
Changes in ventilation, perfusion, and gas exchange
• Pulmonary circulation develops • Pulmonary diffusion increases • Arterial oxygen tension increases • Maximal oxygen uptake increases
Changes in nervous system
• Myelination of upper motoneuron tracts increases • Myelination of somatosensory pathways increases • Myelination of pre- and post-thalamic proprioceptive • pathways increases • Myelination of pre- and post-thalamic exteroceptive • pathways increases • Development of primary sensorimotor areas • Development of secondary sensory and motor areas • Continues • Inputs and outputs from cerebellum increase • Elaboration of reticular formation pre-motor interneurons • Descending inputs from forebrain to rCPG

PREMATURITY: RESPIRATORY DEVEVLOPMENT & COMPLICATIONS

Preterm Infants and Lung Development

The respiratory function of the lung is to supply oxygen to the systemic blood and excrete carbon dioxide from the venous blood (Taussig & Helms, 1993). However, when infants are born too soon this task can be nearly impossible depending on their stage of lung development. Human lung development is divided into five stages: embryonic, pseudoglandular, canalicular, saccular, and alveolar stages ("Module 18 Respiratory Tract," 2008). Infants born prematurely have often reached only the saccular stage (24-36 weeks). During this stage, alveoli develop from terminal saccules and surfactant becomes evident in amniotic fluid (Whitsett, Rice, Warner, Wert, & Pryhuber, 2005). The saccular stage is followed by the alveolar stage (36 weeks –8 years of age). During this stage, true alveoli are formed and throughout life the number of alveoli increase to 300 million in the adult lung (Whitsett, et al., 2005).

Premature Infants and Respiratory Complications

Insults during early respiratory maturation may alter the developmental programming of neuronal respiratory networks leading to respiratory control abnormalities that can persist into adulthood (Gaultier & Gallego, 2005). Premature infants born between 24 – 28 weeks GA, or with extremely low birth weight (<1000g) are most susceptible to lung injury because their lungs are delicate and have small gas exchange volumes (Stevenson, et al., 1998). When infants are born too soon, they often sustain respiratory complications, such as apnea, respiratory distress syndrome (RDS), bronchopulmonary dysplagia (BPD), and hypoxia.

Typically, apneic events are prolonged respiratory pauses of ten or more seconds (Alden, et al., 1972; Daily, Klaus, & Meyer, 1969; Kattwinkel, Nearman, Fanaroff, Katona, & Klaus, 1975). Apnea is usually associated with ventilator and cardiovascular sequelae, namely

hypoxemia, hypercapnia, and bradycardia (Miller, Martin, & Haxhiu, 2003). Often, the lower the GA and birth weight, the higher the incidence of apnea (Henderson-Smart, 1981; Miller, Behrle, & Smull, 1959). In one clinical study, apnea was found to occur in over 80% of infants born at less than 30 weeks GA, 50% of infants at 30 to 31 weeks GA, 14% at 32 to 33 weeks GA, and only 7% at 34 to 35 weeks GA (Henderson-Smart, 1981). Because there is such a close relationship between gestational age and incidence of apnea, it is likely that immaturity of neural pathways in the brainstem that regulate breathing may be responsible.

One of the most common lung issues threatening premature infants soon after birth is RDS. Frequently the preterm lung does not produce enough surfactant which allows the inner surface of the lungs to expand. Surfactant therapy along with oxygen supplementation is often necessary to treat RDS. Infants requiring prolonged ventilation to treat RDS or infants who are still on oxygen by 36 weeks GA are classified as BPD.

The development of BPD occurs over the course of weeks and is characterized by scarring of the lungs. Respiratory complications can severely hinder lung and brain development. In fact, neonatal auditory brainstem responses in premature infants with BPD reveal poor myelination and synaptic function that impairs brainstem integrity (Wilkinson, Brosi, & Jiang, 2007). The brainstem houses critical life-sustaining circuitry needed for breathing, sucking, and feeding in the young neonate. Invasive respiratory therapies, necessary to treat BPD, are trussed to the face and are capable of altering the expected range of sensory experiences and have been hypothesized to impair the brainstem circuitry essential for suck and feed development (Barlow, Finan, Lee, & Chu, 2008; Estep, Barlow, Vantipalli, Finan, & Lee, 2008; Stumm, et al., 2008). Gray matter, or cell bodies, in subcortical areas can also be damaged as a result of BPD. Infants

with BPD can exhibit a movement disorder with neuronal loss to the caudate, putamen, and globus pallidus (Perlman & Volpe, 1989).

Another respiratory related complication that preterm infants are at risk for is hypoxia. Hypoxia occurs when the body is deprived of adequate oxygen supply. A fetal sheep model revealed that even a brief period of hypoxia during mid-gestation results in changes to cortical white matter, or myelinated axons, and reduced number of Purkinje cells in the cerebellum (Rees, et al., 1998). Severe respiratory illness can impact brain development and increase the risk factors for neurodevelopmental impairments.

Preterm Infants and Chest Wall Development

Anatomy of the breathing apparatus is relatively undeveloped in preterm infants. There is a higher prevalence of paradoxical breathing in preterm infants due to increased chest wall compliance (Davi, et al., 1979). This is associated with insufficient outward elastic recoil of the chest wall and contributes to a low functional residual capacity and chronic pulmonary failure in preterm infants (Gerhardt & Bancalari, 1980). It is clear that premature infants are at a breathing disadvantage due to immature chest wall musculoskeletal anatomy and neural pathways.

THE NEONATAL INTENSIVE CARE UNIT (NICU)

NICU Environment

The development of the brain requires a complex temporal and sequential order of events that is initiated soon after conception and continues into the second decade of life (Allin, et al., 2001; Brown & Minns, 1999). The NICU environment can disrupt the sequential order of events needed for brain development and is considered a rate-limiting environment that is likely to

deprive infants of sensory stimulation they would otherwise receive *in utero*. Neonatal complications, invasive oxygen therapies, numerous daily medical procedures, and confining isolettes all reduce the amount of vestibular, kinesthetic, tactile, auditory, and visual information available to the infant (Schaefer, Hatcher, & Barglow, 1980). The duration of these maladaptive exposures can last from a few days to a few months depending on the stability and co-morbidities of the preterm infant. Premature infants are receiving these noxious stimuli during a critical period where sensorimotor experience is hypothesized to plays a vital role in brain circuitry and development (Barlow, et al., 2008).

NICU and Vestibular Stimulation

With the number of preterm births increasing, experimental application of supplemental sensory stimulation is a salient and needed research avenue to gain further knowledge of the relation between human brain plasticity and the infant's environment (Dieter & Emory, 1997). Because the vestibular system is one of the first sensory systems to develop, the premature infant may be more receptive to stimulation in this modality than in any other. Morphogenesis of the vestibular apparatus in humans is complete by the 49th day *in utero* and the vestibular nerve is myelinated and functional between the 8th and 9th month of intrauterine life (Blayney, 1997; Humphrey, 1965; Nandi & Luxon, 2008). Response to vestibular stimulation has been observed as early as 25 weeks GA (Hooker, 1969). Fetal flotation in amniotic fluid essentially creates a whirl-pool like milieu stimulating and protecting the developing fetus thereby providing potent vestibular stimulation (Korner, Kraemer, Haffner, & Cosper, 1975; Rice, 1979). Due to the early maturation of the vestibular system, it is one the best mechanisms for providing developmentally appropriate stimulation to the infant (Korner, et al., 1975).

Rocking is one way to elicit vestibular stimulation and mimics certain features (rhythmicity) of maternal walking and infant movement *in utero* (Korner, 1990). Rocking has been shown to encourage later emerging sensory modalities including more accurate visual and auditory pursuits (Korner, et al., 1975; Korner, Schneider, & Forrest, 1983; Neal, 1969). Rocking stimulation prevents apneic attacks and subsequently decreases the need for respiratory therapies (Farrimond, 1990; Korner, et al., 1975; Tuck, Monin, Duvivier, May, & Vert, 1982). These findings show the potent effect vestibular stimulation can have on many physiological systems, including respiration. The increased neural integrity afforded by rocking, reduces the intensity on internal needs (crying and/or disorganized states) and allows the focus to be more on external events, such as responding to the local environment (Korner, Ruppel, & Rho, 1982).

VESTIBULAR ANATOMY

Vestibular Apparatus

The vestibular system, located in the inner ear, has two main components: the semicircular canals and the otolith organs. There are three semicircular canals, including the horizontal, superior, and posterior canals, arranged orthogonal to one another. This organizational scheme allows the canals to detect angular acceleration through inertial forces acting on the endolymph within each canal. Head rotation encoded by the vestibular system along the three orthogonal axes (yaw, pitch, and roll) is then sent to the brain. Together the saccule and utricle make up the otolith organs and send signals to the brain regarding head position relative to the force of gravity and linear acceleration. The utricle and saccule are tiny sacs, lined with hair cells. Small calcium carbonate particles, called otoliths, rest on these hair cells. These otolith organs act as linear accelerometers. When the head translates, rotates, or tilts

relative to gravity, the weight and movement of the otoliths stimulate the nerve endings surrounding the hair cells.

During head movement, both gravitational and translational accelerations occur. According to Einstein's equivalence principle, inertial accelerations during translational motion are physically indistinguishable from gravitational acceleration experienced by tilting movements (Angelaki, McHenry, Dickman, Newlands, & Hess, 1999; Einstein, 1908). The translational and gravitational components result in linear acceleration and are encoded via primary afferent otolith signals in the brain (Anderson, Blanks, & Precht, 1978; Dickman, Angelaki, & Correia, 1991; Fernandez & Goldberg, 1976; Loe, Tomko, & Werner, 1973; Si, Angelaki, & Dickman, 1997). Therefore, when infants receive linear vestibular stimulation, both translational and gravitational accelerations are encoded via the otolith organs. Otolith signals related to gravity or translational head movements are critical for many important life functions. In fact, head tilt signals are essential for the autonomic control of the respiratory and cardiovascular systems (Uchino, Kudo, Tsuda, & Iwamura, 1970; Yates, 1992; Yates, Aoki, Burchill, Bronstein, & Gresty, 1999; Yates & Miller, 1994). The vestibular system also plays a critical role in stabilizing images on the retina during head tilts in the vestibular-ocular reflex by producing an eye movement in the direction opposite of the head tilt. This reflex is very important for stabilizing vision.

Vestibular Nucleus

After the semicircular canals and otoliths have been stimulated, the encoded information is transmitted to the central nervous system (CNS) via the eighth cranial nerve, passes the vestibular ganglion and projects to the ipsilateral vestibular nuclei, located in the dorsal part of

the pons and medulla in the floor of the fourth ventricle (Goldberg, 2000). The vestibular nuclei integrate signals from the vestibular apparatus with signals from the spinal cord, cerebellum, and visual system. The vestibular nuclei projects to many areas including, the oculomotor nuclei, reticular formation, spinal centers, vestibular regions of cerebellum (flocculus, nodulus, ventral paraflocculus, and ventral uvula), and the thalamus (Goldberg, 2000).

The vestibular nucleus has the following four components, medial, lateral, superior, and descending nuclei (Figure 2). Each of these different components receives various forms of vestibular inputs and projects to a variety of areas within the CNS (Figure 3). The superior and medial nucleus receives predominantly semicircular canal inputs (medial nucleus receives some otolith inputs) and project to the medial longitudinal fasciculus, oculomotor centers, and spinal cord (Gacek & Lyon, 1974; Goldberg, 2000). Neurons in the medial nucleus are primarily excitatory; whereas, neurons in the superior nucleus are mostly inhibitory. Both the superior and medial nuclei are involved with reflexes that control eye gaze.

The lateral nucleus (Deiter's nucleus) receives inputs from both the semicircular canals and the otoliths and projects to the lateral vestibulospinal tract, thereby contributing primarily to postural reflexes (Gacek & Lyon, 1974; Goldberg, 2000). The descending nucleus receives predominantly otolith inputs (some posterior canal inputs) and projects to the cerebellum, reticular formation, and contralateral vestibular nuclei. The descending nucleus integrates vestibular signals and central motor signals.

Figure 2: Vestibular nucleus and its afferent input adapted from Gacek and Lyon (1974) and Goldberg (2000).

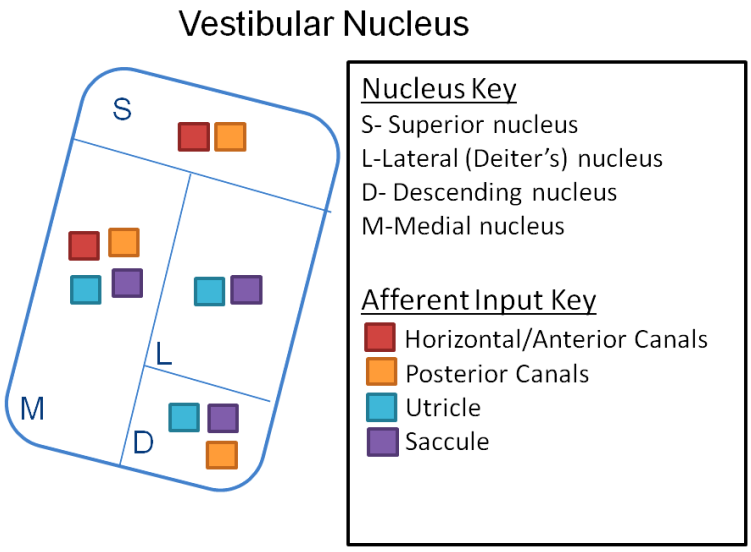
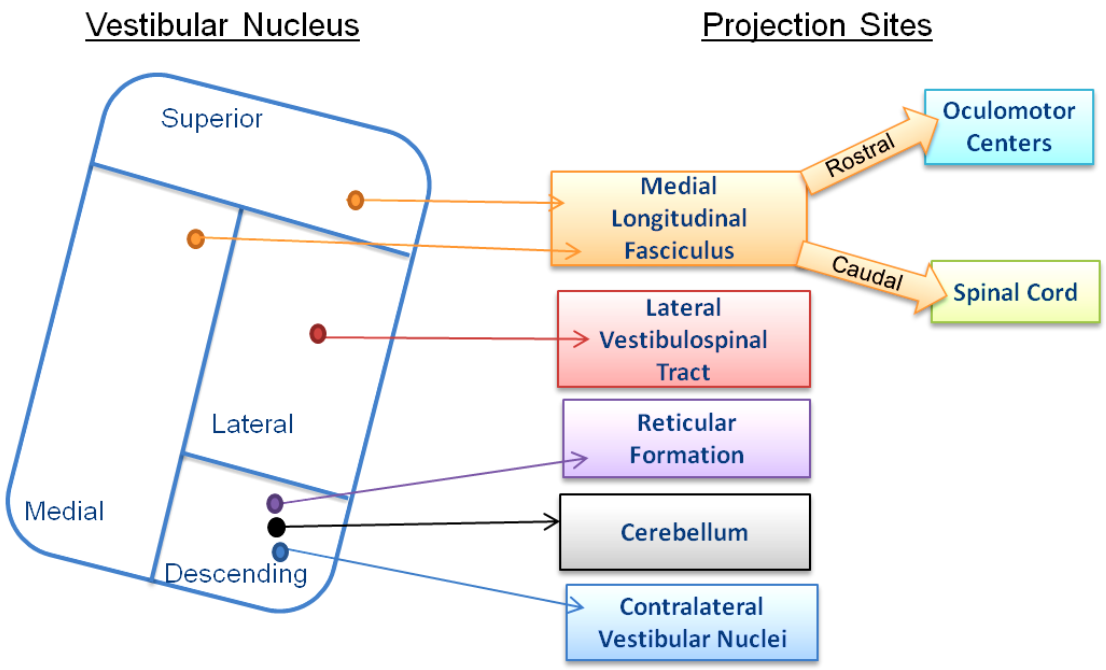


Figure 3: Vestibular nucleus and its projections within the CNS adapted from Gacek and Lyon (1974) and Goldberg (2000).



Although the vestibular nuclei are functionally segregated; natural vestibular stimulation reveals the widest distribution to all in the vestibular nuclei (Wilson, 1978). Therefore, natural stimulation, such as gliding, is a very potent form of vestibular stimulation and can project to numerous areas within the CNS.

Vestibular Connectivity

The vestibular system is instrumental in controlling motoneurons innervating the extrinsic eye muscles (Cohen, 1974; Precht, 1977; Raphan, 1985; Robinson, 1985) and in modulating the activity of alpha-motoneurons and gamma-motoneurons projecting to the neck (Gernandt, 1974; Wilson, 1988; Wilson & Yoshida, 1969), trunk, and limb extensor muscles (Abzug, Maeda, Peterson, & Wilson, 1974; Gernandt, 1974; Pompeiano, 1972). These connections are necessary for maintaining equilibrium and sustaining locomotion. Along with potent connectivity to the eyes, neck, trunk, and limbs, the vestibular system influences motor control of the tongue and jaw.

Vestibular Stimulation and the Jaw

Humphrey (1965) observed mouth opening following movement of a fetus manually and commented that this could be due to vestibular stimulation. There is evidence that patients suffering from a vestibular syndrome show functional impairment of the jaw-closing muscle, the masseter (Hopf, 1987). Observations linking the vestibular system to the masseter muscle have resulted in several animal and human studies confirming that vestibular input elicits an excitatory tonic control on masseter muscle activity (Deriu, et al., 2000; Tolu, et al., 1996; Tolu & Pugliatti, 1993). There is some debate regarding how the vestibular apparatus connects to the masseter

muscle. One study used retrograde labeling in rats and showed that a monosynaptic pathway exists between the medial vestibular nucleus, prepositus hypoglossi, and masseter motoneurons (Cuccurazzu, Deriu, Tolu, Yates, & Billig, 2007). Another study revealed that the latencies of responses recorded from the masseter motoneurons in the guinea pigs suggests that polysynaptic pathways are involved in connecting the vestibular system to the trigeminal complex (Tolu & Pugliatti, 1993). More research in the human model needs to be completed to examine these pathways further.

Vestibular Stimulation and the Tongue

Animal and human studies have shown that the vestibular system influences tongue activity (Anker, et al., 2003; Cotter, et al., 2004; Elmund, Bowman, & Morgan, 1983). Many experiments have demonstrated that macular (otolith) and ampullar (semicircular) inputs influence the activity of the intrinsic and extrinsic tongue muscles (Mameli & Tolu, 1986; Mameli, Tolu, Melis, & Caria, 1988; Mameli, 1985, 1986). These vestibulo-hypoglossal connections are important in controlling the tongue position in the mouth during head displacement (Tolu & Pugliatti, 1993).

Visual and vestibular inputs can converge on the same hypoglossal neuron and visual input can significantly modify the vestibular influence on the hypoglossal nuclei (Mameli, Melis, & De Riu, 1994). These hypoglossal visuo-vestibular neurons operate as more than a relay station for visual and vestibular impulses. They appear to process retinal, ampullar, and macular signals resulting in unitary spatial drive to the tongue muscles (Mameli, et al., 1994). Thus, tongue muscles may be controlled or modulated in part by visual, somatosensory, and vestibular inputs.

Vestibular Stimulation and Tongue and Jaw

Vestibular stimulation provided to the young neonates has been shown to improve NNS, feeding skills, and increases weight gain and growth rates (Gregg, Haffner, & Korner, 1976; Kramer & Pierpont, 1976; Neal, 1968; Rice, 1979; Scarr-Salapatek & Williams, 1973; White & Labarba, 1976). The vestibular system influences suck, feed, and growth outcomes due to its interconnectivity with the tongue and jaw musculature. This influence likely alters later developing ormotor skills such as mastication and speech.

RESPIRATORY CENTRAL PATTERN GENERATOR (rCPG)

Central pattern generators are located throughout the nervous system, including the brainstem, spinal cord, and cerebral tissues and are composed of a network of interneurons that activate groups of motoneurons to generate a specific motor pattern (Barlow, Lund, Estep, & Kolta 2010). These internuncial circuits can be modified by sensory stimulation, which can change the cycle duration and intensity of motoneuron burst responses in the CNS (Grillner, 1991, 2002; Grillner, Hellgren, Menard, Saitoh, & Wikstrom, 2005). The rCPG is a complex of several bilateral modules within the medulla, including the pre-Bötzinger complex (pre-BötC).

Pre-Bötzinger Complex

The pre-BötC is most essential for rhythmic control of breathing (McCrimmon, Ramirez, Alford, & Zuperku, 2000; McKay, Critchley, Murphy, Frackowiak, & Corfield, 2009; Reckling & Feldman, 1998; Smith, 1997; Smith, Ellenberger, Ballanyi, Richter, & Feldman, 1991; Wenninger, et al., 2004). In fact, lesioning this region results in cessation of breathing (McCrimmon, et al., 2000; McKay, et al., 2009; Reckling & Feldman, 1998; Smith, 1997; Smith, et al., 1991; Wenninger, et al., 2004). The pre-BötC is bilaterally symmetric and can

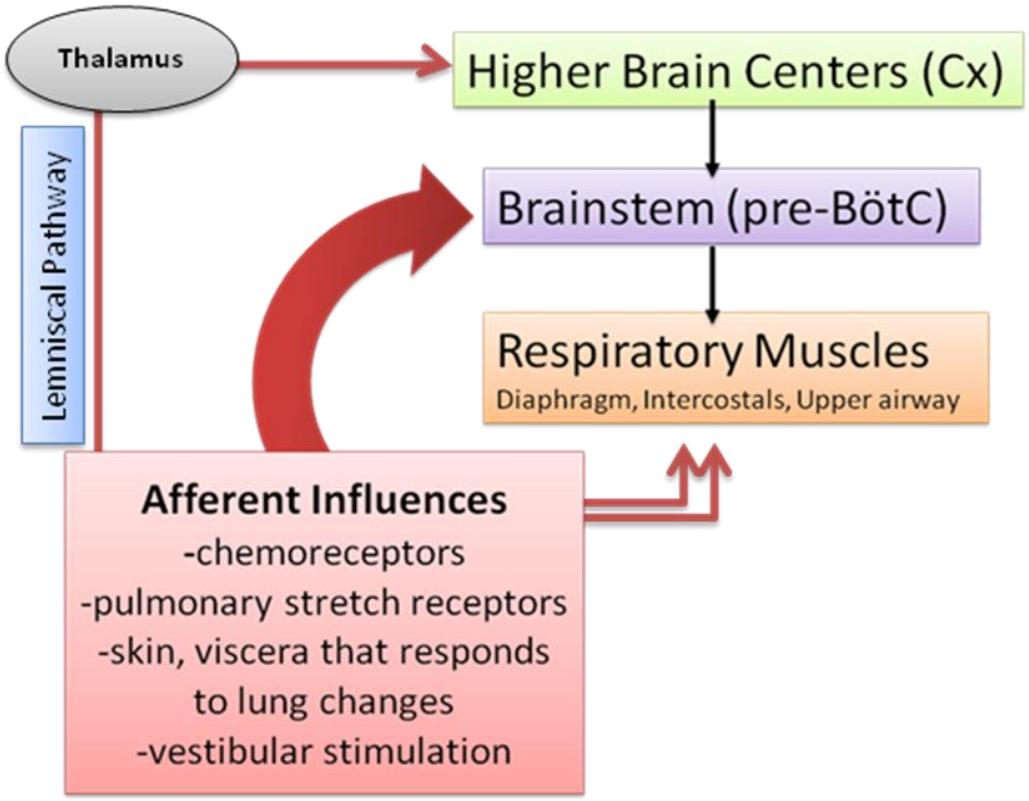
independently generate a respiratory rhythm (Gromysz & Karczewski, 1984). Interneurons in this region generate inspiratory rhythm that propagates through premotoneuron circuits to spinal and cranial nerves (Feldman & Smith, 1995; Reckling & Feldman, 1998; Smith, et al., 1991). Premotoneurons and motoneurons share a related set of synaptic electrophysiological properties hypothesized to represent a common electrophysical foundation for neurons functioning as rhythmic drive transmission elements (Koizumi, et al., 2008)

Within the pre-BötC, there are two distinct pacemaker bursting patterns that are part of the inspiratory pattern generator termed persistent sodium current and non-specific calcium-dependent cation current (Ramirez & Viemari, 2005). Both pacemakers and their connections are modulated with contributions of different pacemaker types and of synaptic interactions producing a dynamic function of modulation (Dickinson, 2006). Because of this, the same neural network can produce several types of breathing patterns: normal breathing (eupnea), sighs, and gasps (Barlow, et al., 2010; Dickinson, 2006). The rCPG is incorporated into a larger neural system and operates under control of central and peripheral inputs.

The rCPG is active throughout the lifespan and subject to adaptation caused by changes in metabolic demands and various task dynamics such as vocalization and speech. The rCPG is highly adaptable and easily modified by central and peripheral inputs (Figure 4) (Rubin, Shevtsova, Ermentrout, Smith, & Rybak, 2009). Inspiratory and expiratory neurons are under the command of a central neural oscillator that when perturbed, the intrinsic rhythm is slowed down or accelerated, depending on the moment in the cycle when the stimulation occurs (Baconnier, Benchetrit, Pachot, & Demongeot, 1993). Sensory modulation results in reassembly of the neuronal networks that compose the rCPG, and therefore produces new motor forms (Grillner,

1991). This adaptive and flexible neural substrate allows the infants to adapt according to task dynamics and environmental conditions (Barlow & Estep, 2006).

Figure 4: Adaptation of the rCPG.



Vestibular inputs to the Respiratory Central Pattern Generator (rCPG)

Stimulation of vestibular afferents through various positional changes is highly effective in altering neural activity associated with respiration (Rossiter, Hayden, Stocker, & Yates, 1996; Rossiter & Yates, 1996; Yates, Billig, Cotter, Mori, & Card, 2002). It is well established that the vestibular system contributes to making adjustments in the thoracic and abdominal respiratory pump muscles and muscles that regulate the resistance of the upper airway (Arshian, et al.,

2007). Respiratory muscle coordination occurs in the spinal cord and brainstem, specifically the rCPG. The rCPG has spatially distributed populations of interneurons and premotoneurons that serve functional roles in respiration (Billig, Foris, Card, & Yates, 1999; Rybak, Abdala, Markin, Paton, & Smith, 2007). The motoneuron pools that receive projections from the rCPG encode periodic contraction of respiratory muscles (Bellingham, 1998; Rubin, et al., 2009).

Different components within the rCPG are highly sensitive to vestibular stimulation. In fact, half of the respiratory neurons in the ventral respiratory group (VRG) of the rCPG, where the pre-BötC is located, contribute to the vestibulo-respiratory reflex (Miller, Yamaguchi, Siniaia, & Yates, 1995). Electrophysiological studies have confirmed that respiratory neurons, including those projecting to the VRG, respond to electrical stimulation of the vestibular nerve (Miller, et al., 1995; Shiba, Siniaia, & Miller, 1996). However, lesions of the VRG do not abolish vestibulo-respiratory responses. Therefore, neurons in addition to the brainstem respiratory premotor neurons must be involved in the relaying vestibular signals to respiratory motoneurons in the spinal cord (Shiba, et al., 1996; Yates & Miller, 1998). It is likely that these pathways include vestibulospinal and medial reticulospinal neurons that are also responsible for relaying vestibular signals to limb and neck motorneurons (Yates & Miller, 1998).

ENTRAINMENT

Entrainment is defined as the synchronization of an endogenous oscillator to external periodic events (Glass & Mackey, 1988; Kriellaars, Brownstone, Noga, & Jordan, 1994; Pavlidis, 1973). For a given stimulus with fixed displacement and period, a stable phase relationship between the stimulus and oscillator must exist to satisfy the conditions for entrainment. One such internal oscillator in the human neonate is respiration. An external

stimulus capable of entraining respiration is rocking (Sammon & Darnall, 1994). Entrainment of respiration by rocking is indicated by the infant breathing in synchrony with rocking (Elliott, Fisher, & Ames, 1988). The ability of an oscillator to synchronize to an external periodic signal provides adaptive and predictive control that allows fast and reliable responses to external changes (Pavlidis, 1973). This type of adaptation greatly benefits the preterm infant in controlling and modifying their respiration to external inputs. The brain's ability to modify central brainstem mechanisms to peripheral inputs is essential for the infant to adapt to their local environment, an important component for early learning.

Preterm Infants and Respiratory Entrainment

The ability of the chest wall to entrain to mechanical ventilation has been widely studied and shown effective (Baconnier, et al., 1993; Simon, Habel, Daubenspeck, & Leiter, 2000; Simon, Zurob, Wies, Leiter, & Hubmayr, 1999). Many researchers have expanded on the early ventilation studies to find new and innovative ways to entrain respiration. Ingersoll & Thoman (1994) examined the ability of preterm infants to match their respiration to that of a "breathing" bear (BrBr) placed in their isolette. An air pump, located in the bear's abdomen, simulated breathing at one-half the infant's breathing rate. Infants who were provided with the BrBr showed significantly more quiet sleep, less active sleep, and increased respiratory regularity. This study demonstrated that premature infants with an irregular medullary oscillator (irregular breathing pattern) can entrain to a regular external oscillator (regular breathing pattern afforded by the BrBr) to stabilize respiration.

Korner and colleagues (1990) placed premature infants on head-to-toe rocking waterbeds. This stimulus reduced apnea and increased auditory and visual ability (Korner, 1990; Korner, et

al., 1983). Although the infant waterbed showed many positive effects, there remained a risk of the waterbed leaking and potentially harming the infant.

Another team of investigators developed an automatic 2-speed (40 and 57 cpm) rocking bed to examine respiratory entrainment (Elliott, et al., 1988). This study revealed that 2:1 entrainment frequently occurred when infants were rocked at 40 cpm; whereas 1:1 synchronization was observed less frequently in infants rocked at 57 cpm (Elliott, et al., 1988). No quantified measures of acceleration were provided rendering limited interpretation of the results.

Variations to rocking frequencies (0-70 cpm) and displacements up to 5 inches were examined with two-month old full term infants placed in an aluminum bassinet that rocked vertically (Vrugt & Pederson, 1973). Higher frequencies were more effective than lower frequencies and within each frequency condition and higher displacements were more effective than lower displacements. This study emphasized that both frequency and displacement determine the effectiveness of rocking. The authors of this study realized the importance of acceleration on the effectiveness of rocking but measured it retrospectively and therefore did not quantitatively measure the respiratory response to acceleration. The outcomes measures of this study were based on behavioral state observations and not on respiratory entrainment mechanisms.

A study by Sammon and Darnall (1994) completed coherence spectra analysis on respiratory-abdominal movements in neonates. Eighteen premature infants (born between 28-34 weeks GA and studied two weeks after birth) were manually rocked in a conventional rocking chair at varying frequencies between 30 and 60 cpm paced by a metronome. Spectral analysis reported by these authors revealed an overall coherence of >.85, indicating strong entrainment to

rocking. At least one incidence of 2:1 entrainment was seen at rocking rates 30-40 cpm and 1:1 entrainment at rates of 42-50 cpm. This study found that infants $\geq$ 35 weeks exhibited higher coherence than those $\leq$ 35 weeks PMA, demonstrating a maturational change in the reflex. This study suggested that natural stimulation via rocking provides phasic inputs to the rCPG capable of resetting the system's oscillation and entraining its rhythm (Sammon & Darnall, 1994)

Previous rocking studies did not control the stimulus over an extended operating range for frequency or acceleration. Because these studies failed to quantify the nature of the stimulus being provided and had poor study designs making the outcomes questionable. The vestibular otoliths respond to linear acceleration; however, many vestibular studies have used conventional rocking chairs under manual control that produce a nonlinear (arc) displacement trajectory. Highly controlled vestibular stimulation with clearly defined parameters for use in the NICU is needed to fully explore the effects of this important sensory channel on motor and behavioral state control. The proposed experiments benefited from innovation in precise stimulus control for both cycle rate and linear acceleration. The vestibular otoliths were driven by linear acceleration using a servomotor glider chair apparatus operating under position feedback (*see* VestibuGlide System).

RATIONALE FOR FREQEUNCIES AND ACCELERATIONS:

Rationale for Frequency Rate: The present study examined the role of vestibular stimulus rate on sensorimotor integration of the rCPG by using rates ranging from 30-57 cpm. These frequencies lie within the physiologic operating range for chest wall breathing patterns in preterm infants and should allow a test of entrainment (coherence) between vestibular stimulus rate and chest wall movement patterns.

Rationale for Acceleration: Rocking studies report the use of alternating displacement on the order of 101.6 mm (4 inches) (Sammon & Darnall, 1994; Vrugt & Pederson, 1973). The vestibular system responds effectively to linear acceleration. Therefore, peak accelerations of .21, .36, and .51m/s^2 (27.904, 53.34, 75.44 mm displacement) delivered at a rate of .65 Hz were implemented in an effort to understand how acceleration impacts chest wall motor control, suck, feeding skill attainment, and state control.

SALIENT MEASURES:

Respiratory development was assessed by measuring rib cage (RC) and abdominal (AB) kinematics, pulse rate, and oxygen saturation (SpO_2). Non-nutritive suck was also assessed during the gliding protocol. Measures of feeding skill included measurement of the transition time (days) to ≥90% oral feed. Length of stay (LOS) in the NICU was measured from admission date (birth date) to discharge date.

OVERALL PURPOSE:

To evaluate the effect of a respiratory stimulation program utilizing a new system developed at the University of Kansas, known as the VestibuGlide System (Barlow, Kieweg, & Zimmerman, 2011). This device was developed to generate highly controlled programmable vestibular stimuli to assess the effects of rate and acceleration on the dynamics of breathing (chest wall motions), sucking, and feeding performance in preterm infants. This project digitally sampled NNS and chest wall kinematics as well as synthesized the stimuli and control signals to drive a medical-grade instrumented glider chair at specified frequencies and linear accelerations commonly associated with 'rocking' and feeding in the NICU environment.

SUMMARY AND KNOWLEDGE TO BE GAINED:

This project was designed to investigate the role of vestibular stimulation on sensorimotor integration of the rCPG through physiologically appropriate rates (30, 39, 48, 57 cpm) and peak accelerations (.21, .36, .51 m/s^2). Many research studies have shown the potent influences vestibular stimulation has on the rCPG; however, none have provided linear gliding stimulus with modifications to rate and acceleration while measuring breaths per minute (BPM), suck, and oral feed performance.

CHAPTER TWO: METHODS

The four study aims in this project were designed to assess the potential effects of vestibular stimulation rate and acceleration on sensorimotor integration of the rCPG for chest wall kinematics, suck dynamics, and oral feed skill attainment among a group of healthy preterm infants. The participants and methods to achieve these aims are described in the following sections.

PARTICIPANTS

The efficacy of the respiratory stimulation program was studied in 12 preterm infants (7 females, 5 males, with no exclusion based on race or ethnicity), see Table 2. These premature infants were born healthy with no abnormalities or specific diagnoses. All participants were recruited from the NICU at Stormont-Vail Healthcare, Topeka, KS.

Table 2: Participant information for VestibuGlide infants.

Infant ID	**Sex**	**Birth GA** (wks;days)	**Birth weight** (gms)	**Birth Length** (cm)	**Birth Head Circumference** (cm)	**O_2 Hx** (days)	**Study PMA** (wks; days)	**Number of VestibuGlide Sessions**
W5	F	33;0	2010	43	30.0	3	33;5	29
W6	F	32;2	1850	41	31.5	2	34;1	30
W7	F	33;1	2000	42	29.5	0	33;4	24
W8	M	34;1	2665	47	35.0	5	36;0	19
W9	M	31;3	1610	41	28.0	0	33;4	21
W10	F	32;0	1770	44	29.5	4	33;6	29
W11	M	31;3	1740	44	28.7	5	32;4	28
W12	M	33;1	2340	46	31.5	2	34;0	25
W13	M	34;3	1800	45	30.5	0	34;5	20
W14	F	32;1	1720	43.5	29.5	2	33;4	29
W15	F	33;2	1850	42	30.0	2	34;1	19
W16	F	33;2	1780	46	30.5	2	34;1	20
MEAN		32;6	1927.92	43.7	30.35	2.25	33;7	24.41
SD		0.96	298.47	2	1.78	1.76	0.82	4.44

Each infant enrolled in the study received the gliding protocol and served as his/her own control (within-subject design) for all of the respiratory and suck outcomes. However, when analyzing feeding outcomes and length of stay in the NICU, enrolled infants were compared to a control group matched for birth GA (n=12, 7F/5M, GA 33; 2, BW 1950g, see Table 3) from an ongoing NIH trial underway in the mentor's laboratory (NIH R01 DC-003311, Barlow-PI) recruited from Stormont-Vail Healthcare NICU in Topeka, KS and Overland Park Regional Medical Center NICU in Overland Park, KS. These control infants were given a sham stimulus—where they are held by an experienced NICU researcher for 15-30 minutes prior to their daily feed 3x/day for 10 days and offered a Soothie® pacifier.

Table 3: Participant information for the control infants.

Infant	**Sex**	**Birth GA** (wks;days)	**Birth weight** (gms)	**Birth Length** (cm)	**Birth Head Circumference** (cm)	**O_2 Hx** (days)
T208	M	33;0	1700	42.00	30	2
T209	F	33;0	1660	43.00	29	2
T230	F	34;2	1940	44.00	30	2
T237	F	35;2	2420	46.00	31	0
T241	M	34;3	2130	46.00	31.5	0
T243	F	30;5	1520	41.50	27.5	0
T256	M	34;4	2290	44.50	31.5	0
T262	F	30;0	1325	37.00	28	2
T274	M	35;3	3070	47.00	35.5	2
T275	F	33;6	2620	48.00	32	0
O48	F	31;3	1017	37.00	25	0
O58	M	31;0	1710	43.30	29.3	2
Mean		33;2	1950.17	43.28	30.03	1.00
SD		1.84	581.73	3.53	2.64	1.04

HUMAN SUBJECTS REVIEW

This research project was approved on 11/24/2009 by the University of Kansas Human Subjects Committee—Lawrence KS (HSCL protocol # 18285). Approval from the Stormont-Vail Regional Hospital institutional review board occurred on July 23, 2010. A subsequent change to the IRB to include infants on caffeine was approved on November 18, 2010. After low enrollment in the study, another modification to the IRB was submitted to include infants ranging from 28-34 weeks GA, and approval was attained on December 8, 2010. The primary investigator and associated research staff completed the required tutorials for human research for the University of Kansas and Stormont-Vail Regional Hospital.

INCLUSION CRITERIA

Born between 28 and 34 weeks GA, as determined by obstetric ultrasound and clinical examination, currently receiving tube feedings, minimal or no oxygen history (≤ 5 days of ventilator, CPAP, & nasal cannula), head circumference within 10–90th percentile of mean for PMA, neurological examination showing no anomalies for PMA (response to light, sound, and spontaneous movements of all extremities), and with stable vital signs (heart rate, blood pressure, age appropriate respiratory rate, baseline target SpO_2 range appropriate for PMA to allow for stimulation, and at least 32 weeks PMA at the initiation of study.

EXCLUSION CRITERIA

Intraventricular hemorrhage grades III and IV, periventricular leukomalacia, necrotizing enterocolitis, neonatal seizures and culture-positive sepsis or meningitis at time of testing, chromosomal anomalies or craniofacial malformation, nervous system anomalies, cyanotic

congenital heart disease, gastroschisis, omphalocele, mothers with diabetes, diaphragmatic hernia, and/or other major gastrointestinal anomalies, or not ready for oral feedings as determined by the health care team.

INFORMED CONSENT

Recruitment was by word of mouth from the investigator to parents in the NICU at Stormont-Vail HealthCare in Topeka, KS. Before the initiation of the study, each parent or guardian signed an informed consent. Parents/caregivers were compensated for their time with a $25 gift card to *Babies R' Us* upon the completion of the study.

EQUIPMENT

Respitrace™ Device: A battery-powered variable inductance plethysmograph, clinical Respitrace™, was used to measure chest wall kinematics and is considered the gold standard in respiratory kinematic monitoring. The sensor bands were gas sterilized (ethylene oxide) prior to the enrollment of a new infant using the Anprolene™ standard ethylene oxide protocol. These sensor bands were placed on the infant's chest wall before the gliding protocol was initiated (Figures 5 and 6). These soft cloth bands encircled the infant's chest wall (rib cage and abdomen) and sense changes in circumference (size). The upper band was placed around the axillae and its lower edge below the nipples. The lower band was placed below the costal margin and its lower edge above the iliac crest (Boliek, et al., 1996; Stradling, Chadwick, Quirk, & Phillips, 1985). The signal outputs from the Respitrace™ sensor bands were used to quantify the infants' BPM and were also used in the coherence analysis.

Figure 5: Respitrace™ diagram adapted from Bolick, et al., 1996 and Stradling, et al., 1985.

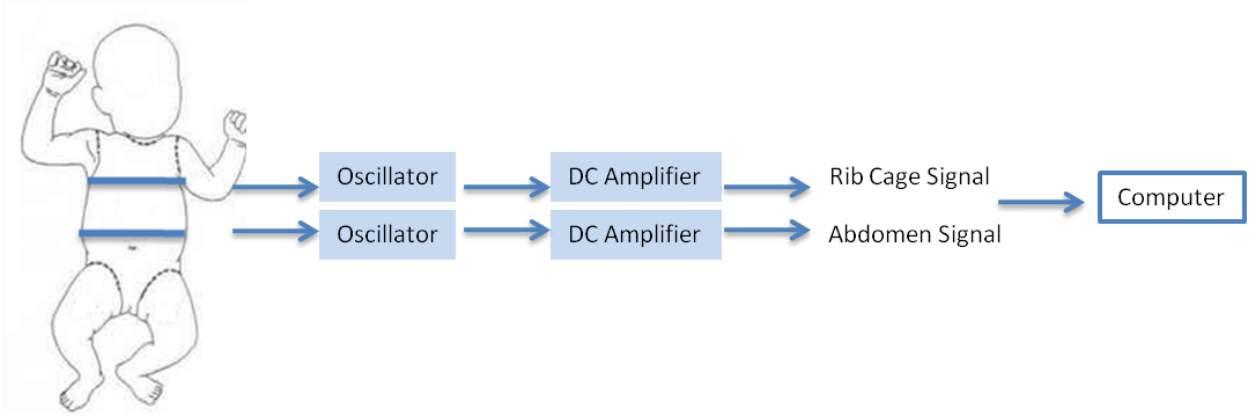
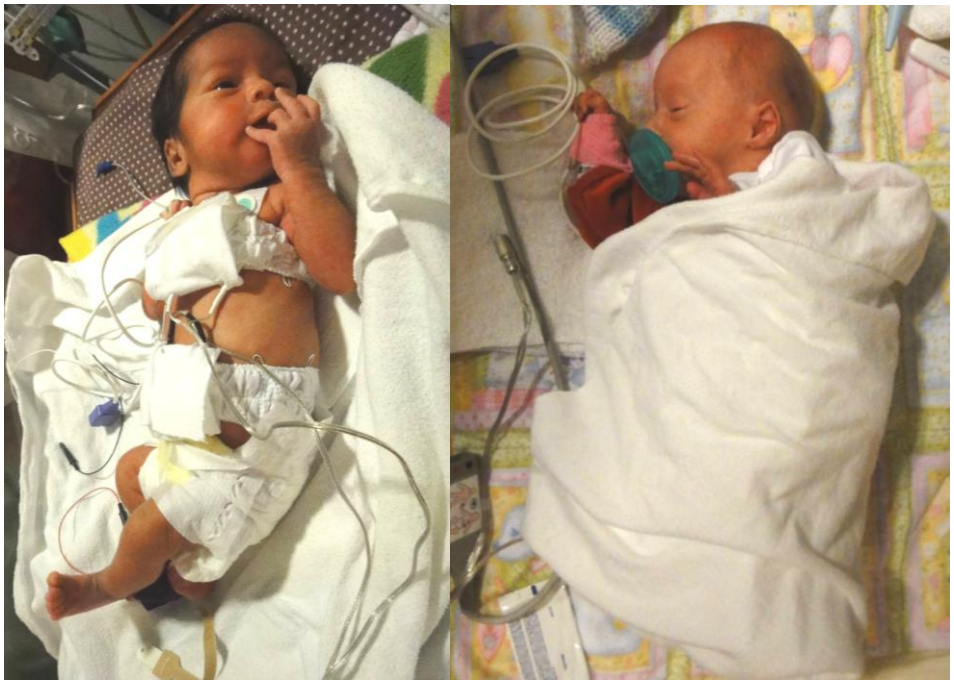


Figure 6: Left: infant fitted with Respitrace™ bands. Right: infant with the bands under her blanket with only the Respitrace™ output cord (gray) evident.



NELLCOR OxiMAX™ N-600 Pulse Oximeter: Pulse rate and SpO_2 signals from a NELLCOR OxiMAX™ N-600 pulse oximeter were transduced by a neonatal oxygen sensor which was placed on the infant's wrist. Pulse-ox signals were monitored and digitized during the study for each infant.

VestibuGlide System

The major components of the VestibuGlide System included a glider chair, linear servo motor (H2W Technologies, Inc., Santa Clarita, California), servo electronics, and PC-interfaced National Instruments cRIO FPGA (field programmable gate array) programmed as a motion control and data acquisition system. The PC-based data acquisition computer allowed for quick touchpad operation and real-time data display of the infant's physiology. Figure 7 shows a screen shot of the tablet PC during a VestibuGlide session. The top trace is the glider chair position in cm (straight line because it is in a baseline condition), second trace down is the Respitrace™ band output (abdominal output in red and rib cage output in white), bottom trace is the suck displacement in cmH_20. The SpO2 and Pulse output from the neonatal oxygen sensor are seen in the far right column.

Figure 7: Screen shot of the glider interface.

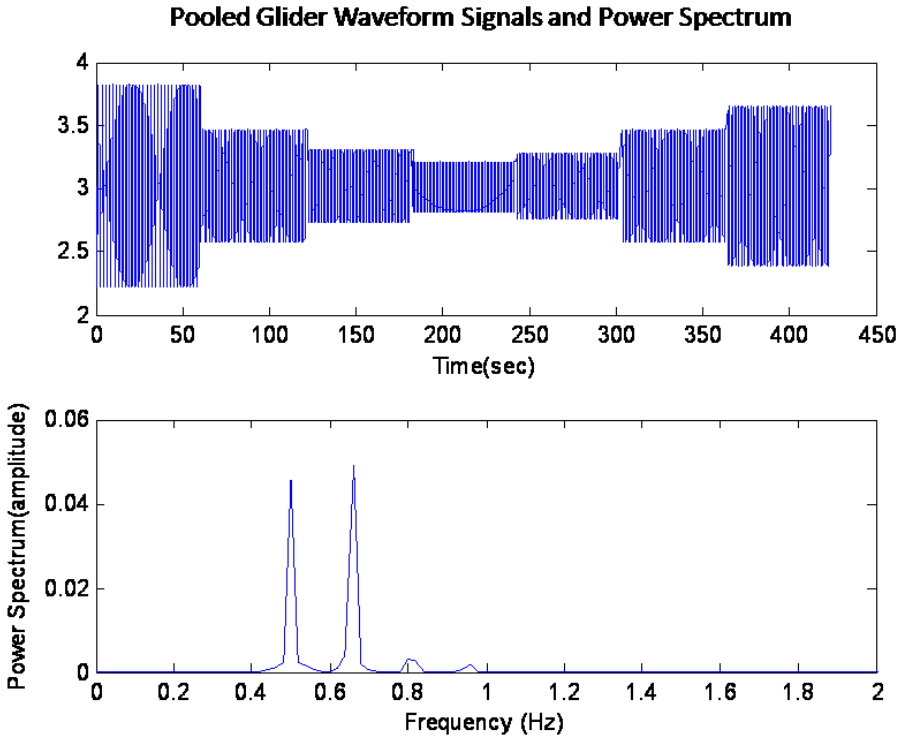
The chair began as a hospital-grade glider, upholstered in a moisture barrier vinyl material (Carolina Business Furniture, Inc., Archdale, North Carolina). The Communication Neuroscience Laboratory Bioengineering group at KU-Lawrence modified and instrumented this glider chair with a special linear servomotor (H2W Technologies, San Clarita, California) and designed a control module to operate the chair (chair, tester, preterm infant) smoothly under position feedback. To accommodate the servo linear motor, the stock factory gliding assembly was removed and the tubular steel sub-frame of the glider chair was fit with a custom machined ¼" thick aluminum base in order to increase platform stability and load-bearing capacity (1000 lbs). The specially designed linear motor from H2W Technologies provided horizontal translation on a dual-track roller bearing stage instrumented with both a digital linear encoder and analog position sensor. The four hospital-grade antibacterial rubber wheels (load rated at 400 lbs each) bolted to the underside of the chair base platform made it possible to move the chair easily around the hospital and NICU. Stable positioning at crib side within the NICU was

assured by engaging each of the load bearing lift-locks which physically elevated the wheels and entire VestibuGlide System by 2” from the floor (Figure 8).

Figure 8: VestibuGlide chair in two different NICU suites at Stormont-Vail HealthCare.

The servo controller was programmed to generate the control signal protocol to 'glide' the chair according to sinusoidal input functions at rates from 0.5 to 0.95 cycles per second at glide displacements ranging from 2.4 cm to 8.9 cm. A power spectrum was completed on the glider signals to ensure that the power spectrum frequencies match the desired stimulus rates (Figure 9).

Figure 9: Glider waveform signals (top) and power spectrum (bottom) for the entire gliding stimulus [frequency resolution equals 0.05Hz].



For safety, the servo featured an electronic safety limiter (governor) to limit the rate at 1.5 Hz and the linear motor included mechanical stops to limit displacement of the glider translation stage to 14 cm. Thus, the resulting stimulus regimen delivered by the VestibuGlide chair includes linear accelerations and cyclic rates well below the vestibular stimulation possible

with a conventional rocking chair in the clinic or home environment. The data acquisition microprocessor (National Instruments cRIO, see Figure 10) was programmed to synthesize control signals for the linear motor and perform all real-time digitization of the biological signals, including NNS compression pressure, Respitrace™ chest wall displacement for rib cage and abdomen, and pulse-ox signals at 50 Hz/channel at 16-bits of voltage resolution. A medical grade isolation transformer was configured between the AC-line source and all signal conditioning and digital electronics (Figure 10).

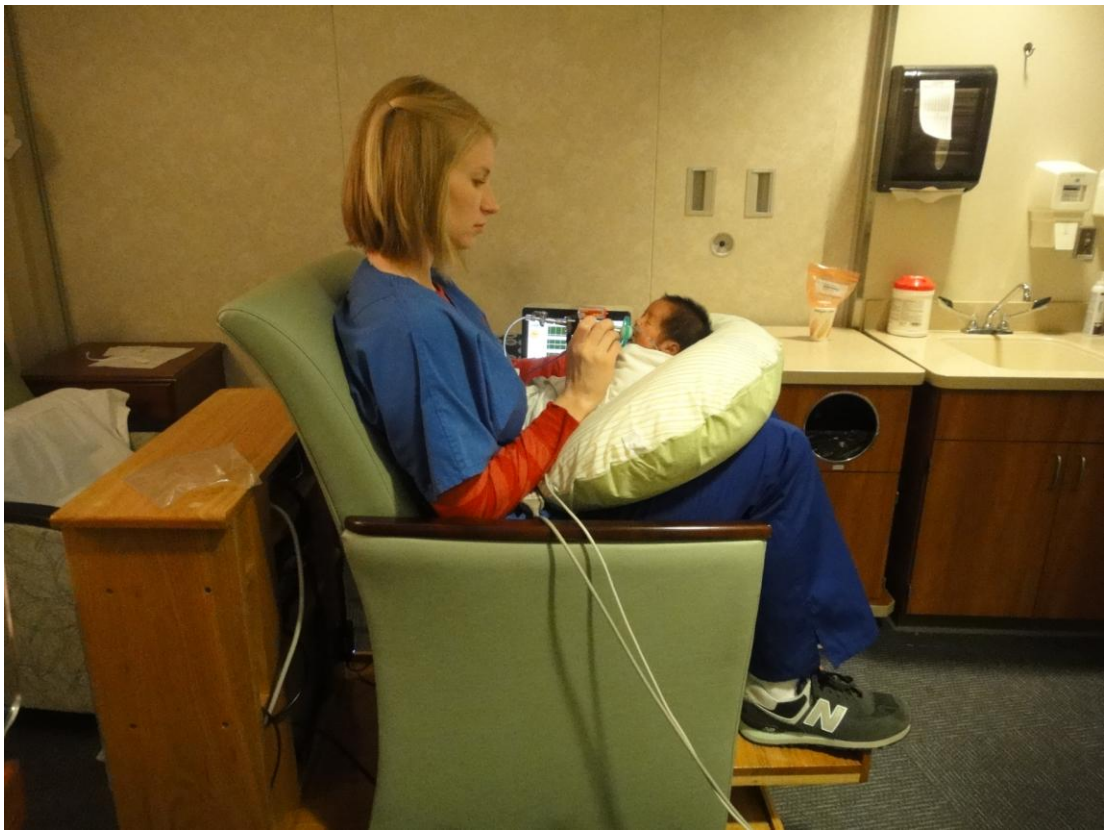
Figure 10: Back of the VestibuGlide chair. Upper right: *NELLCOR OxiMAX™ N-600 Pulse Oximeter,* middle shelf: cRIO FPGA and motor controller, bottom shelf: isolation transformer and power on/off switch.

Infant Feeding Pillow

Infants were place on the researcher's lap, by either the nursing staff or the infant's parent/caregiver, in a semi-inclined position against a Boppy® Pillow (Figure 11). The Boppy® Pillow was fitted with a hypoallergenic water-resistant cover as well as a cotton cloth cover, both of which were gas sterilized (ethylene oxide - EtO) prior to the enrollment of a new infant using the Anprolene™ standard EtO protocol. The Boppy® Pillow not only ensured ergonomic semi-

inclined positioning for the infant but is also considered the standard in infant feeding pillows used in the NICU and various feeding clinics.

Figure 11: VestibuGlide System with infant placed against Boppy® Pillow.



Accelerometer

In an effort to assess the acceleration the infant received during the gliding stimulus, an accelerometer was mounted to the infant's pacifier receiver (Figure 12). This location provided the best estimate of head acceleration without having to position the accelerometer directly on the infant's head. The uniaxial PBS Piezotronics (Model 3711B122G) accelerometer was mounted to a specially machined Delrin receiver using Velcro™. A line bubble meter was mounted to the receiver to ensure the accelerometer was held on the appropriate plane. The

infant's Soothie® pacifier was attached to the Delrin receiver and offered to the infant every session.

Figure 12: Accelerometer (white arrow) and line mount (red) mounted on infant's pacifier receiver.

GLIDING PROTOCOL

Infant Preparation-Positioning (*applicable to all stimulation and recording sessions*). During the gliding protocol, the infant was swaddled in a blanket, with limbs positioned at midline, background/overhead lighting dimmed to promote eye contact with the tester and placed in a supportive semi-inclined position against the Boppy® Pillow (Figure 12). The gliding stimulus was not initiated until the infant was in an optimal behavioral state, i.e., drowsy to

active alert (state 3, 4, or 5 as described by the Naturalistic Observation of Newborn Behavior, Newborn Individualized Developmental Care and Assessment Program; NIDCAP, (Als, 1995)).

Gliding Procedure: All infants in the study received the gliding protocol (Table 4) 3x/day 15 minutes before the infant's scheduled feeding for 10-days distributed over a two week period (Sat-Sun excluded).

Table 4: Linear (horizontal plane) gliding stimuli.

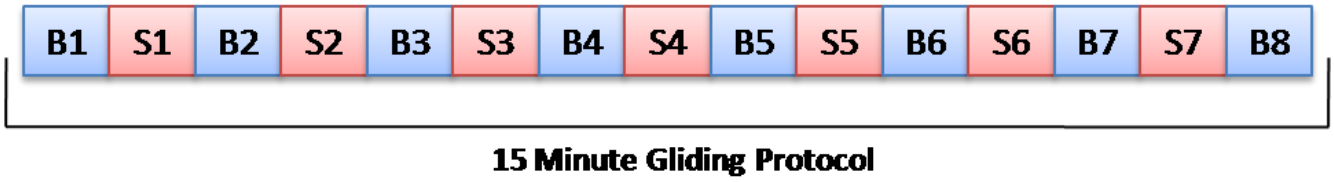
Glider Stimulus (S)	Frequency (Hz)	Cycles/Min	Displacement (mm)	Peak Acceleration (m/s^2)
1	0.50	30	88.90	0.36
2	0.65	39	53.34	0.36
3	0.80	48	34.04	0.36
4	0.95	57	24.64	0.36
5	0.65	39	27.94	0.21
6	0.65	39	53.34	0.36
7	0.65	39	75.44	0.51

The gliding protocol took approximately 15 minutes. With assistance from the NICU nurse or parent, the infant was placed against the infant feeding pillow on the lap of an experienced NICU researcher (E. Zimmerman), who monitored the preterm infant**.** Infants also remained connected to their NICU monitors at all times for observation of respiration, heartbeat, and oxygen saturation by the nursing staff. Before the gliding protocol was initiated, infants were fitted with a dual-channel clinical Respitrace™ device. This involved the placement of two soft cloth inductance bands around the rib cage and abdomen. Pulse rate and SpO_2 signals were

also measured throughout the gliding protocol with a neonate oxygen sensor placed around the infant's wrist.

The 15-minute gliding protocol alternated between baseline (B1-B8) and stimulus (S1-S7) conditions every minute (see Figure 13). During the baseline conditions, the glider chair did not move and only respiration and suck were monitored. Overall, there were seven gliding stimuli and eight baseline conditions. Stimulus order among the baseline conditions was varied among participants and session by using 15 different stimulus sequences (see appendix) that were presented to the infants in a counterbalanced sequence.

Figure 13: Sample 15 minute gliding protocol. Blue: baseline conditions (B) and red: stimulus conditions (S).



INFANT VESTIBULAR STIMULATION

The VestibuGlide system was designed to provide linear acceleration in the horizontal plane to the infant. Linear acceleration primarily stimulates the otoliths within the vestibular apparatus. During the VestibuGlide protocol, infants often moved their head or neck in the pitch, yaw, and roll planes, thereby stimulating the semicircular canals. The only way to truly assume that the semicircular canals were not being stimulated would be to surgically obstruct the lumens of the canals. Therefore, it must be assumed that the infant received both otolithic and semicircular canal stimulation during the VestibuGlide protocol.

OUTCOME MEASURES:

Chest wall displacements provided by the clinical Respitrace™ device were digitized and BPM were analyzed for the entire gliding protocol. The BPM were calculated by counting the numbers of inhalations that occurred in one minute using a peak detection software program coded in LabVIEW v.9.0.

Pulse and oxygen saturation (SpO_2) signals were digitized and analyzed for the entire gliding protocol. Minute averages were attained for SpO_2 and pulse for every baseline (B1-B8) and stimulus (S1-S7) condition.

Another specialized software program coded in LabVIEWv.9.0 allowed for visualization of the suck waveforms. Algorithms within this program calculated the following suck parameters: total oral compressions per minute, burst cycles per minute, non-NNS compressions per minute (extraneous mouthing movements), NNS bursts per minute, mean NNS cycles per burst, mean amplitude of NNS cycles per minute, mean NNS intraburst cycle period, mean period between NNS bursts, NNS cycles as a percent of the total oral compressions, and the NNS spatiotemporal index (NNS STI).

The NNS STI was used to characterize the emergence and integrity of the sCPG through quantitative and statistical analyses of suck pattern stability. This procedure involved calculating the variability of four nipple compression pressures across four multiple suck bursts. By calculating the cumulative sum of the standard deviations of an amplitude-and time-normalized set of NNS pressure trajectories, suck development was represented by a single numerical value known as the NNS STI. The mathematics underlying STI are well suited to quantitatively track the emergence of ororhythmic stereotypy during NNS development in preterm infants (Poore, Barlow, Wang, Lee, 2008). The STI indicates the degree to which the set of motor trajectories

converges on a single underlying template, or the stability of the neuromotor sequences exhibited by the newborn infant. A high STI value (80-90) indicates poor suck pattern stability, whereas, a low STI value (30-40) indicates excellent suck pattern stability.

Power spectrums are plots of the portion of a signal's power (energy per unit time) falling within given frequency bins. Power spectrums were calculated for the best 15 minutes of abdominal Respitrace™ data for the first baseline (B1), stimulus (S1-S7), and the post-baseline conditions (B2-B8). All abdominal waveforms were plotted. Records with movement artifact, or episodes of apnea were discarded leaving the most patterned 15 minutes of respiratory output for extended data analysis. The data was then pooled across infants to examine the amplitude of the spectra. The abdominal Respitrace™ output was used for analysis because preterm infants are predominantly belly breathers. Abdominal respiratory waveforms were filtered with a digital Butterworth band-pass filter (0.6 – 4 Hz). Power spectrums plots were completed using MATLAB® with a frequency resolution of 0.03 Hz.

Coherence describes the correlation between physical quantities (e.g., frequency content) of waveforms. Coherence analysis was calculated for the best 15 minutes of pooled stimulus (S1-S7) data across infants to examine the relation between the abdominal motion and the glider chair motion. Abdominal respiratory waveforms were filtered with a Butterworth band-pass filter (.6-4Hz). Coherence plots were completed using MATLAB® with a frequency resolution of 0.03 Hz.

Oral feeds were measured in days to achieve ≥90% oral feed. Daily oral feeds were documented by the nursing staff and a daily percentage was calculated across the eight daily feeds for all infants in the study and was compared to a cohort of untreated preterm infants matched for birth GA.

The length of stay in the NICU was measured from admission date (birth date) to discharge date for all infants in the study and was compared to the cohort of untreated preterm infants matched for birth GA.

Secondary Outcome Measures:

1. Weight Gain (gms/kg/day) = [wt (gms) at 10 days – bw (gms)] / 10 days

2. Head Growth (cm/wk) = [hc (cm) at 10 days – hc (cm) at birth] / 2 wks

- Occipitofrontal circumference = place measuring tape around the front of the head, above the brow and the occipital area. The measuring tape should be above the ears.

3. Length Growth (cm/wk) = [len (cm) at 10 days – len (cm) at birth] / 2 wks

Abbreviations: birth weight (bw), weight (wt), grams (gms), head circumference (hc, centimeters (cm), length (len), weeks (wks).

POWER ANALYSIS:

The sample size (n=12) selected for this study was based on previous measurements of the response variables (means, variance) for the proposed study and will yield statistical power greater than 0.80, medium-large effects size, and $p<.05$.

STATISTICAL ANALYSIS:

In the current study it was essential to recognize the hierarchical nature of the data; observations on outcome variables are repeatedly measured under different stimulation conditions at multiple days (level-1), which are nested within subjects (level-2). When nested data are analyzed without regard to interdependency within a setting, Type I error is inflated

leading to unwarranted rejection of the null hypothesis (Dorman, 2009; Hedges, 2007). Thus, general mixed modeling, which accounts for the lack of independence among observations, was used for analysis. This approach expands general linear modeling such as repeated measures analysis of variance (RM ANOVA) by supporting more variations in specifying the covariance structure of the repeated measures (Raudenbush, 2002). The compound symmetry (CS) covariance structure of the repeated measures yielded smaller Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC) than did the unstructured (UN), first-order autoregressive (AR), and variance component (VC) covariance structures and thus was chosen for current mixed models. For parameter estimation, maximum likelihood method that accommodates the observations missing at random (Little, 1987) was used. Statistical significance of model parameters was determined at 0.05 alpha level. All analyses were conducted using SAS 9.2 (SAS Institute, 2002-2008).

For each of the outcome variables, an individual growth model (Singer, 1998) was fitted in order to examine the day (level-1; e.g., linear or quadratic change over days) effect as well as stimulation condition (level-2) effect. When the day and/or stimulation condition effect(s) were significant, their interaction (cross-level) effect was further examined. Infants' birth weight, oxygen history, and caffeine intake (yes/no), were also included into the model as covariates to account for differences in these factors and thereby further increasing the power to detect significant effects. When the stimulation condition effect was significant, adjusted means were pair-wise compared using a Bonferroni-corrected *p*-value.

Data plots were completed in addition to the multi-level regression models to show the trends prior to adjusting for the covariates. A daily average for all of the respiratory, pulse, SpO_2,

and suck dependent measures was completed per infant and then the 12 averages were combined and standard errors were created for each graph.

Hypotheses:

H_0 #1 (Aim 1). It is hypothesized that vestibular stimulation at the selected rates with peak acceleration held constant will modulate chest wall movements associated with breathing among preterm infants. Infants glided at the higher frequencies (.80 Hz and .95Hz) with a constant peak acceleration of 0.36 m/s^2 will likely yield the greatest respiratory response because these gliding rates match the endogenous rhythmic frequency optimal for a premature infants' breathing rate. Infants that are able to modulate their chest wall displacement frequencies to match external stimuli are at an advantage for rapid adaptive control of their breathing mechanism. This type of adaptive response is vital in order to respond to various task demands, such as feeding and early vocalizations.

H_A #1 (Aim 1). The alternative hypothesis suggests that that vestibular stimulation at the selected rates with peak acceleration held constant will not modulate chest wall movements associated with breathing among preterm infants. If the H_A is supported by the present study, it would be in disagreement with several findings that show infant's are able to modulate their breathing patterns in response to rocking stimulus (Elliot, Fisher, & Ames, 1988; Ingersoll & Thoman, 1994; Korner, 1990; Korner, et al., 1983; Pederson & Vrugt, 1973; Sammon & Darnall, 1994)

H_0 #2 (Aim 2). It is hypothesized that the degree of chest wall modulation will vary as a function of vestibular acceleration among preterm infants. When infants are glided at the highest

peak acceleration of 0.51 m/s^2 (stimulus 7), they likely experience the most vestibular stimulation. Vestibular otoliths respond best to linear acceleration; therefore, the highest peak acceleration will increase otolith stimulation resulting in strengthened sensorimotor connectivity between the vestibular system and the rCPG.

H_A #2 (Aim 2). The alternative hypothesis states that the degree of chest wall modulation will not vary as a function of vestibular acceleration among preterm infants. If the H_A hypothesis is supported by the present study, it would provide further insight into the connectivity between the vestibular apparatus and the rCPG. Previous studies have shown that the rCPG is sensitive to vestibular stimulation (Miller, et al., 1995), however, it may not be capable of re-setting the rhythm generating circuitry.

H_0 #3 (Aim 3). It is hypothesized that preterm infants exposed to daily regimens of vestibular stimulation at the prescribed rates and accelerations will manifest a significant decrease in the time (days) to attain ≥90% oral feed compared to a group of control infants, who did not receive vestibular stimulus. Previous studies have shown that vestibular stimulation enhances feeding outcomes (Gregg, et al., 1976; Kramer & Pierpont, 1976; Neal, 1968; Rice, 1979; Scarr-Salapatek & Williams, 1973; White & Labarba, 1976).

H_A #3 (Aim 3). The alternative hypothesis suggests that preterm infants exposed to daily regimens of vestibular stimulation at the prescribed rates and accelerations will not manifest a significant decrease in the time (days) to attain ≥90% oral feed compared to a group of control infants, who did not receive vestibular stimulus. If the H_A is supported by the present study, it would contradict many studies that have revealed an increase in feeding outcomes and weight

gain associated with vestibular stimulation (Gregg, et al., 1976; Kramer & Pierpont, 1976; Neal, 1968; Rice, 1979; Scarr-Salapatek & Williams, 1973; White & Labarba, 1976).

H_0 #4 (Aim 4). It is hypothesized that vestibular stimulation will increase suck development in preterm infants. The increased vestibular stimulation afforded by the high peak acceleration of .51m/s^2 (stimulus 7) will subsequently increases the firing rate to the masseter and genioglossus muscles which are essential for sucking and feeding.

H_A #4 (Aim 4). The alternative hypothesis proposes that vestibular stimulation will not increase suck development in preterm infants. If the H_A is supported by the present study, it would suggest the connectivity between the vestibular apparatus and the genioglossus and masseter muscles that are evident in the animal models (Anker, et al., 2003; Cotter, et al., 2004; Cuccurazzu, et al., 2007) may not translate to the human model.

SUMMARY

The exceptional degree of control inherent to the position servo VestibuGlide System allows for the first time a formal test of the therapeutic effects of linear (horizontal plane) vestibular stimulation to the medically stable preterm infant. The results of this study are expected to translate into a new regimen of assessment and therapeutic paradigms for the fragile premature infant in order to improve respiratory patterning, oromotor control, state control, and accelerate the transition to oral feeding skills in the challenging environment of the neonatal intensive care unit.

CHAPTER FOUR: RESULTS

RESPIRATORY OUTCOMES

Rib Cage Breaths per Minute

After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant quadratic trend was observed in rib cage BPM change as a function of days: $F(1, 4321) = 88.04$, $p < .01$. More specifically, rib cage BPM increased over days with the amount of increase becoming smaller as days advanced (Figures 14, 15, and 16). Stimulus condition had a significant effect on the rib cage BPM: $F(7, 77) = 25.53$, $p < .01$. Given the significant stimulus condition effect, adjusted means were subject to pairwise comparisons (see Table 5). Stimulus 7 yielded significantly greater rib cage BPM than stimuli 1, 4, and 5. Stimuli 2-7 all had significantly greater rib cage BPM compared to the average baseline rib cage BPM condition. Figure 16 shows that the average baseline condition (pink line) is clearly lower than all stimulus conditions (S1-S7) and that the fastest acceleration seen in stimulus 7 (light blue line) has the highest BPM compared to the other stimulus and average baseline conditions.

Figure 14: Rib cage BPM for pooled stimulus conditions.

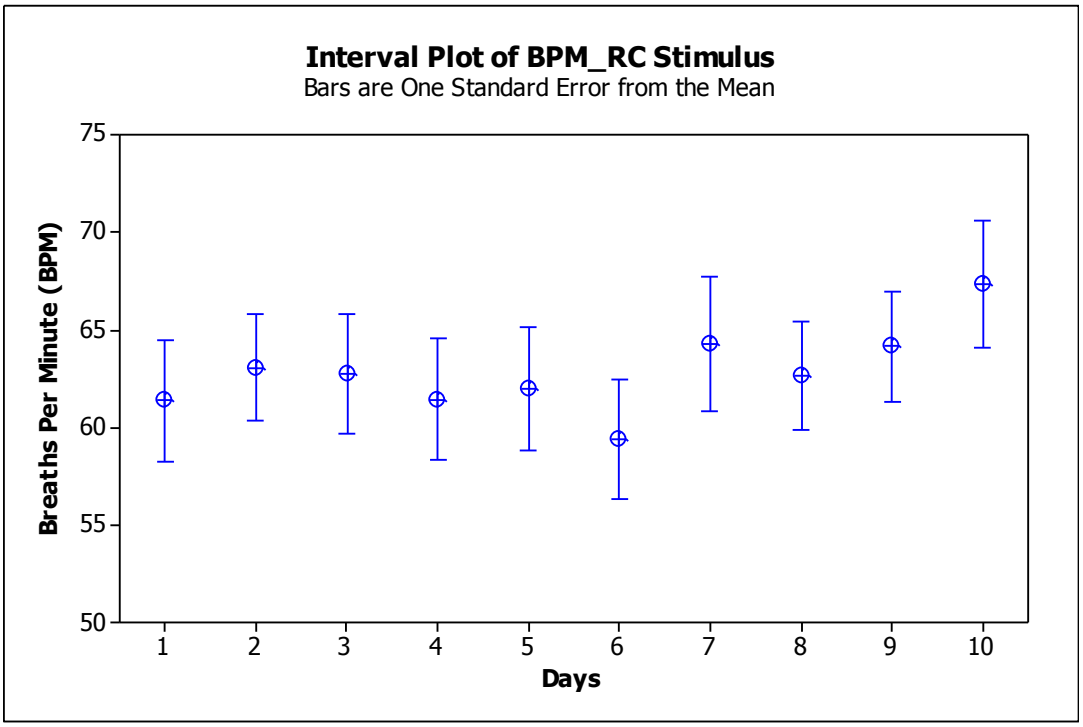


Figure 15: Rib cage BPM for pooled baseline conditions.

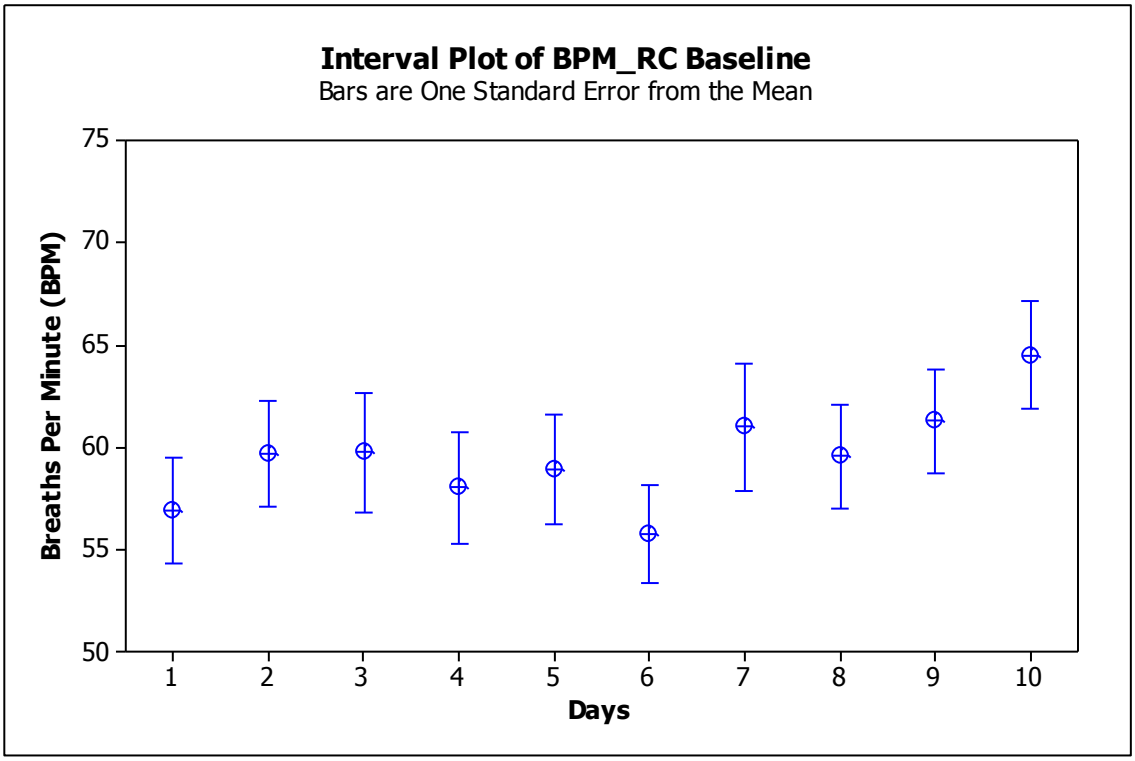


Figure 16: Estimated rib cage BPM across days.

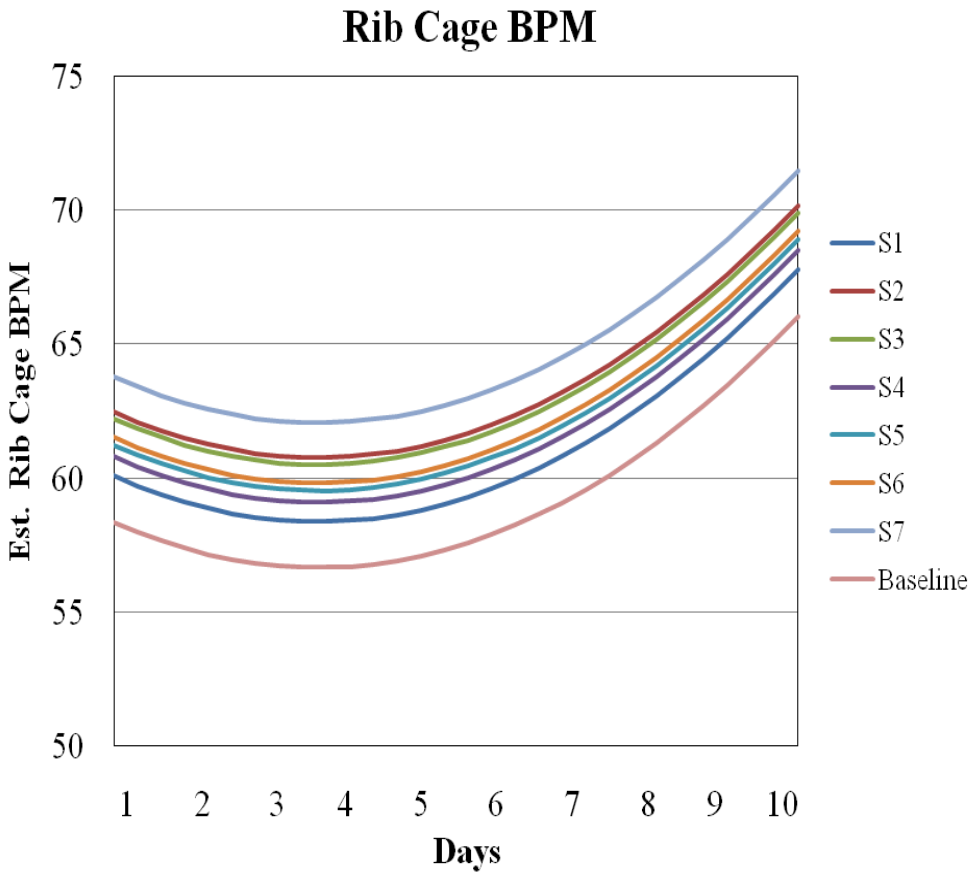


Table 5: Adjusted means and SE for rib cage BPM.

Rib Cage BPM

Condition	*M*	*SE*
S1	60.42	2.28
S2	62.80	2.28
S3	62.55	2.28
S4	61.14	2.28
S5	61.57	2.28
S6	61.86	2.28
S7	64.11	2.28
B Average	58.70	2.23

Abdominal Breaths per Minute

After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant quadratic trend was observed in the abdominal BPM: F (1, 4261) = 84.73, p <.01, see Figures 17 and 18. More specifically, abdominal BPM increased over days with the amount of increase becoming smaller as days advanced (Figure 19). Stimulus condition had a significant effect on the abdominal BPM: F (7, 77) = 23.60, p <.01. Given the significant stimulus condition effect, adjusted means were pairwise compared (see Table 6). Stimulus 7 yielded significantly greater abdominal BPM than stimuli 1 and 4. Stimuli 2-7 all had significantly greater abdominal BPM compared to the average baseline abdominal BPM condition.

Figure 17: Abdominal BPM for pooled stimulus conditions.

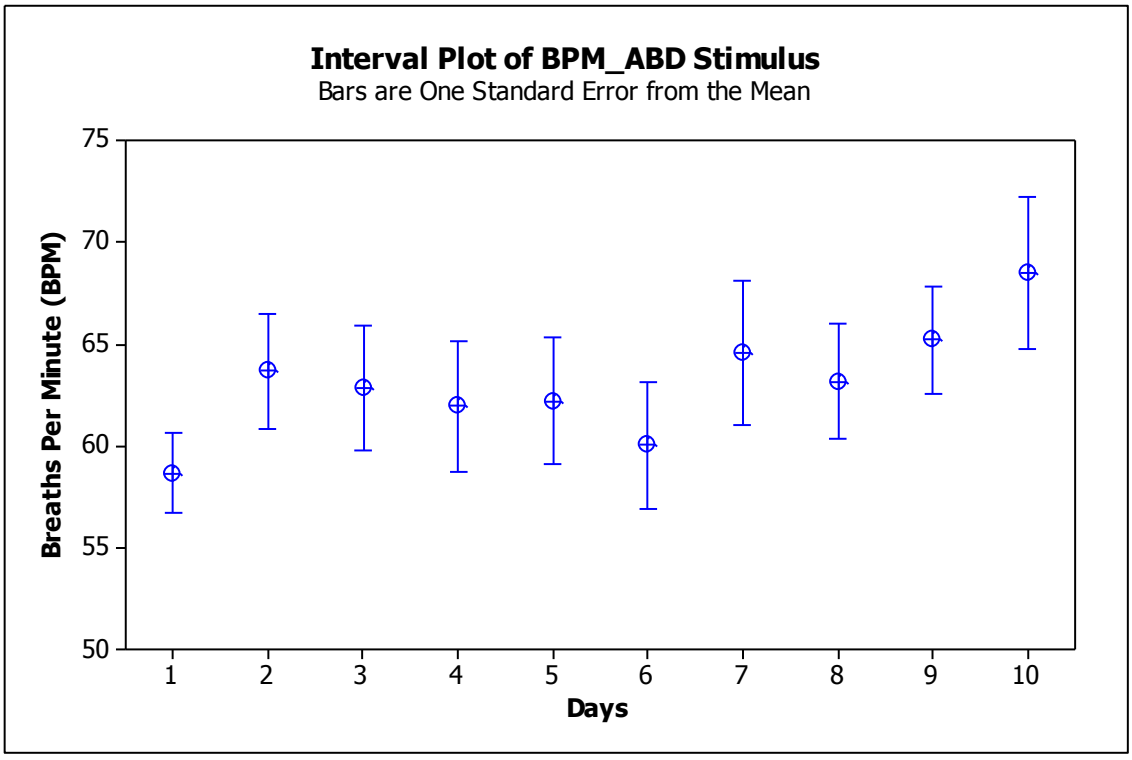


Figure 18: Abdominal BPM for pooled baseline conditions.

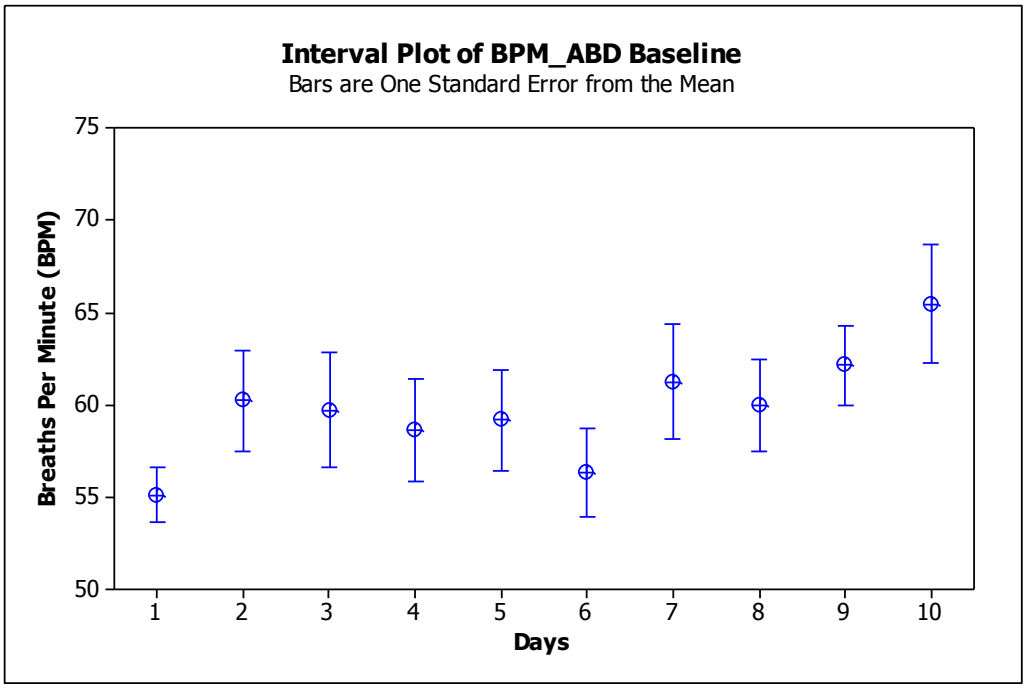


Figure 19: Estimated abdominal BPM across days.

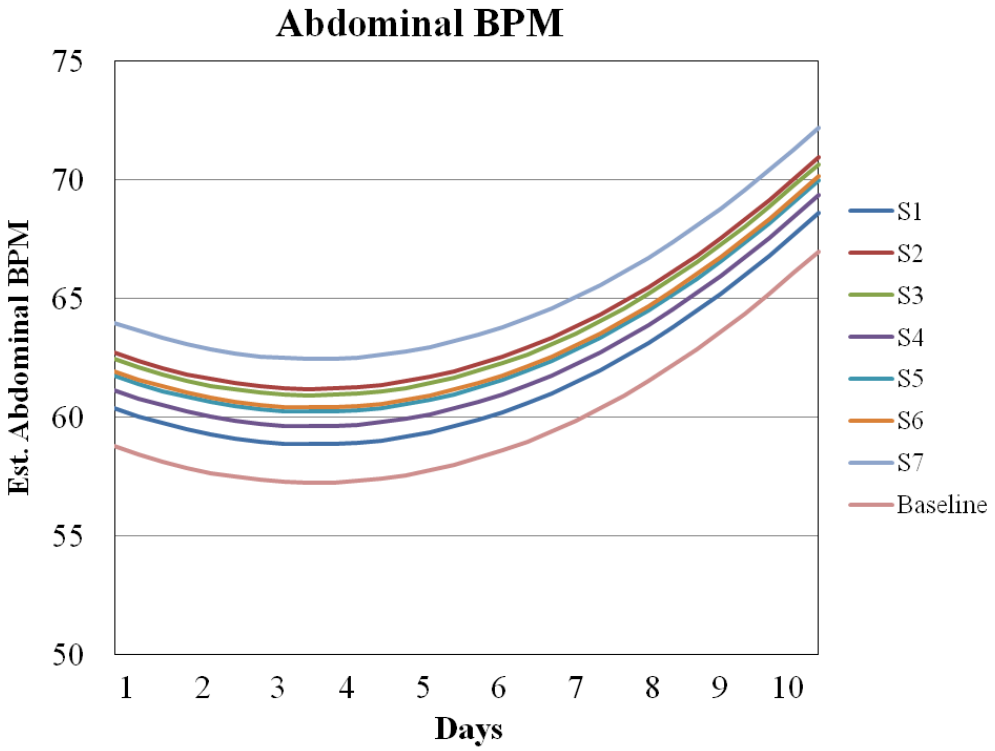


Table 6: Adjusted means and SE for abdominal BPM.

Abdominal BPM

Condition	*M*	*SE*
S1	60.72	2.32
S2	63.05	2.32
S3	62.78	2.32
S4	61.47	2.32
S5	62.09	2.32
S6	62.27	2.32
S7	64.31	2.32
B Average	59.10	2.27

Changes seen in Respiration Across Days

The multi-level regression model reveals that infants significantly increase their BPM for both the rib cage and abdomen across days with the amount of increase becoming smaller with advancing days. These trends increase at approximately day 5 indicating that the infants have a stronger BPM response after repeated exposure to the stimulus. Because preterm infants are deprived of vestibular stimulation, it likely takes a few days of VestibuGlide stimulus before the infant responds with a large increase in BPM.

PULSE/ SpO_2 OUTCOMES

Pulse Rate per Minute

Infants had similar pulse rates in the stimulus and baseline conditions: F (7, 77) = .82, p=.57; see Table 7. After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant quadratic trend was observed in the pulse: F (1, 4260) = 156.37, p <.01 (Figures 20, 21, and 22).

Figure 20: Pulse rate per minute for pooled stimulus conditions.

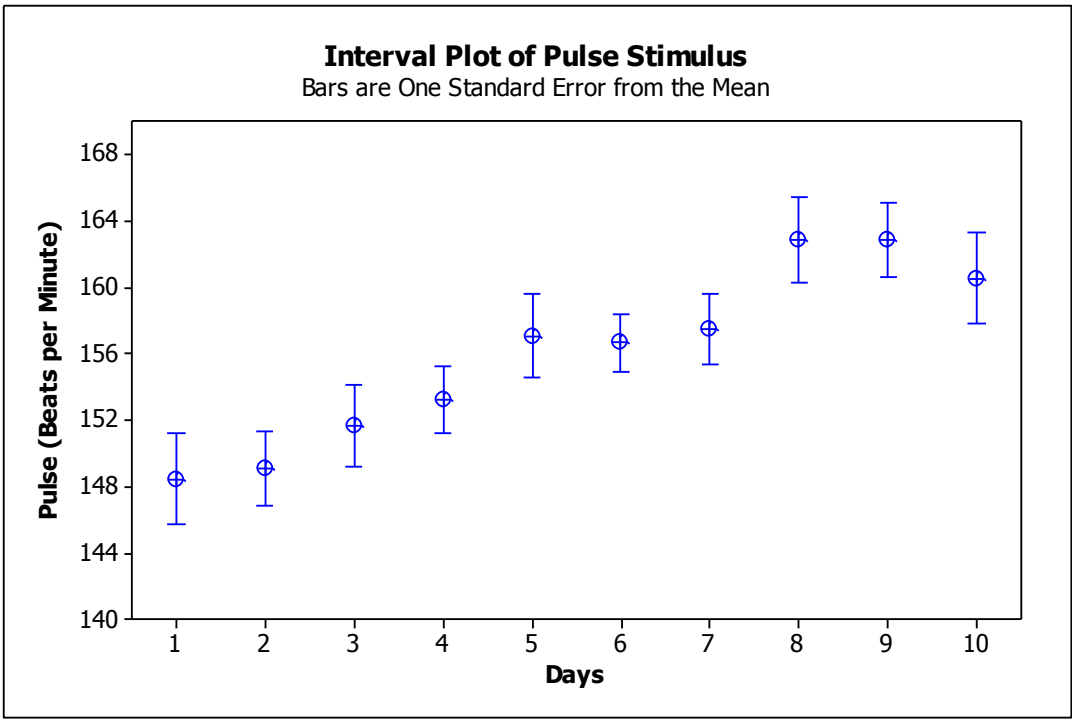


Figure 21: Pulse rate per minute for pooled baseline conditions.

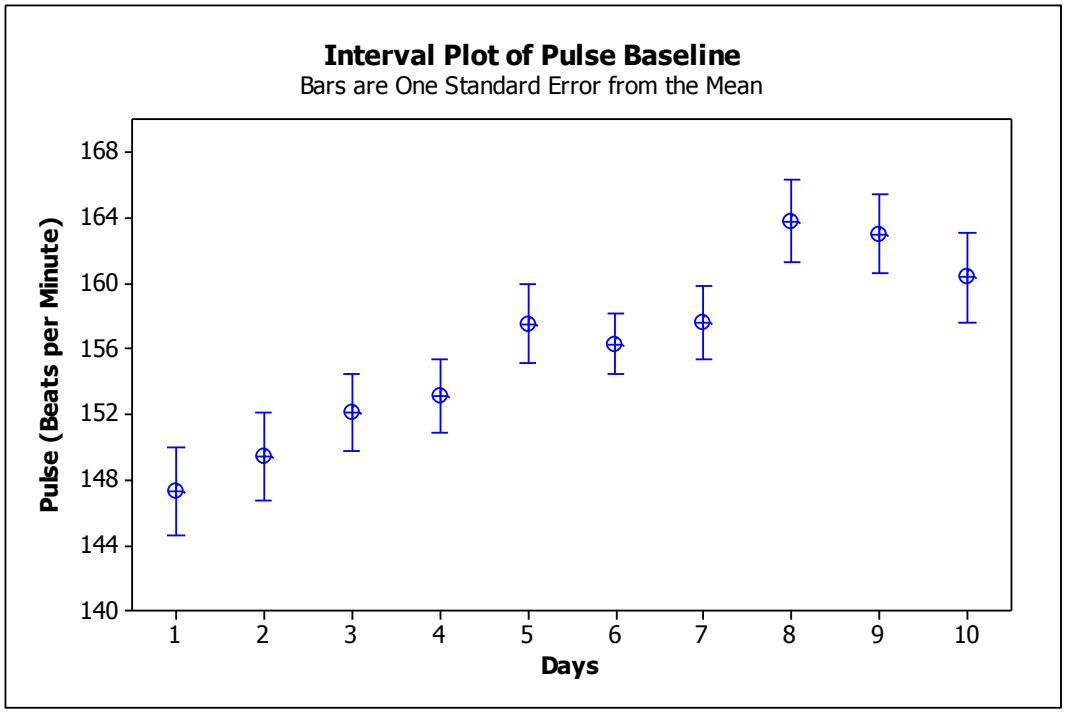


Figure 22: Estimated pulse rate per minute across days.

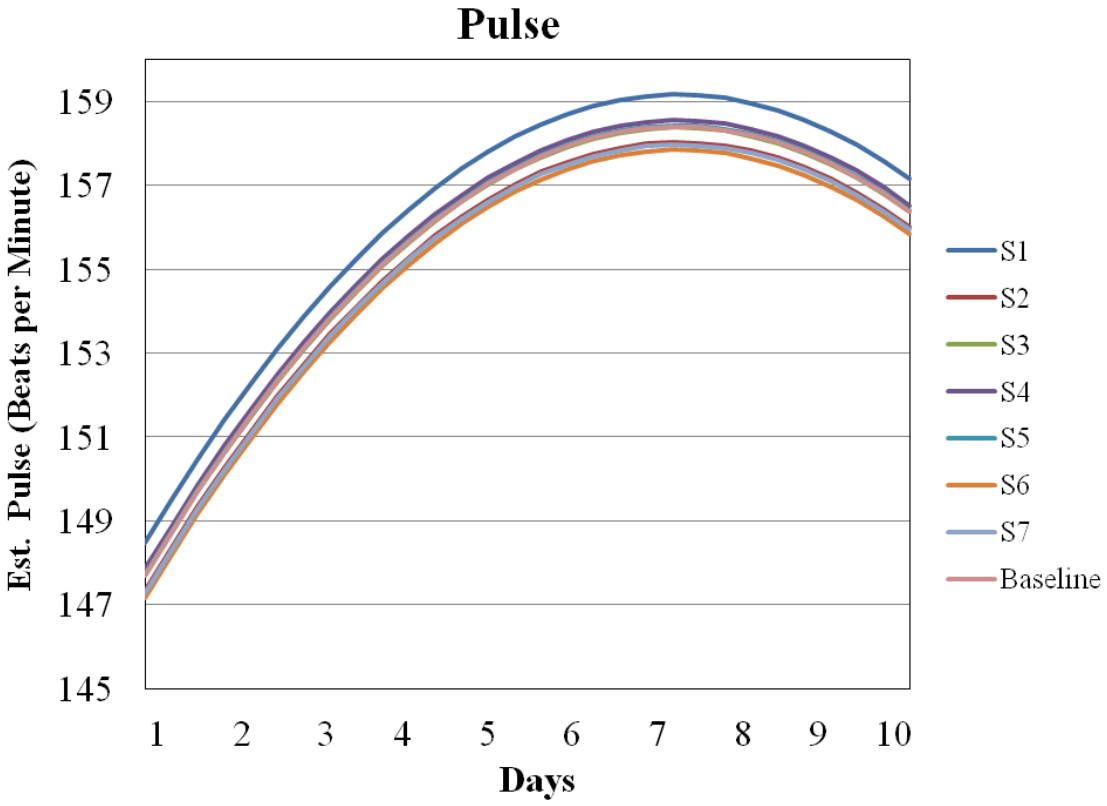


Table 7: Adjusted means and SE for pulse rate per minute.

Pulse/min

Condition	*M*	*SE*
S1	155.00	2.22
S2	153.86	2.22
S3	154.21	2.22
S4	154.38	2.22
S5	154.26	2.22
S6	153.68	2.22
S7	153.80	2.22
B Average	154.23	2.18

SpO_2 Percentage per Minute

Infants had higher oxygen saturation levels in the stimulus condition compared to the baseline condition: F (7, 77) = 2.57, p <.05, (Figures 23, 24, and 25). Stimulus conditions 3, 4, and 6 yielded higher oxygen saturation levels compared to the average baseline (Table 8). However, after a Bonferroni-correction these differences did not reach statistical significance. After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant linear trend was observed in the SpO_2 change across days: F (1, 4261) = 6.67, p =.01.

Figure 23: SpO_2 per minute for pooled stimulus conditions.

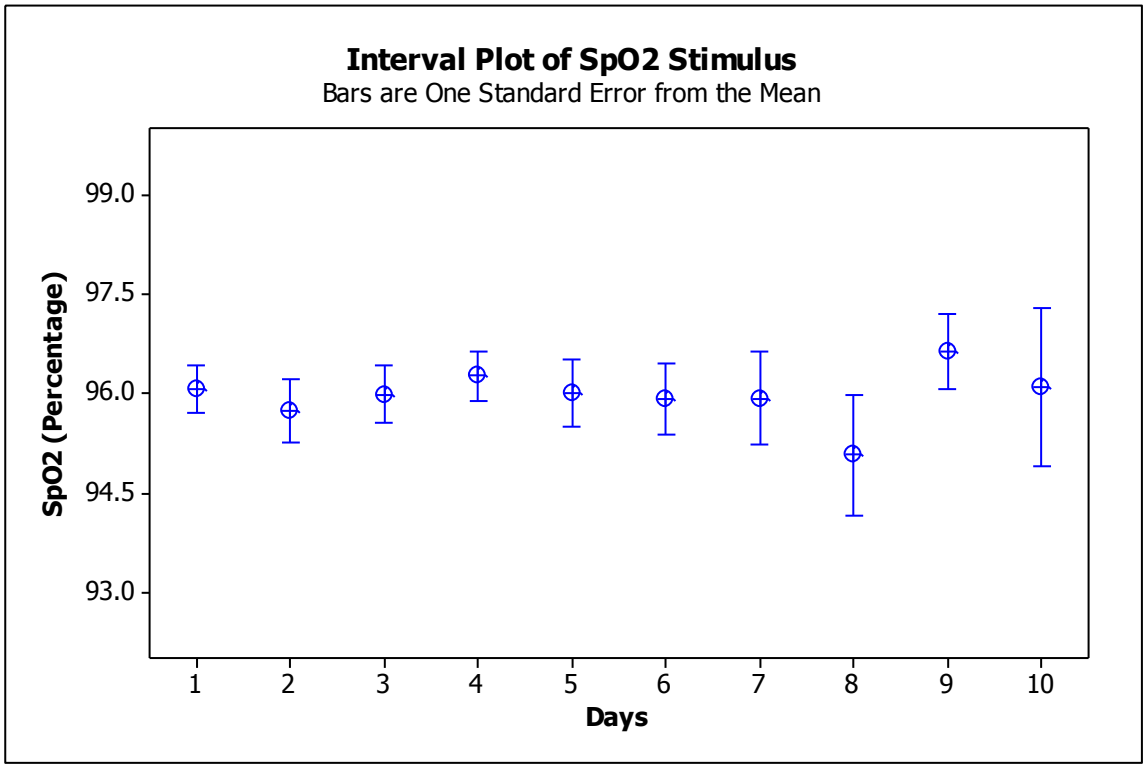


Figure 24: SpO_2 per minute for pooled baseline conditions.

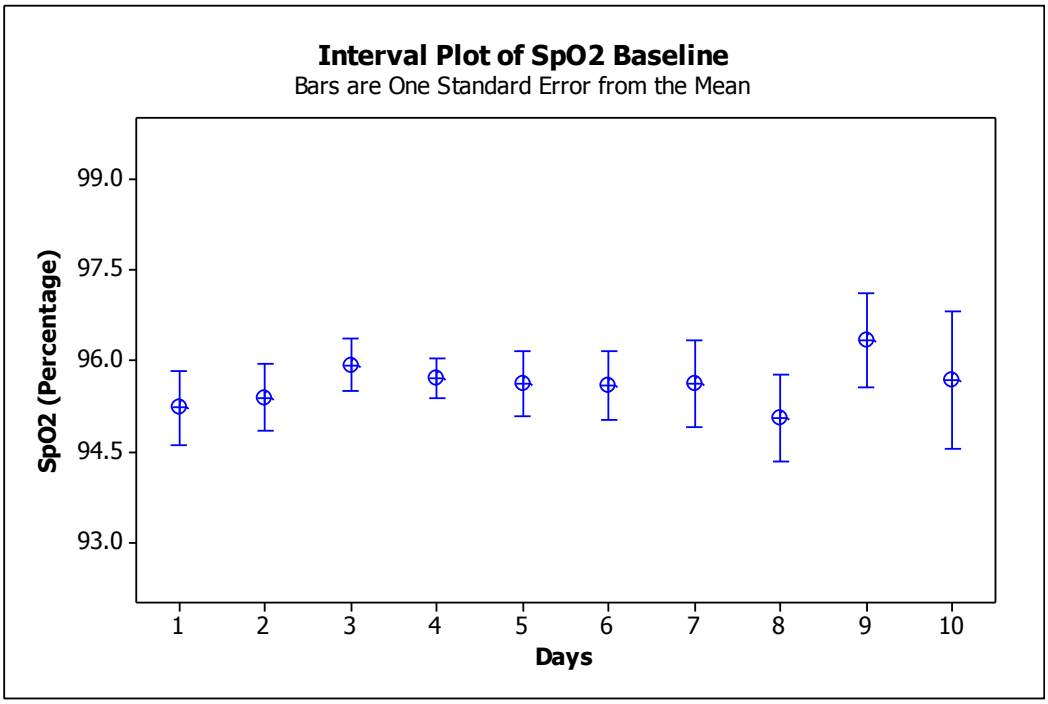


Figure 25: Estimated SpO_2 per minute across days.

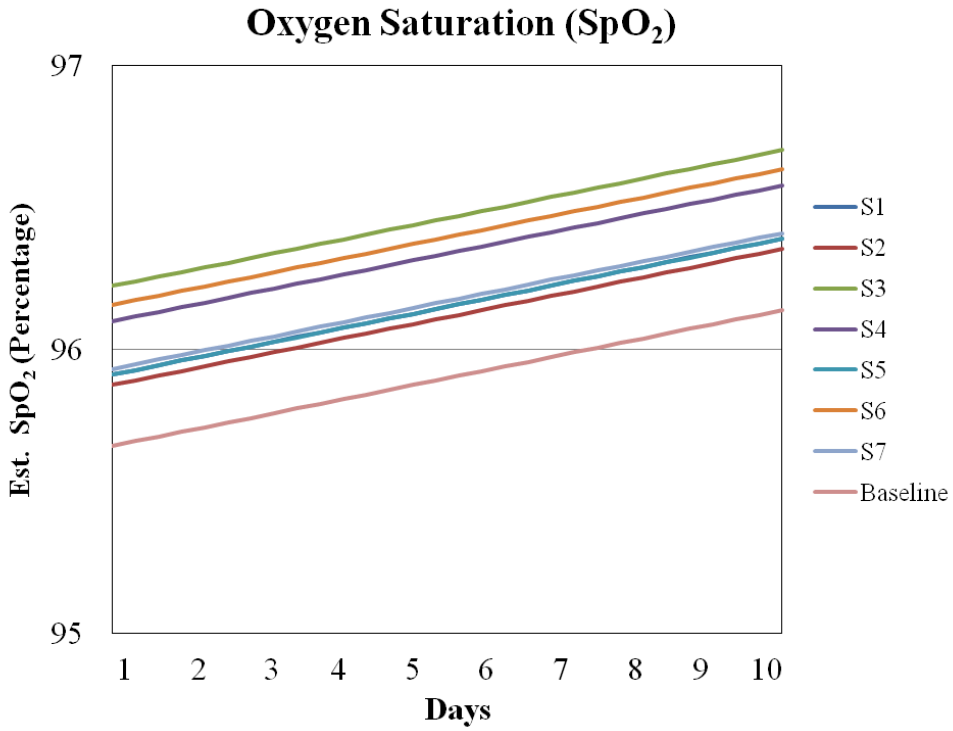


Table 8: Adjusted means and SE for SpO_2 per minute.

	SpO_2/min	
Condition	*M*	*SE*
S1	95.95	0.42
S2	95.91	0.42
S3	96.26	0.42
S4	96.14	0.42
S5	95.95	0.42
S6	96.19	0.42
S7	95.97	0.42
B Average	95.70	0.39

Changes seen in Pulse and SpO_2 Across Days

The multi-level regression model reveals that infants increased their pulse and oxygen saturation across days. Regardless of these trends across days, all pulse and SpO_2 outcomes were within normal limits for preterm infants.

NON-NUTRITIVE SUCK OUTCOMES

Total Oral Compressions per Minute

After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant linear trend was observed in the total oral compressions across days: F (1, 4338) = 107.48, p <.01 (Figures 26, 27, and 28). Stimulus condition had no significant effect on total oral compressions per minute: F (7, 77) = .52, p =.81 (Table 9).

Figure 26: Total oral compressions per minute for pooled stimulus conditions.

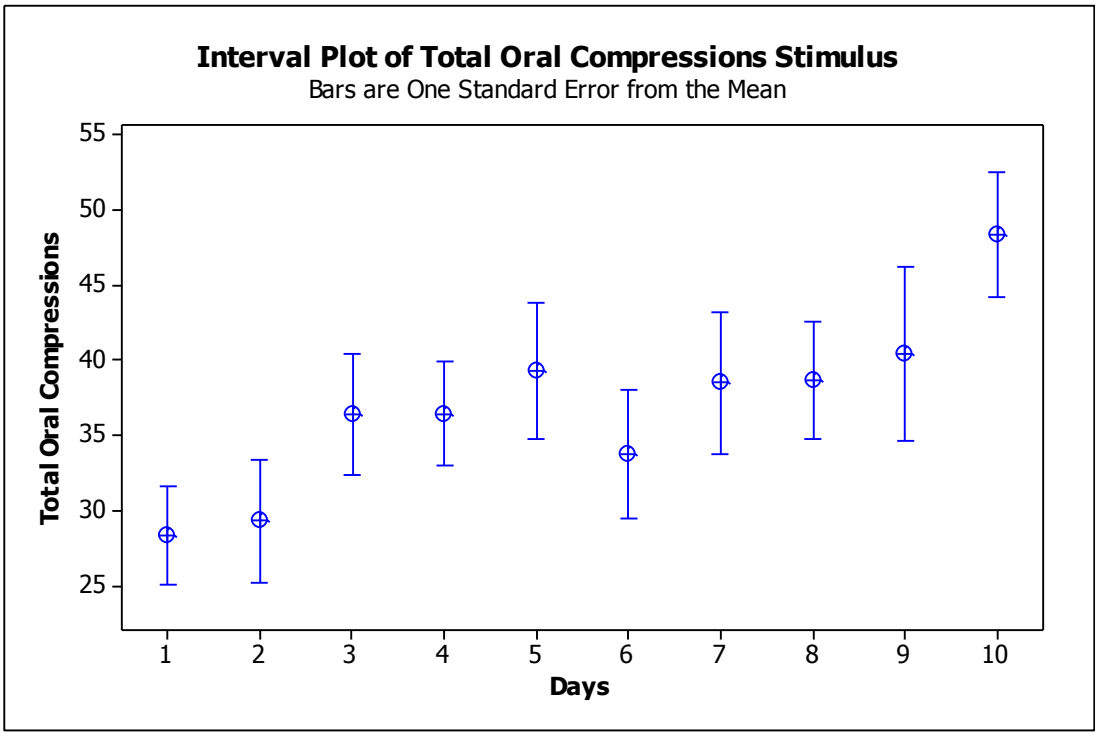


Figure 27: Total oral compressions per minute for pooled baseline conditions.

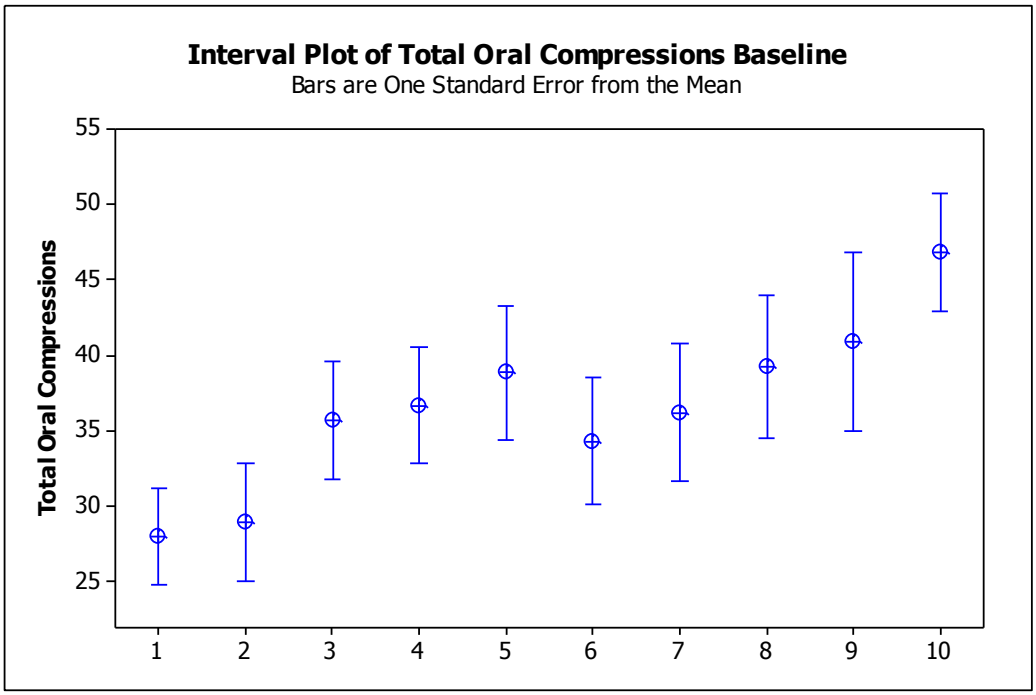


Figure 28: Estimated total oral compressions per minute across days.

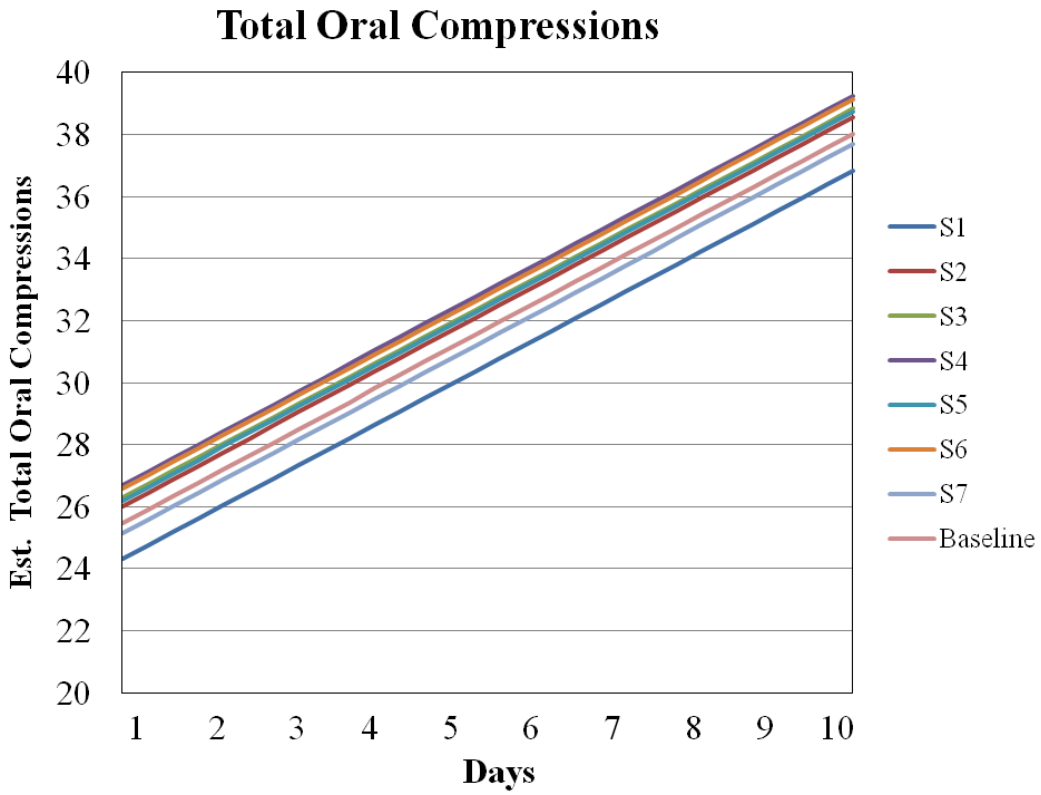


Table 9: Adjusted means and SE for total oral compressions per minute.

Total Oral Compressions/min

Condition	*M*	*SE*
S1	32.65	3.50
S2	34.37	3.55
S3	34.63	3.55
S4	35.05	3.55
S5	34.55	3.55
S6	34.92	3.55
S7	33.49	3.55
B Average	33.83	3.37

NNS Burst Cycles per Minute

Infants significantly increased their minute-rates for NNS burst cycles with advancing days: F (1, 4338) = 161.93, p <.01 (Figures 29, 30, and 31). Stimulus condition had no significant effect on the burst cycles per minute: F (7, 77) = .45, p = .86, see Table 10.

Figure 29: NNS burst cycles per minute for pooled stimulus conditions.

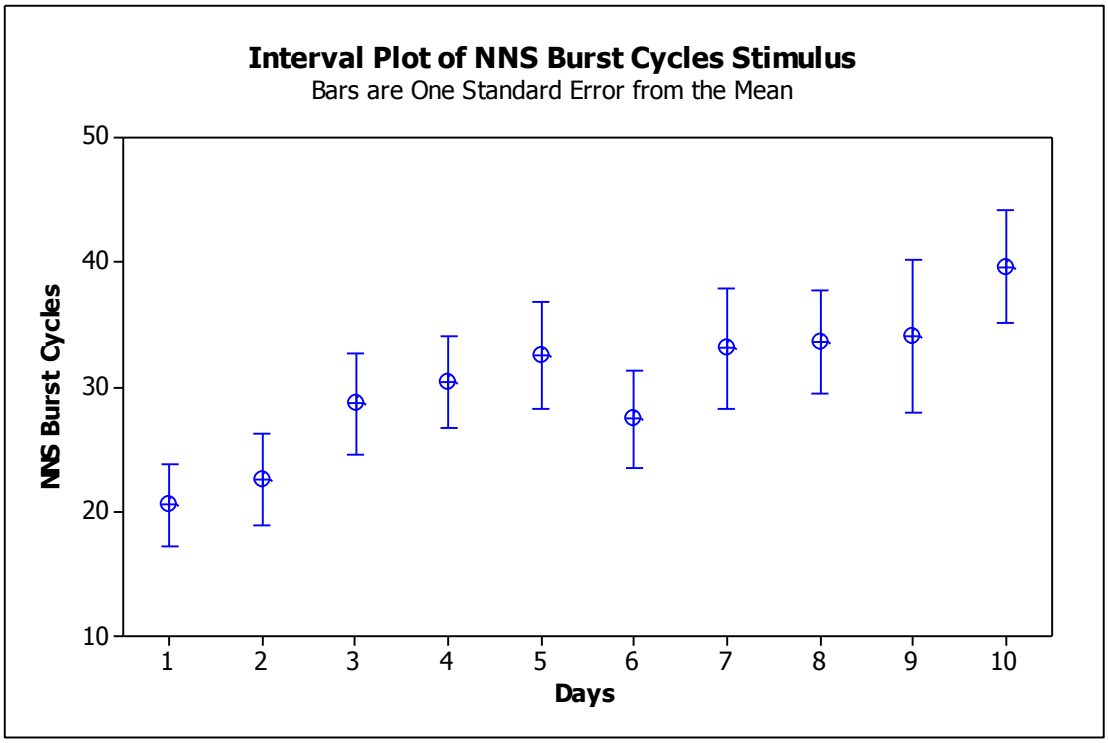


Figure 30: NNS burst cycles per minute for pooled baseline conditions.

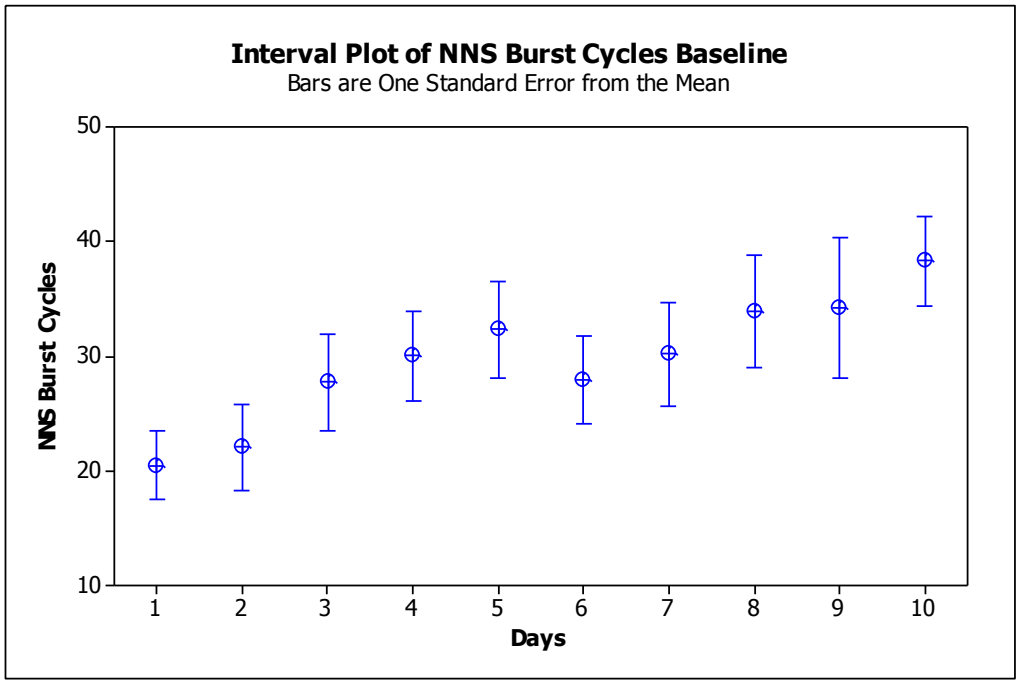


Figure 31: Estimated NNS burst cycles per minute across days.

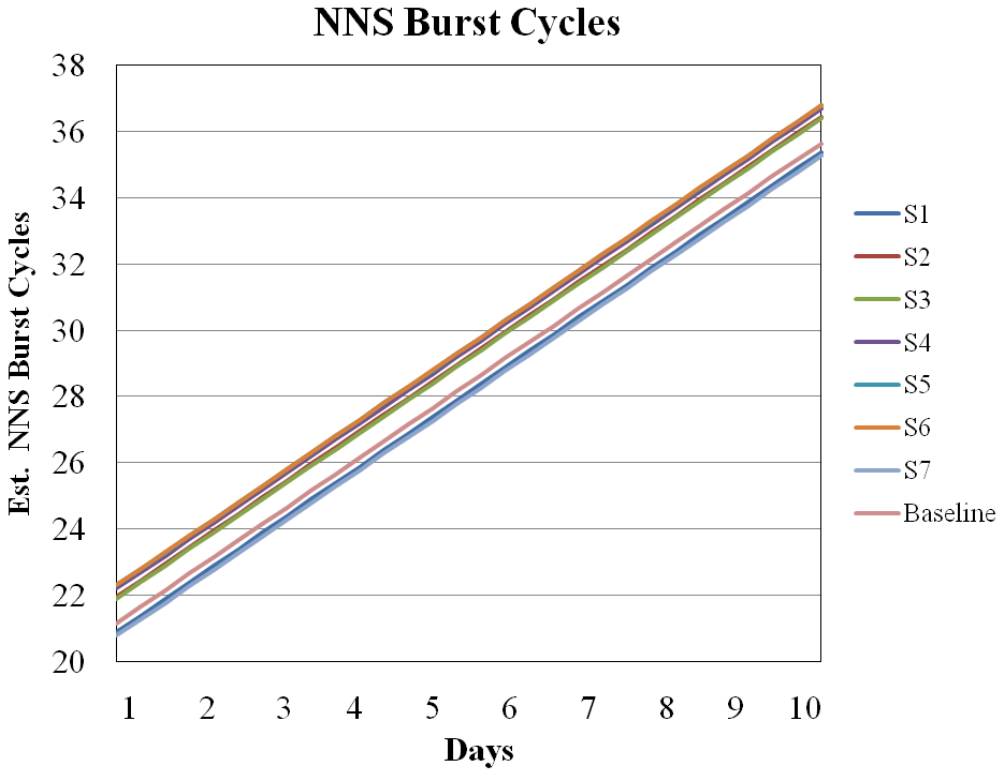


Table 10: Adjusted means and SE for NNS burst cycles per minute.

NNS Burst Cycles/min

Condition	*M*	*SE*
S1	27.49	3.56
S2	28.56	3.56
S3	28.51	3.56
S4	28.80	3.56
S5	28.90	3.56
S6	28.91	3.56
S7	27.38	3.56
B Average	27.76	3.41

Non-NNS Compressions per Minute

Infants had similar non-NNS compressions per minute in the stimulus condition compared to the baseline: F (7, 77) = .73, p =.65, see Table 11 (Figures 32 and 33). After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant positive quadratic trend was observed in the non-NNS compressions change across days: F (1, 4337) = 7.03, $p < 0.01$ (Figure 34).

Figure 32: Non-NNS compressions per minute for pooled stimulus conditions.

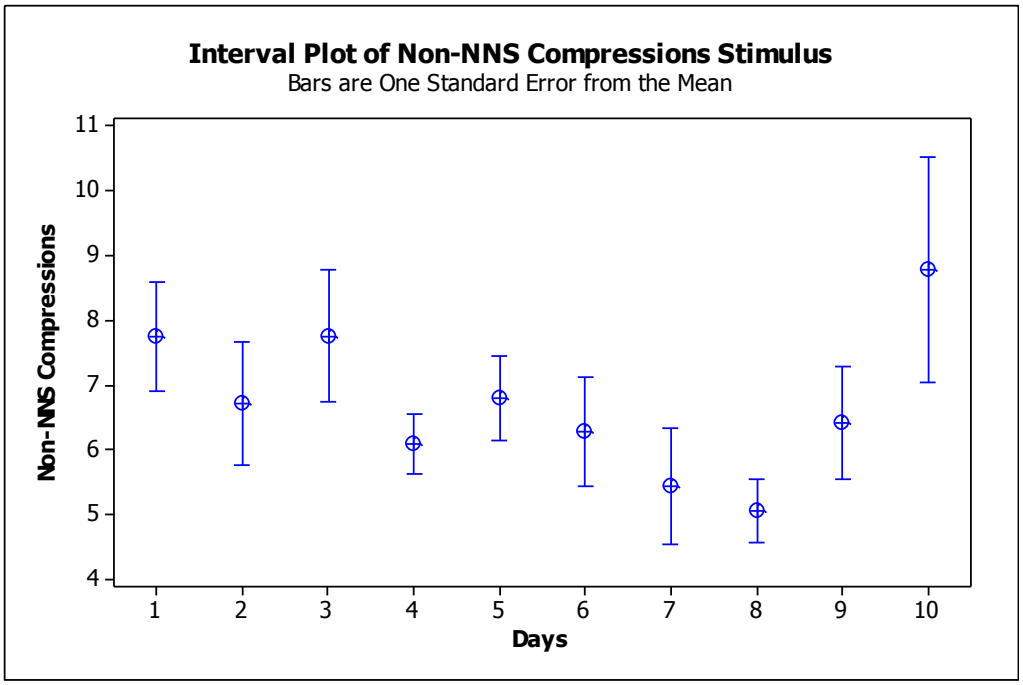


Figure 33: Non-NNS compressions per minute for pooled baseline conditions.

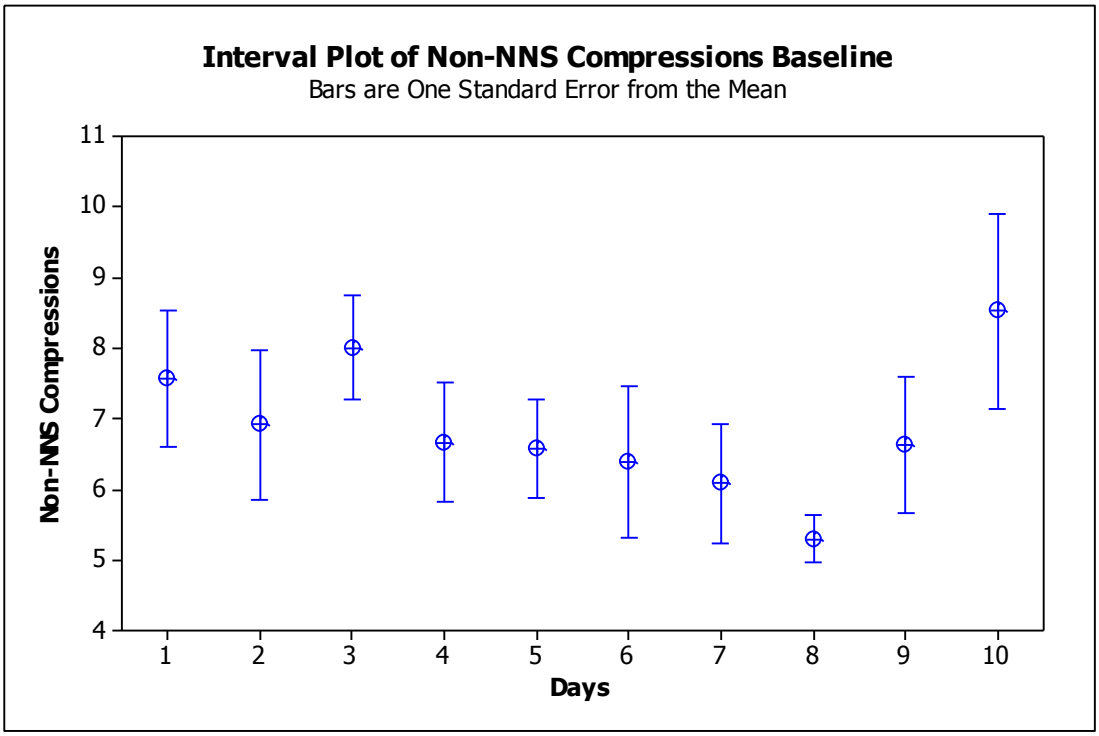


Figure 34: Estimated non-NNS compressions per minute across days.

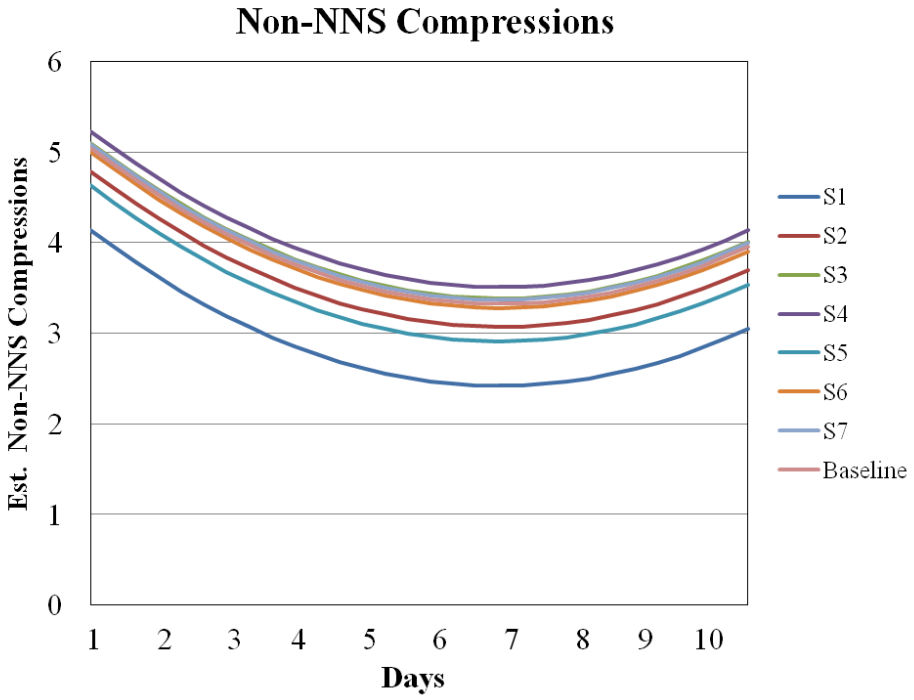


Table 11: Adjusted means and SE for non-NNS compressions per minute.

Non-NNS Compressions/min

Condition	*M*	*SE*
S1	5.23	0.66
S2	5.88	0.67
S3	6.19	0.66
S4	6.32	0.66
S5	5.72	0.67
S6	6.09	0.66
S7	6.18	0.67
B Average	6.13	0.52

NNS Bursts per Minute

After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant linear trend was observed in the NNS bursts per minute across days: F (1, 4337) = 98.27, $p < 0.01$ (Figure 35, 36, and 37). Stimulus condition had no significant effect on the NNS bursts per minute: F (7, 77) = 1.57, $p = .15$, see Table 12.

Figure 35: NNS bursts per minute for pooled stimulus conditions.

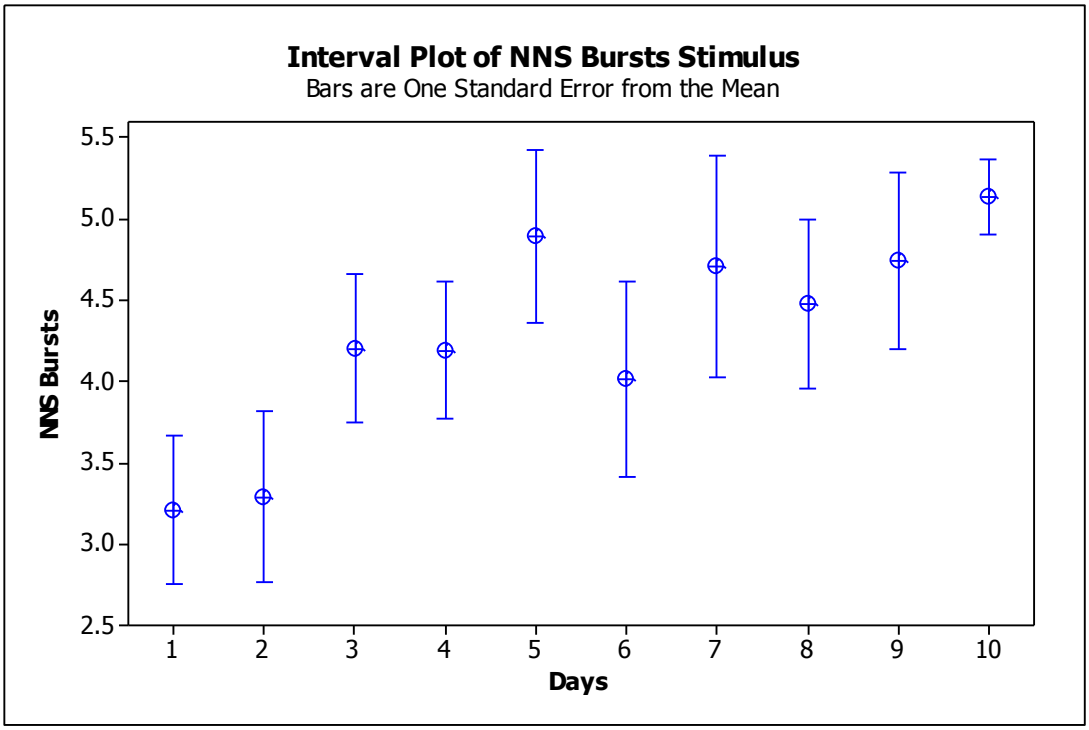


Figure 36: NNS bursts per minute for pooled baseline conditions.

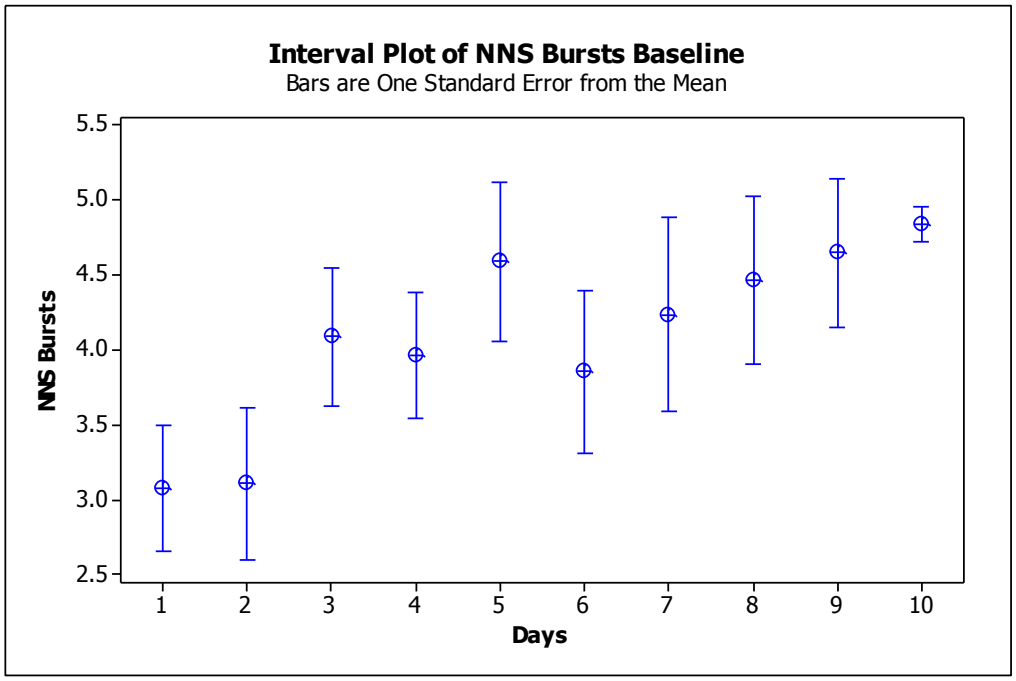


Figure 37: Estimated NNS bursts per minute across days.

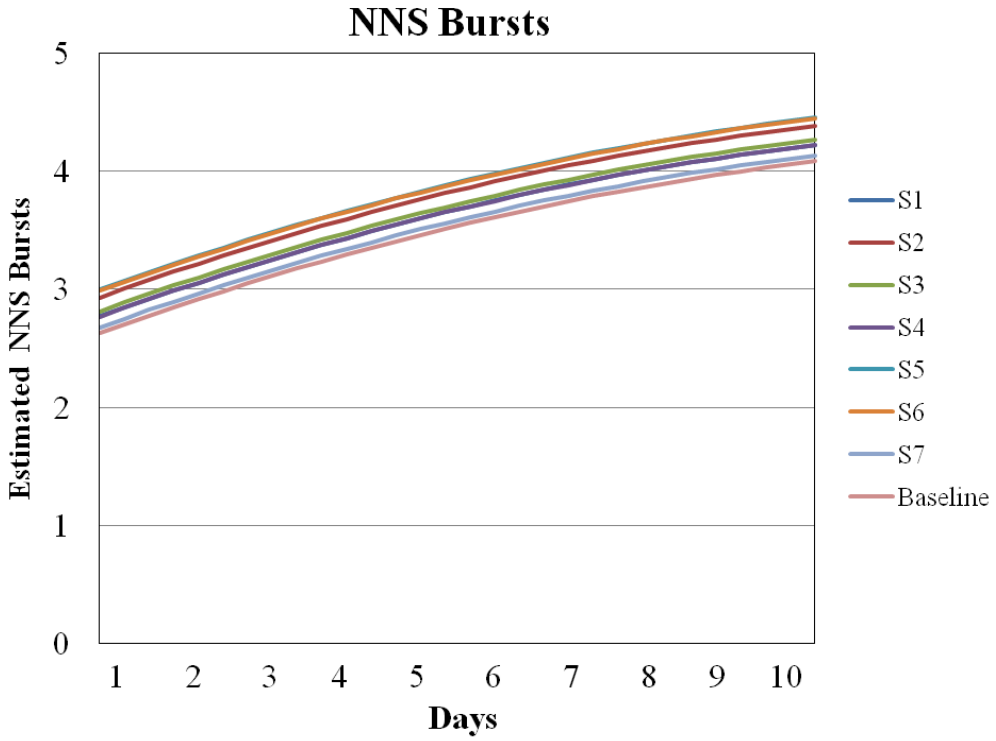


Table 12: Adjusted means and SE for NNS bursts per minute.

NNS Bursts/min

Condition	*M*	*SE*
S1	3.91	0.39
S2	4.07	0.39
S3	3.95	0.39
S4	3.91	0.39
S5	4.13	0.39
S6	4.13	0.39
S7	3.81	0.39
B Average	3.77	0.36

Mean Cycles/Burst per Minute

Infants had similar mean cycles per burst in the stimulus condition compared to the baseline condition: F (7, 77) = .39, p =.90, see Table 13 (Figures 38 and 39). After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant linear trend was observed in the mean cycles per burst change across days: F (1, 4338) = 48.47, $p < 0.01$, see Figure 40.

Figure 38: Mean cycles/burst per minute for pooled stimulus conditions.

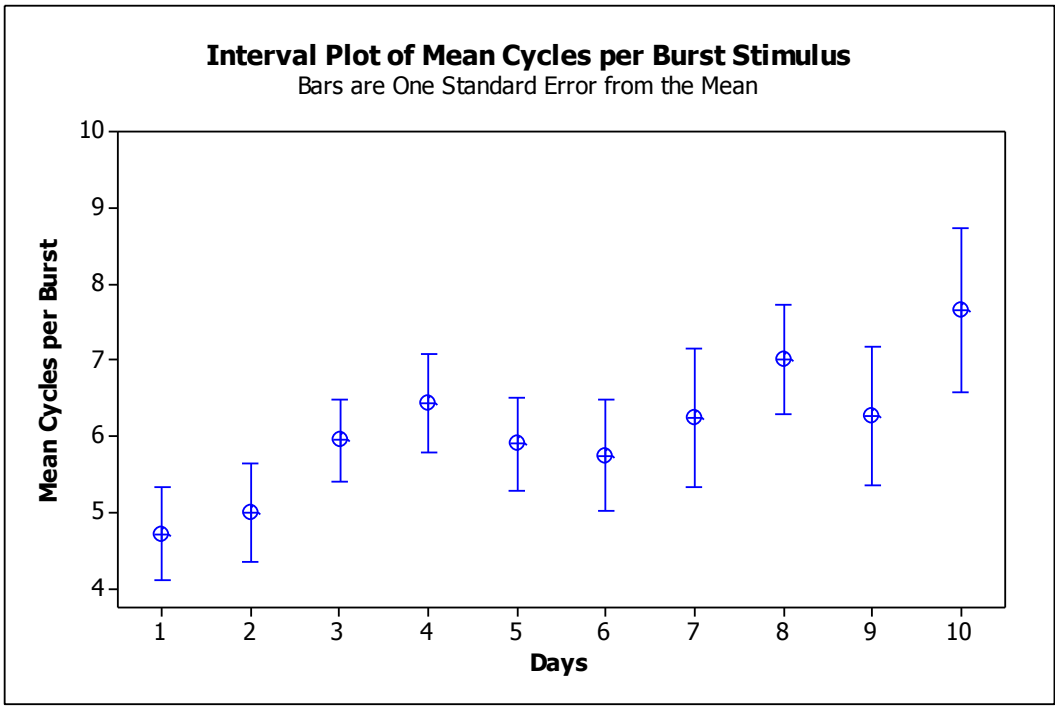


Figure 39: Mean cycles/burst per minute for pooled baseline conditions

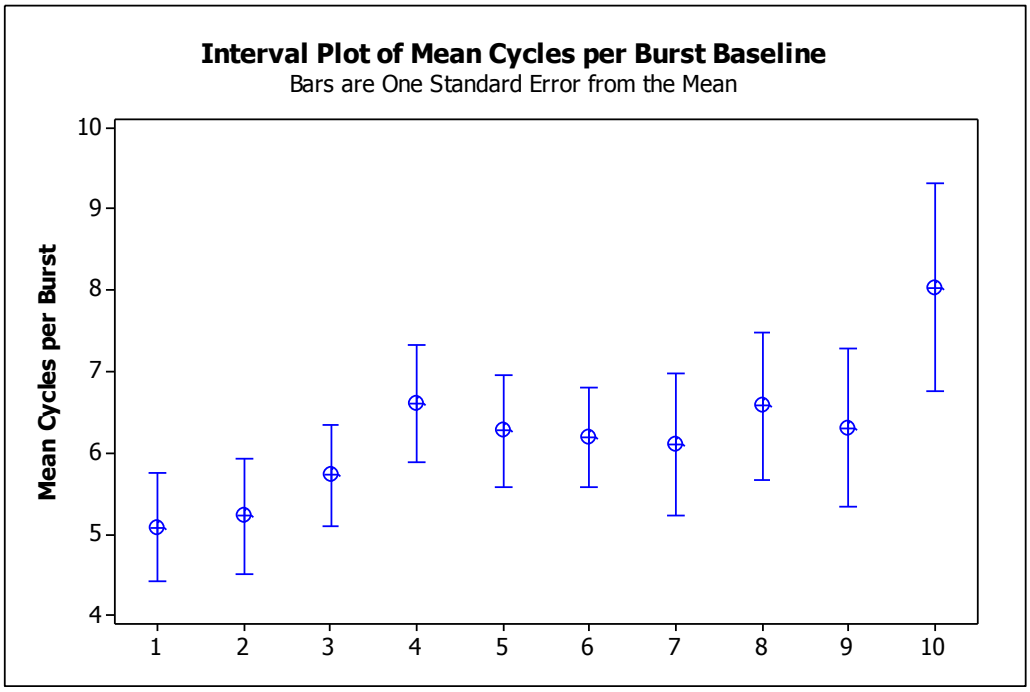


Figure 40: Estimated mean cycles/burst per minute across days.

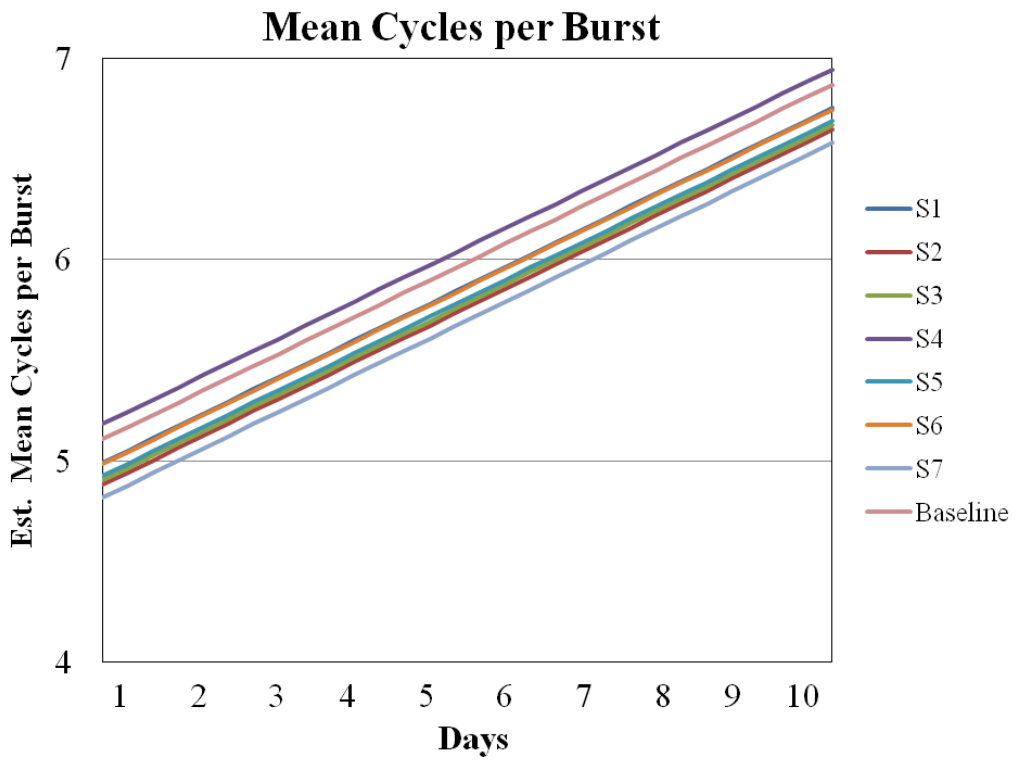


Table 13: Adjusted means and SE for mean cycles/burst per minute.

Mean Cycles/Burst/min

Condition	*M*	*SE*
S1	5.81	0.63
S2	5.71	0.63
S3	5.73	0.63
S4	6.01	0.63
S5	5.75	0.63
S6	5.81	0.63
S7	5.64	0.63
B Average	5.93	0.58

Mean Amplitude/Burst per Minute (cmH_20)

After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant quadratic trend was observed in the mean amplitude per burst change across days: F (1, 4254) = 40.50, $p < 0.01$ (Figures 41, 42, and 43). Stimulus condition had no significant effect on the mean amplitude per min: F (7, 77) = 1.79, p = .10, see Table 14.

Figure 41: Mean amplitude/burst per minute for pooled stimulus conditions.

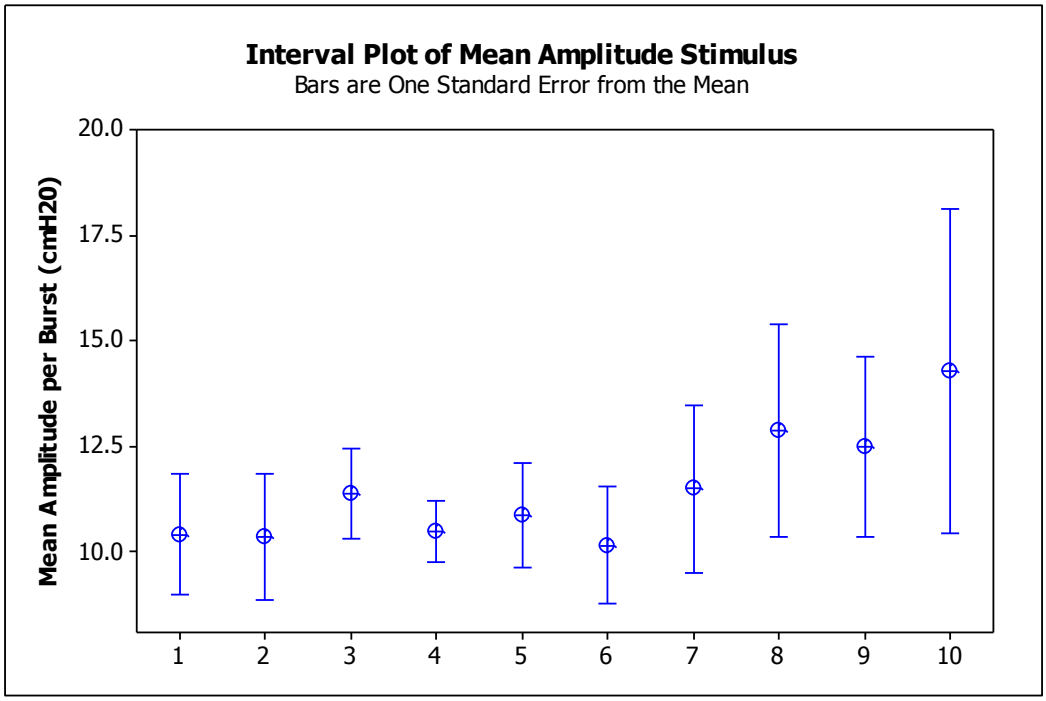


Figure 42: Mean amplitude/burst per minute for pooled baseline conditions.

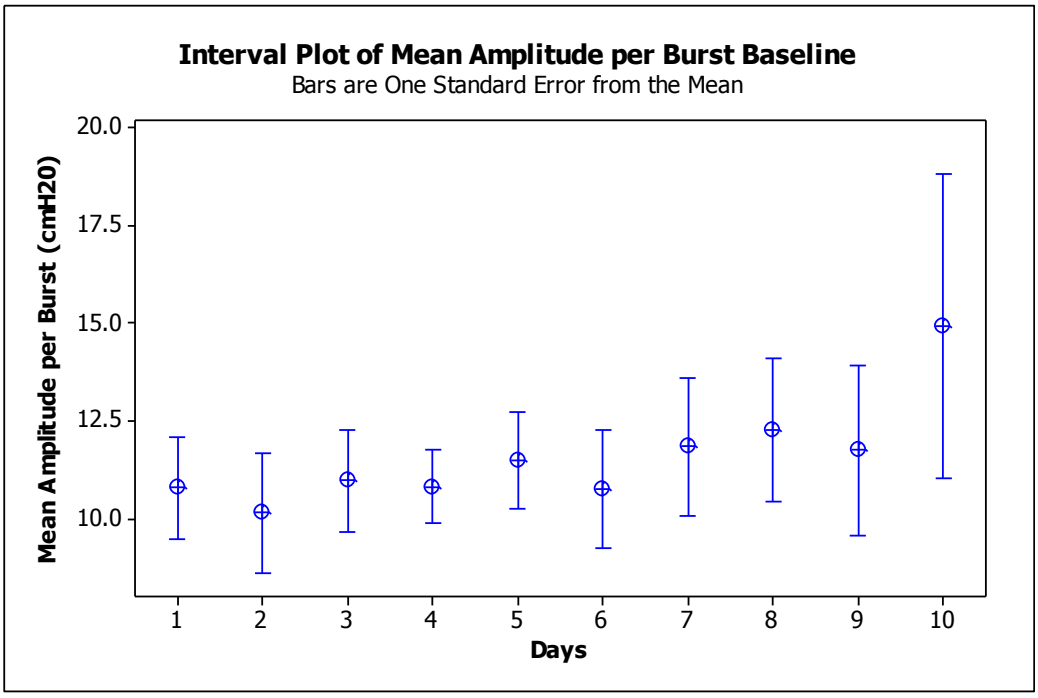


Figure 43: Estimated mean amplitude/burst per minute across days.

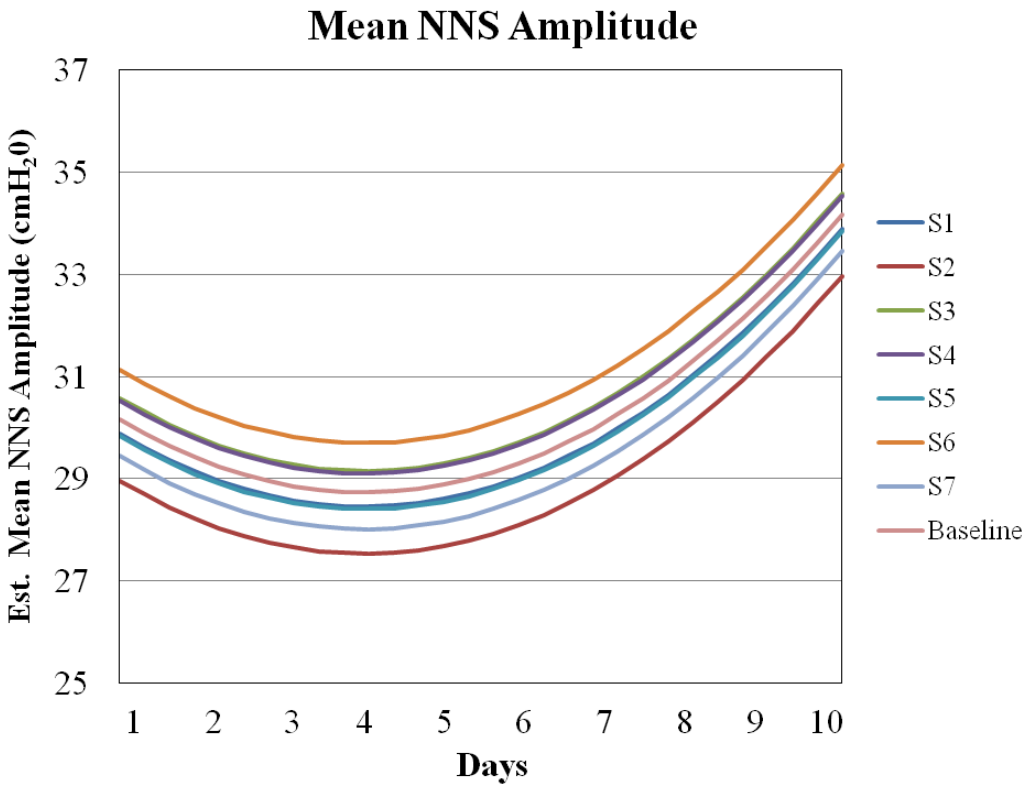


Table 14: Adjusted means and SE for mean amplitude/burst per minute.

Mean Amplitude/Burst/min (cmH_2O)

Condition	*M*	*SE*
S1	11.96	1.17
S2	11.04	1.17
S3	12.65	1.17
S4	12.61	1.17
S5	11.91	1.17
S6	13.20	1.17
S7	11.52	1.17
B Average	12.24	1.07

Mean Intraburst NNS Period per Minute (sec)

There was no difference in mean intraburst NNS period in the stimulus condition compared to the baseline condition: F (7, 77) = .12, p = 1.00, see Table 15 (Figures 44 and 45). After controlling for infants' birth weight, oxygen history, and caffeine intake, the mean intraburst NNS period did not significantly change across days: F(1, 4326) = .68, p =.41 (Figure 46).

Figure 44: Mean intraburst NNS period per minute for pooled stimulus conditions.

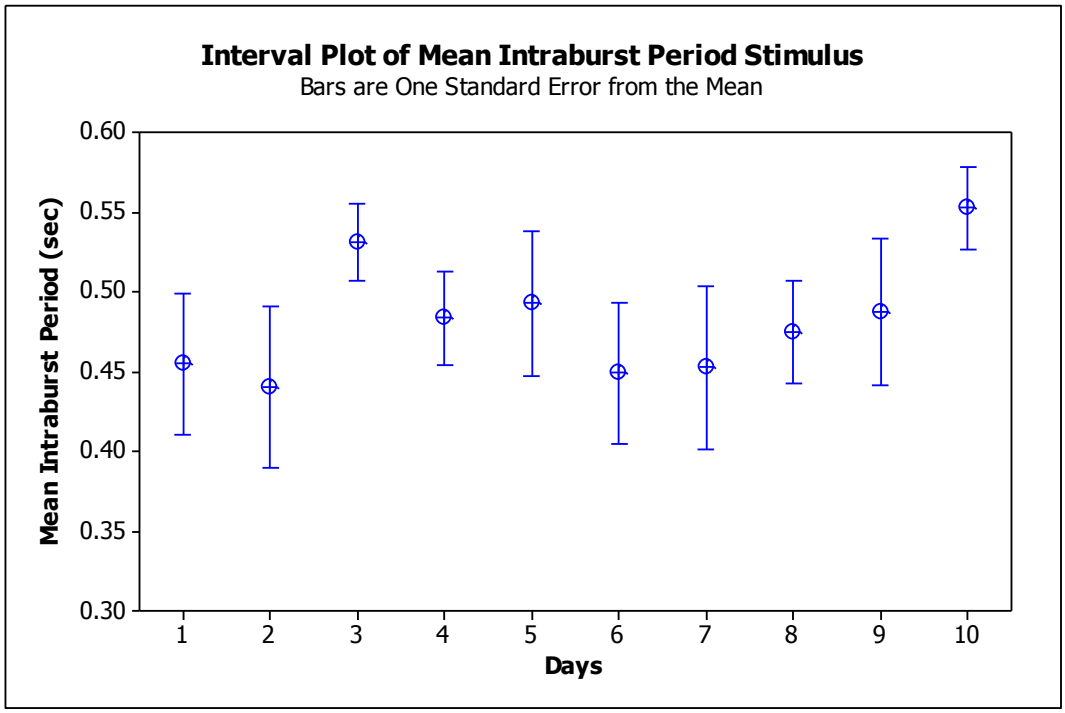


Figure 45: Mean intraburst NNS period per minute for pooled baseline conditions.

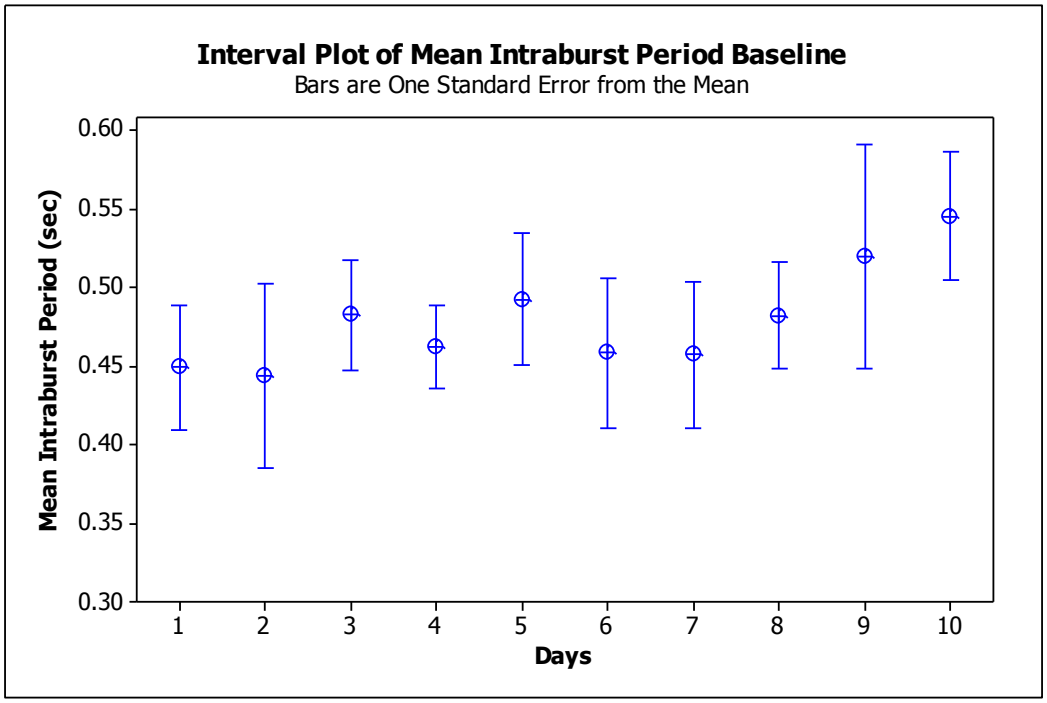


Figure 46: Estimated mean intraburst NNS period per minute across days.

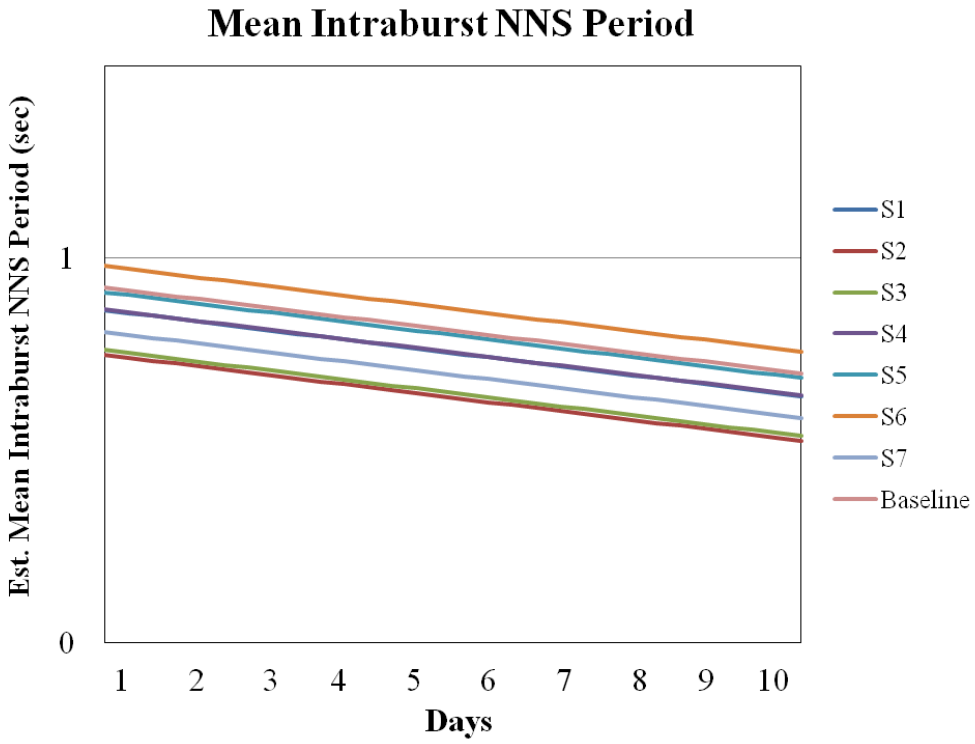


Table 15: Adjusted means and SE for mean intraburst NNS period per minute.

Mean Intraburst Period/min (sec)

Condition	*M*	*SE*
S1	0.46	0.06
S2	0.44	0.06
S3	0.44	0.06
S4	0.47	0.06
S5	0.47	0.06
S6	0.49	0.06
S7	0.45	0.06
B Average	0.48	0.04

Mean Interburst NNS Period per Minute (sec)

Infants had a greater mean interburst NNS period in the stimulus condition compared to the baseline condition: F (7, 77) = 3.52, p < .01 (Figures 47 and 48). Given significant stimulus

condition effect, adjusted means were pairwise compared (Table 16). Stimulus 5 yielded significantly greater interburst NNS period than the average baseline condition. After controlling for infants' birth weight, oxygen history, and caffeine intake, the mean interburst NNS period did not significantly change across days: $F(1, 4091) = .30$, $p = .58$ (Figure 49).

Figure 47: Mean interburst NNS period per minute for pooled stimulus conditions.

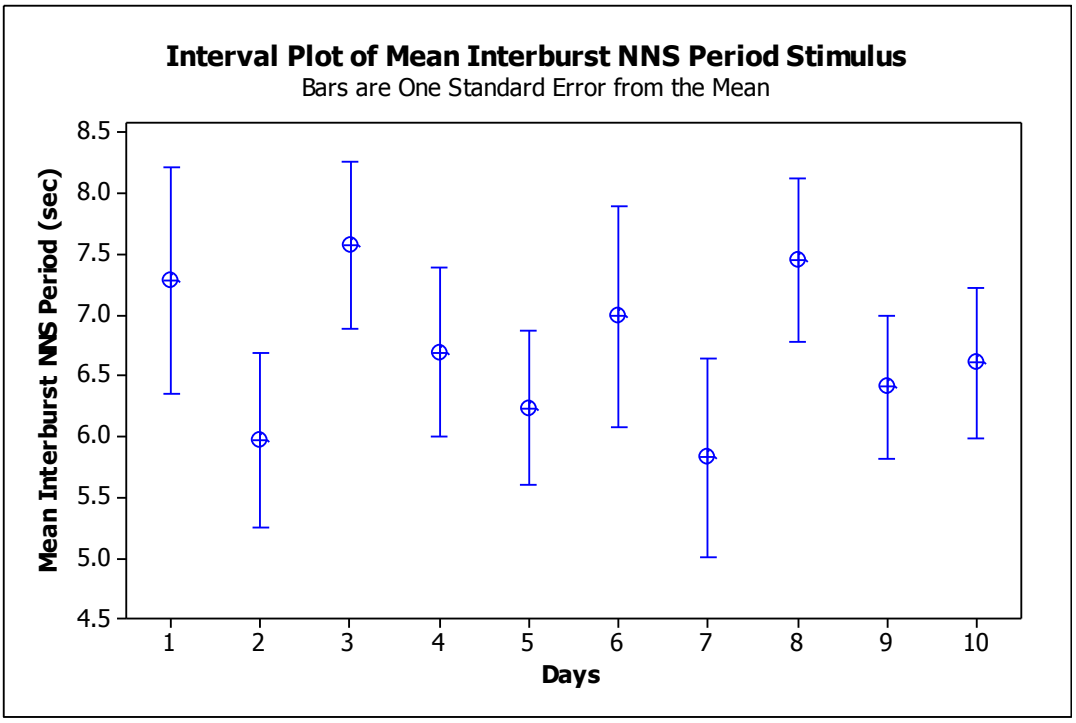


Figure 48: Mean interburst NNS period per minute for pooled baseline conditions.

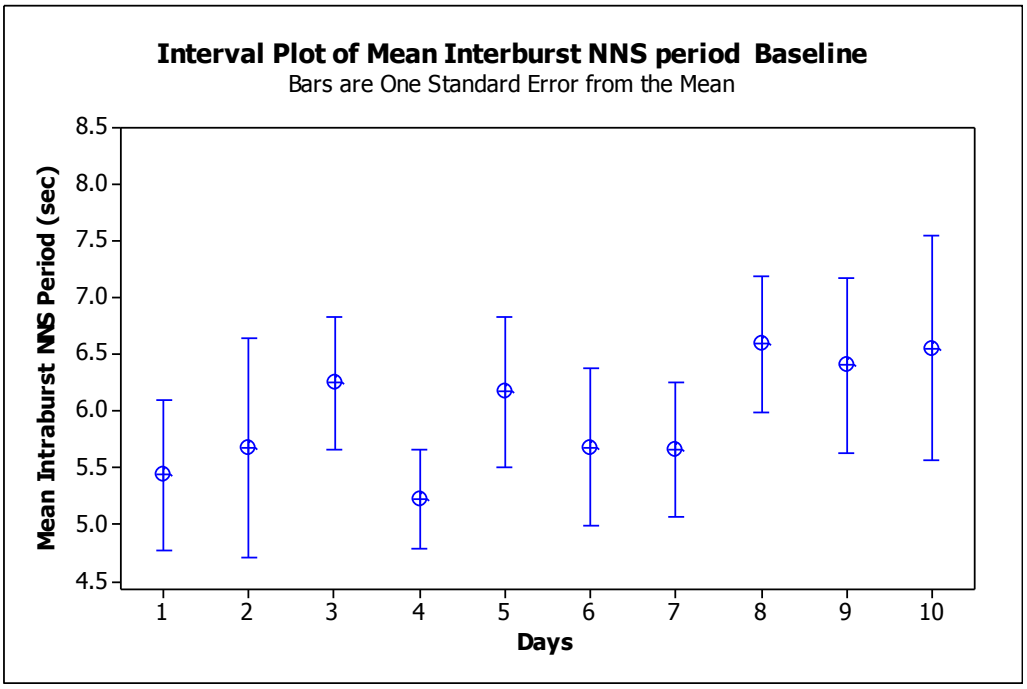


Figure 49: Estimated mean interburst NNS period per minute across days.

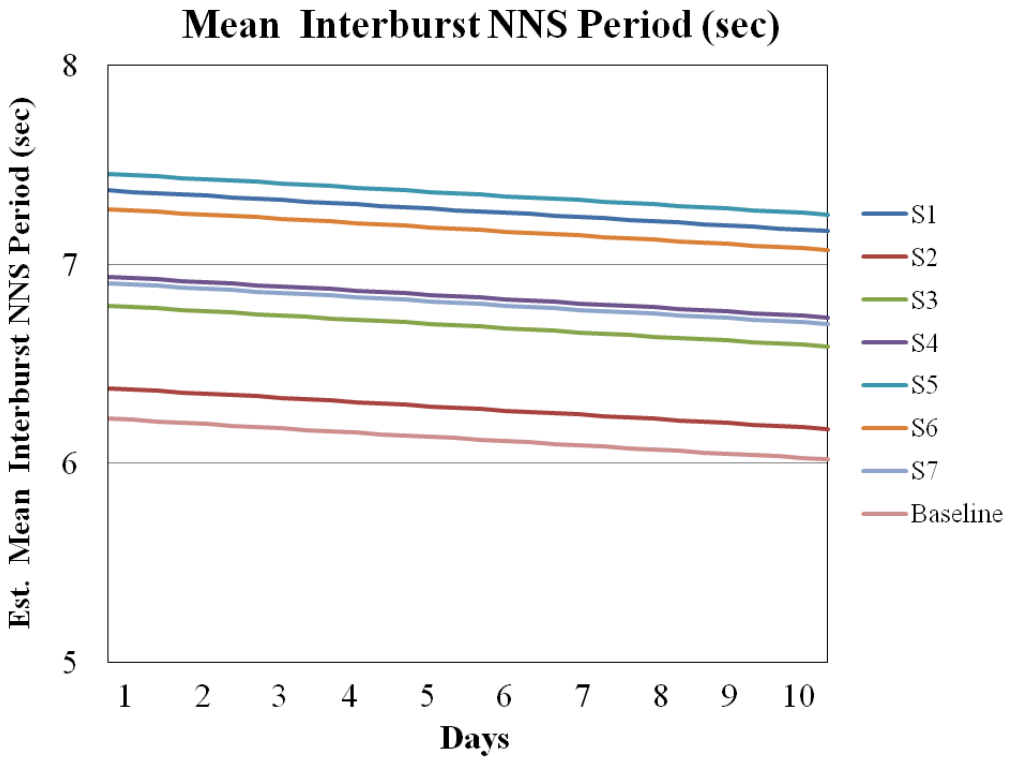


Table 16: Adjusted means and SE for mean interburst NNS period per minute.

Mean Interburst NNS Period/min (sec)

Condition	*M*	*SE*
S1	7.01	0.62
S2	6.02	0.62
S3	6.43	0.62
S4	6.58	0.62
S5	7.10	0.62
S6	6.92	0.62
S7	6.55	0.62
B Average	5.86	0.52

NNS Cycles as a Percentage of the Total Ororhythmic Output per Minute

Infants have similar NNS cycles % total between the stimulus and baseline conditions: F (7, 77) = 1.29, p =.26, see Table 17 (Figures 50 and 51). After controlling for infants' birth weight, oxygen history, and caffeine intake, a significant linear trend was observed in the NNS cycles % total change across days: F (1, 4338) = 92.06, $p < .01$ (Figure 52).

Figure 50: NNS cycles % total output per minute for pooled stimulus conditions.

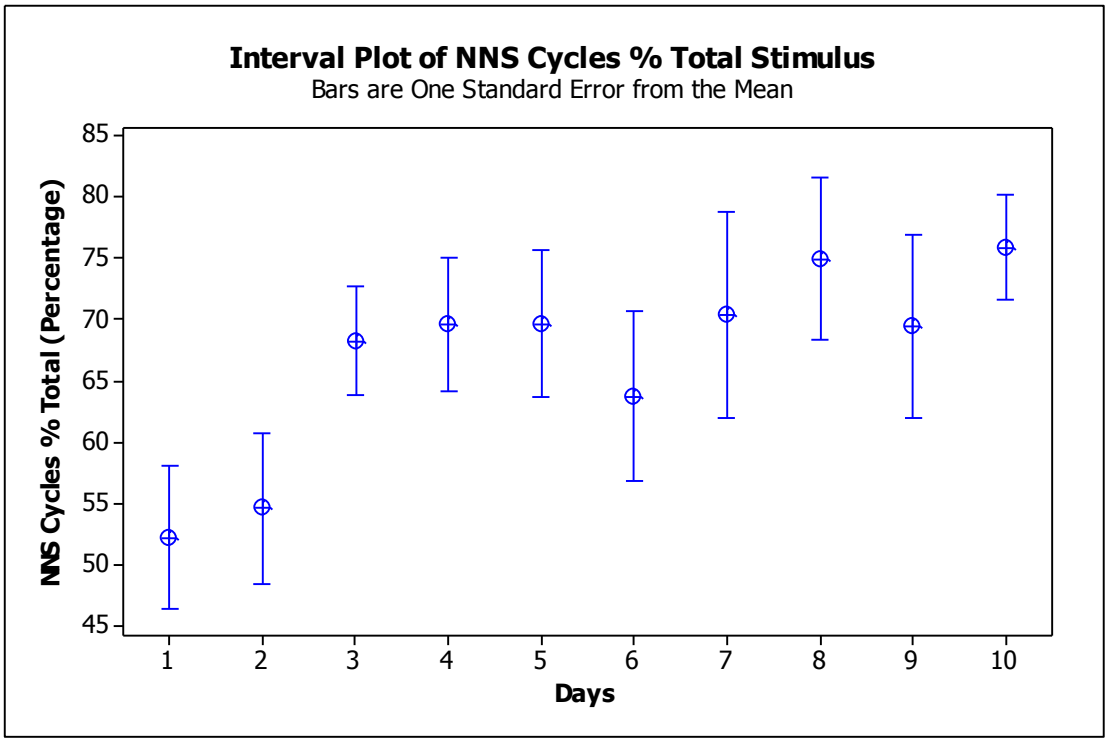


Figure 51: NNS cycles % total output per minute for pooled baseline conditions.

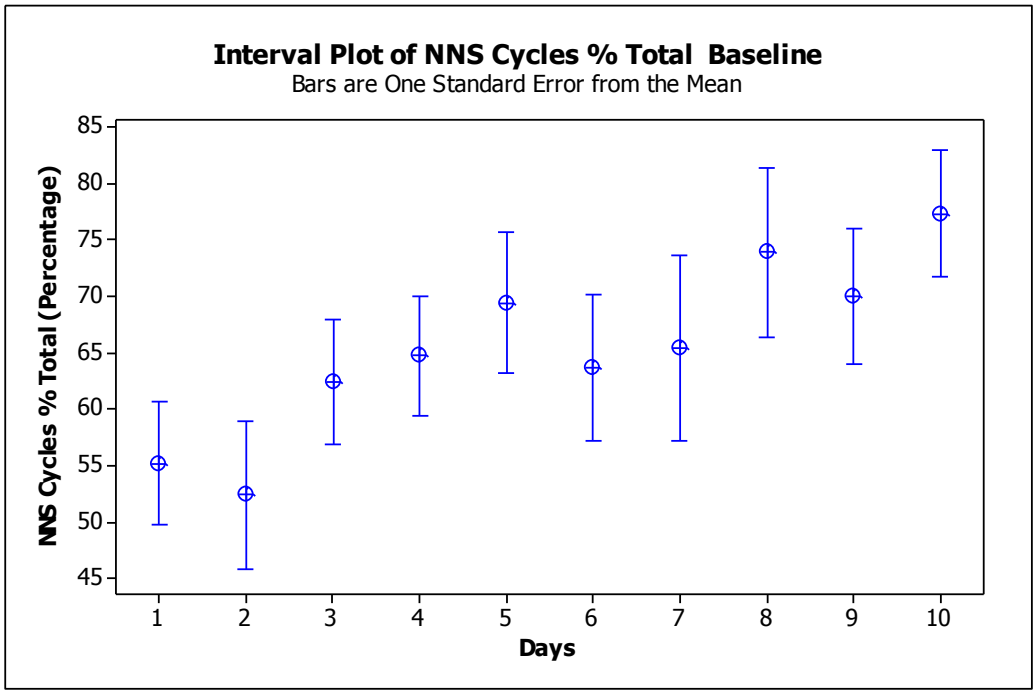


Figure 52: Estimated NNS cycles % total output per minute across days.

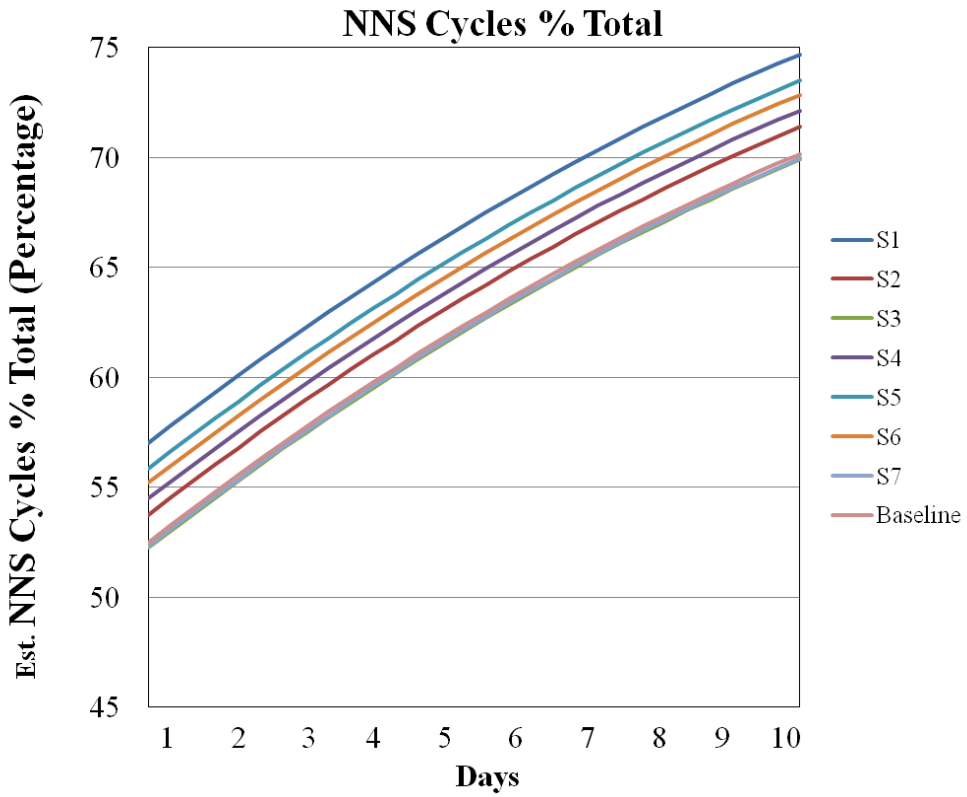


Table 17: Adjusted means and SE for the NNS cycles % total output.

NNS Cycles % Total Output/min

Condition	*M*	*SE*
S1	66.83	4.92
S2	63.53	4.92
S3	62.04	4.91
S4	64.28	4.91
S5	65.65	4.92
S6	64.99	4.92
S7	62.10	4.92
B Average	62.29	4.58

NNS STI per Minute

Infants had similar NNS STI in stimulus and baseline conditions: F (7, 77) = .76, p =.62, (see Table 18, Figures 53 and 54). After controlling for infants' birth weight, oxygen history, and caffeine intake, the NNS STI did not significantly change across days: F (1, 2142) = 1.42, p =.23 (Figure 55).

Figure 53: NNS STI per minute for pooled stimulus conditions.

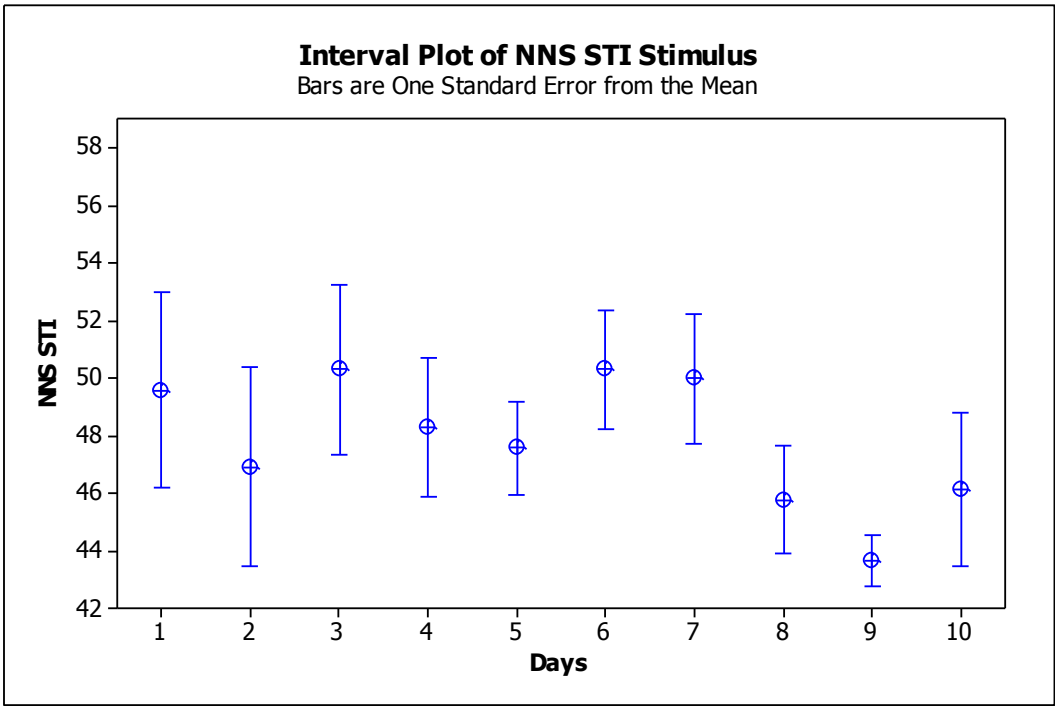


Figure 54: NNS STI per minute for pooled baseline conditions.

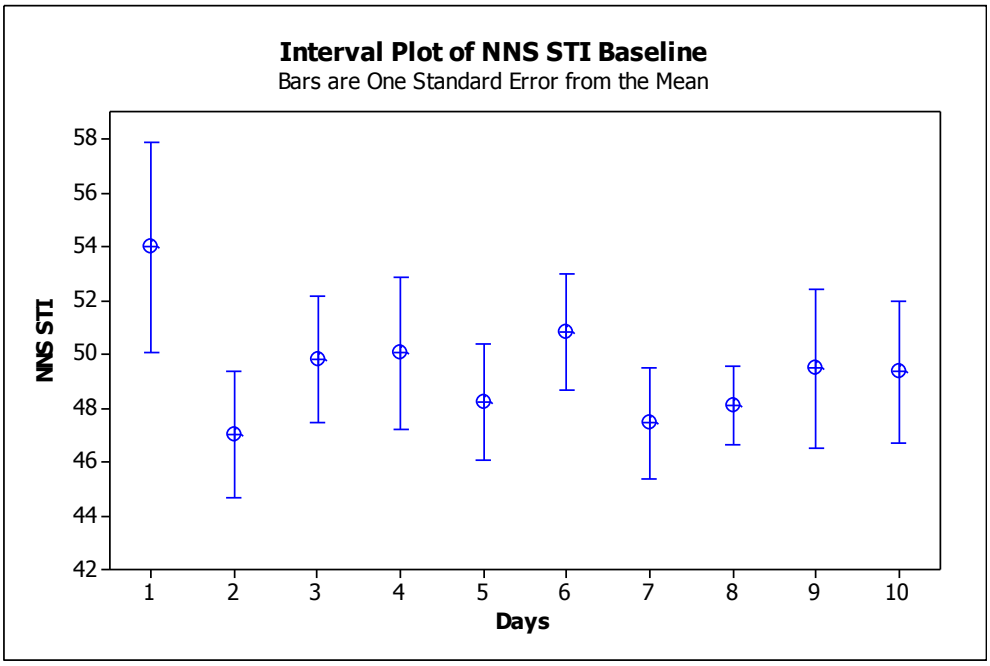


Figure 55: Estimated NNS STI per minute across days.

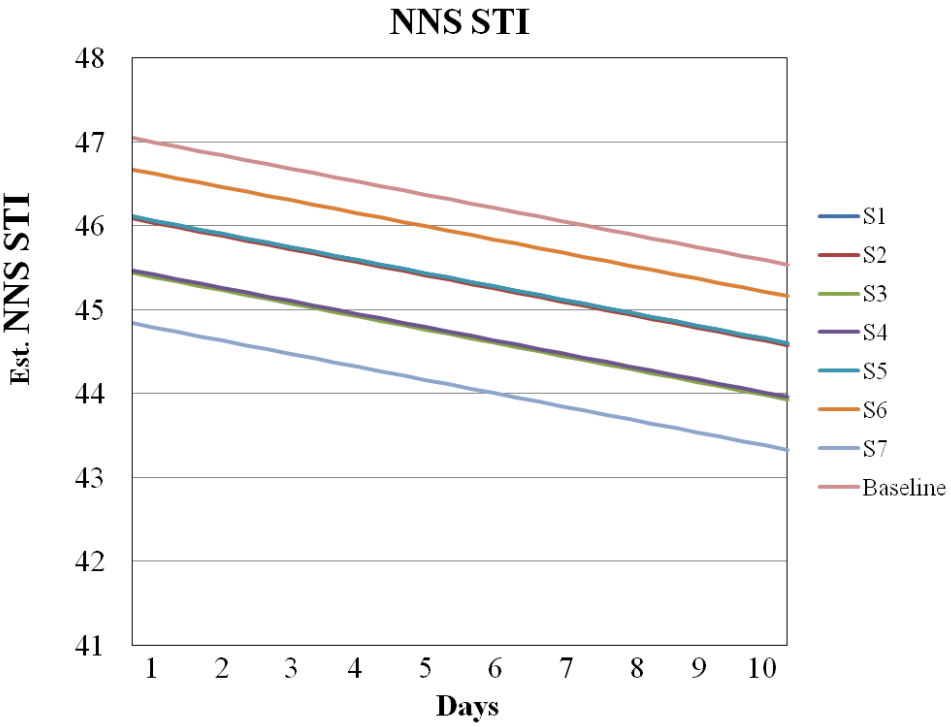


Table 18: Adjusted means and SE for the NNS STI per minute.

NNS STI/min

Condition	*M*	*SE*
S1	47.36	2.30
S2	47.34	2.29
S3	46.69	2.28
S4	46.72	2.27
S5	47.36	2.27
S6	47.92	2.25
S7	46.09	2.28
B Average	48.30	1.98

Observed Changes in Suck across Days

The multi-level regression models reveal significant changes across days in the following suck variables: total oral compressions, NNS burst cycles, non-NNS compressions, NNS bursts, mean cycles per burst, amplitude per bursts, and NNS % total output. The suck changes evident across days are likely due to normal maturation of the suck CPG and not the gliding stimulus—as only one dependent variable (mean interburst NNS period) had a significant stimulus condition effect.

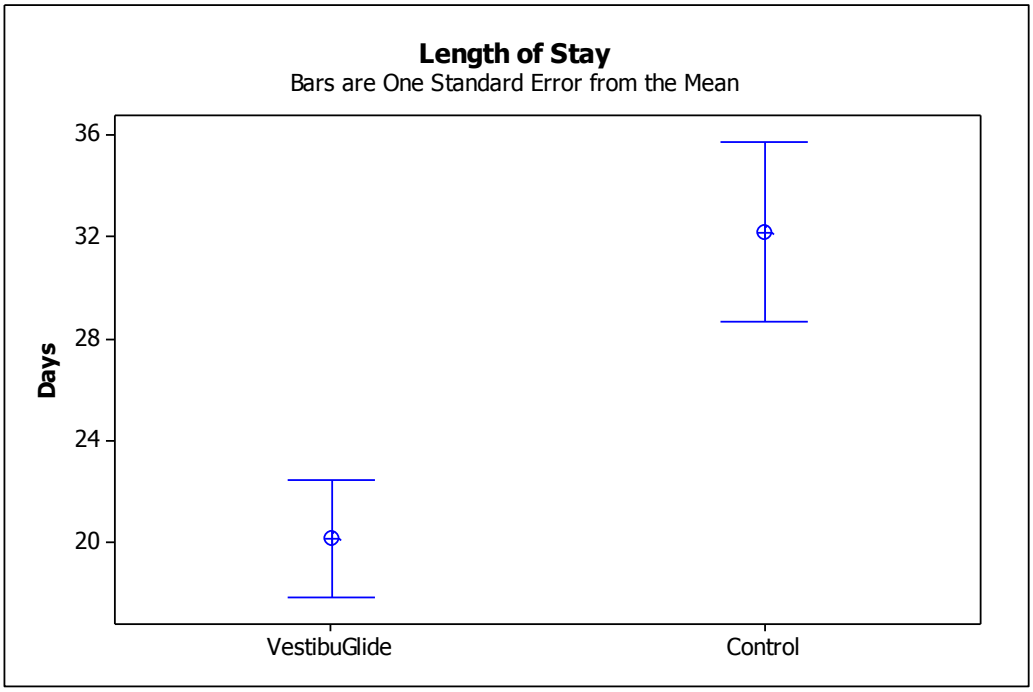
ORAL FEED OUTCOME

ANOVA revealed no significant difference in the oral feed growth slopes between the VestibuGlide treated infants and the 12 control infants: F (1, 22) = .25, p =.625. VestibuGlide infants advanced their oral feeds at 8.17% per day; whereas, control infants advanced their oral feeds at 9.47% per day.

LENGTH OF STAY OUTCOME

Length of stay was compared between VestibuGlide infants and 17 aged-match controls from an ongoing study in the mentor's laboratory. It is extremely important to note that the aged-match controls were held and offered a pacifier for 15 minutes prior to their feed. Thus, the only difference between these two groups is the VestibuGlide stimulus. ANOVA revealed a significant difference between the length of stay for infants in the VestibuGlide group compared to the control group [F (1, 28) =6.71, p=.015]. Infants in the VestibuGlide group discharged from the hospital 12 days sooner than the control infants (Figure 56) resulting in a substantial reduction in hospitalization costs (~$42,000/infant).

Figure 56. Length of stay in the NICU.



Effect Size and Dependent Variables

Effect size is a measure of the strength of the relationship between two variables in a sample. Effect size was calculated for all of the dependent variables, see Table 19. The largest effect sizes (shaded in yellow in Table 19) were seen in the rib cage BPM, abdomen BPM, mean interburst NNS period, oral feed, and length of stay. Medium effects (shaded in orange in Table 19) were evident in SpO_2, mean intraburst NNS amplitude, and Mean intraburst NNS period.

Table 19: Effect size for dependent variables.

Effect Size (Cohen's *f*)		
Dependent Variables in the General Mixed Model	**Time Effect**	**Stimulus Sequence Effect**
Rib Cage BPM	0.14	1.42
Abdominal BPM	0.14	1.36
Pulse	0.19	0.12
SpO_2	0.04	0.36
NNS Total Oral Compressions	0.16	0.20
NNS Burst Cycles	0.19	0.21
Non-NNS Compressions	0.06	0.15
NNS Bursts	0.01	0.22
Mean NNS Cycles/Burst	0.10	0.22
Mean NNS Amplitude/Burst	0.10	0.26
Mean Intraburst NNS Period	0.01	0.27
Mean Interburst NNS Period	0.01	0.46
NNS Cycles % Total	0.05	0.15
NNS STI	0.01	0.14

Dependent Variable	**Effect Size**
Oral Feed	0.59
Length of Stay	1.02

Key
Medium Effect Size ≥.25
Large Effect Size ≥.4

POWER SPECTRUM ANALYSIS OUTCOME

Power spectrums were calculated for the best 15 minutes and pooled across infants for the first baseline conditions (B1), stimulus conditions (S1-S7), and post-stimulus baseline conditions (B2-B8) to examine the amplitude and distribution of the spectra. This analysis reveals that infants have higher power in the first baseline conditions (B1) compared to the stimulus (S1-S7) and post-baseline conditions (B2-B8), see Figures 57-63. The power spectrums for the stimulus and post-baseline conditions are similar indicating that infants never fully go back to their true baseline breathing pattern. It is likely that the breathing pattern used in the stimulus condition persists well into the post-stimulus baseline condition.

Figure 57: Power spectra for Stimulus 1 at first baseline, post-stimuli baselines (pooled), and during vestibular stimulation (pooled).

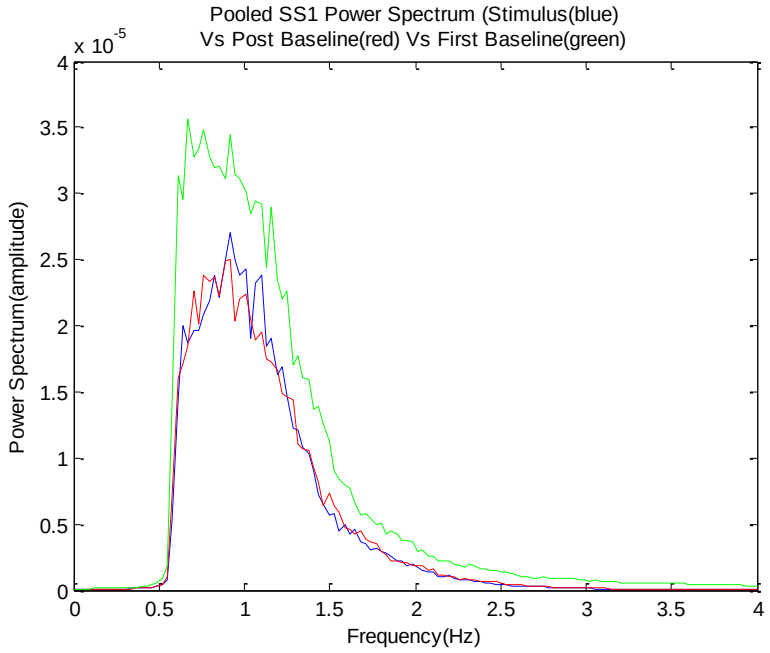


Figure 58: Power spectra for Stimulus 2 at first baseline, post-stimuli baselines (pooled), and during vestibular stimulation (pooled).

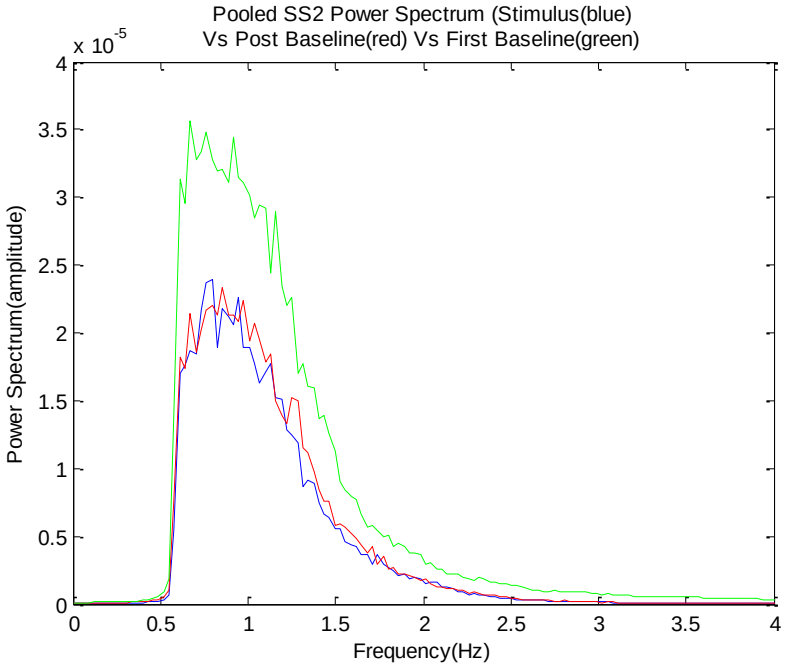


Figure 59: Power spectra for Stimulus 3 at first baseline, post-stimuli baselines (pooled), and during vestibular stimulation (pooled).

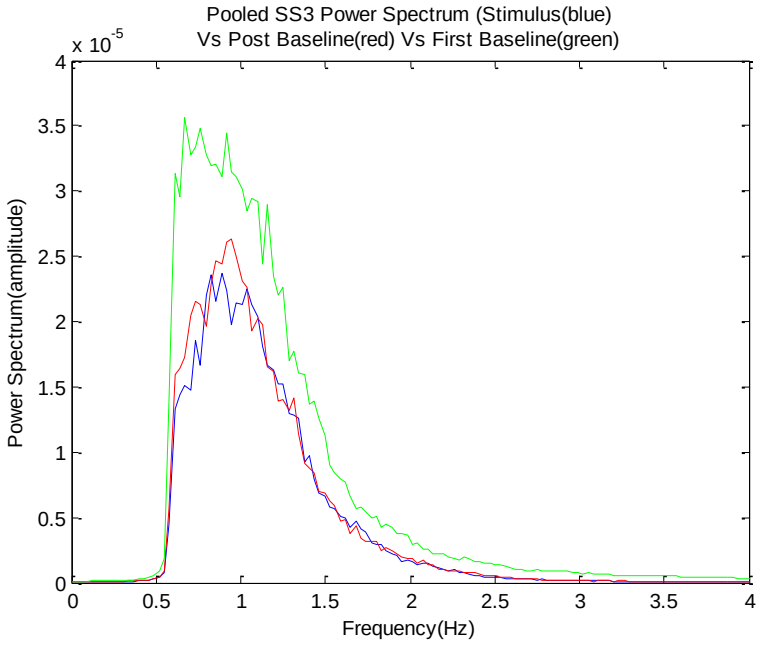


Figure 60: Power spectra for Stimulus 4 at first baseline, post-stimuli baselines (pooled), and during vestibular stimulation (pooled).

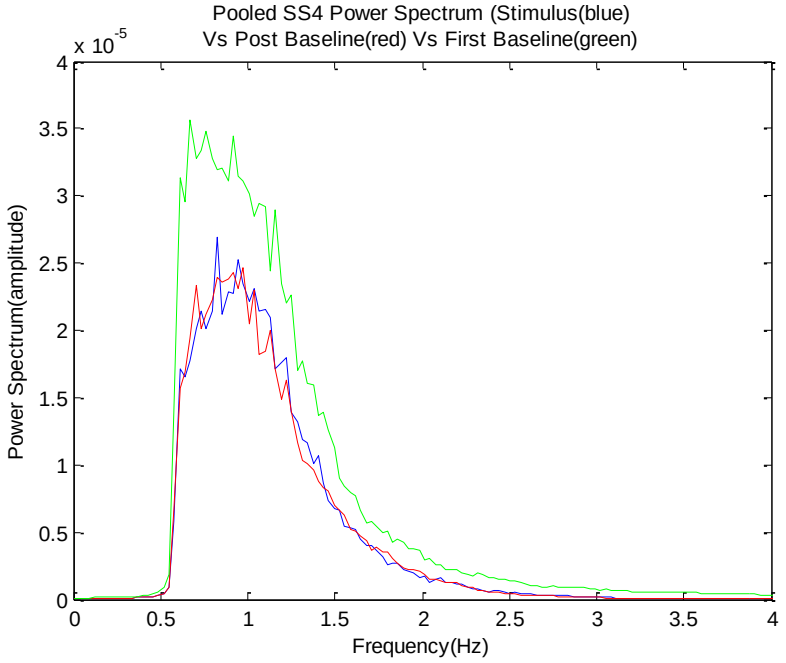


Figure 61: Power spectra for Stimulus 5 at first baseline, post-stimuli baselines (pooled), and during vestibular stimulation (pooled).

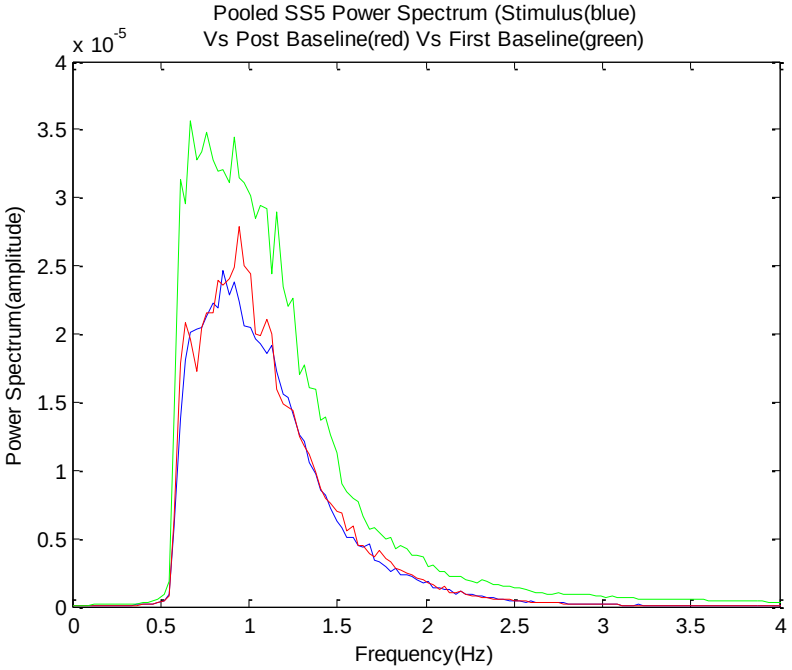


Figure 62: Power spectra for Stimulus 6 at first baseline, post-stimuli baselines (pooled), and during vestibular stimulation (pooled).

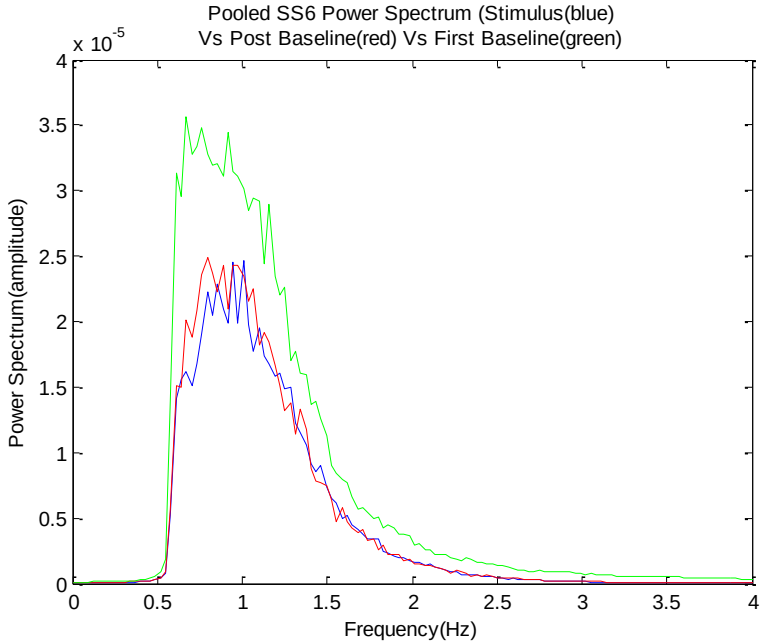
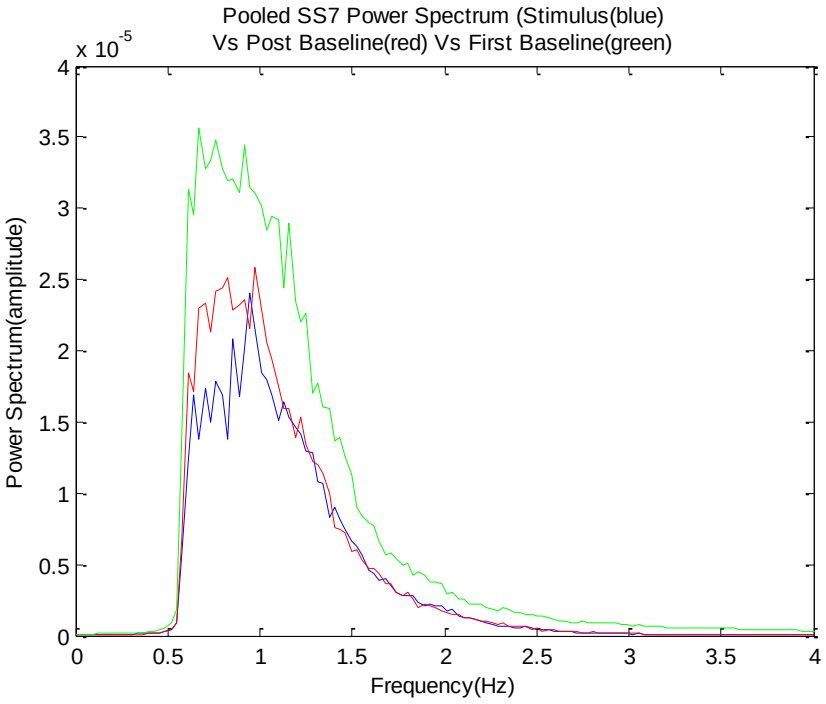


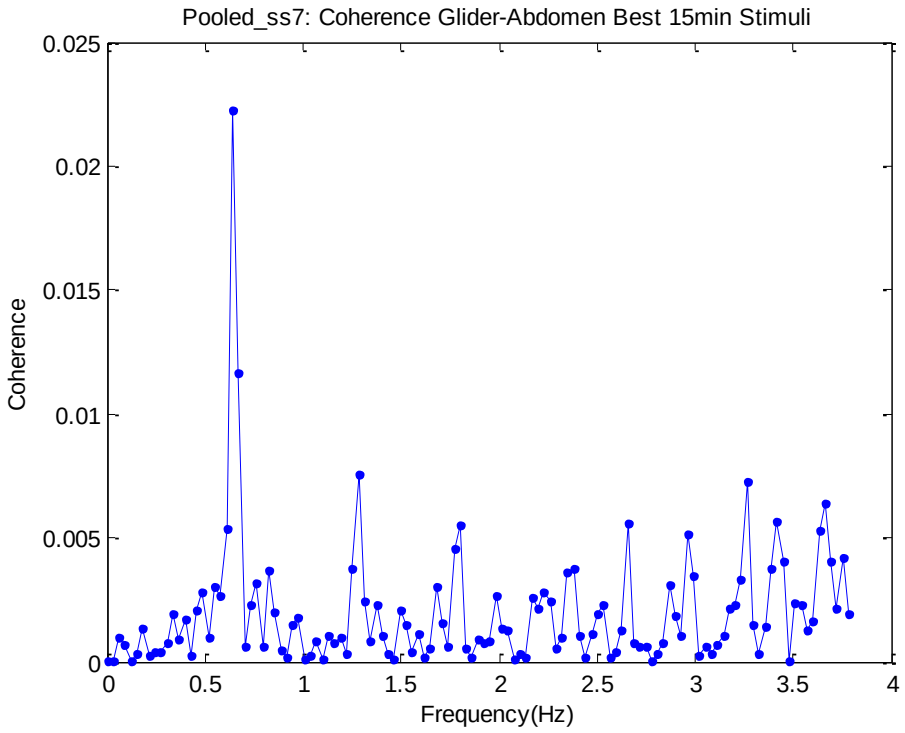
Figure 63: Power spectra for Stimulus 7 at first baseline, post-stimuli baselines (pooled), and during vestibular stimulation (pooled).



COHERENCE OUTCOME

Coherence was completed for the best 15 minutes pooled across infants for stimulus conditions (S1-S7). The highest coherence value between the glider and abdomen (Figure 64) was .023 which was in response to stimulus 7 (highest acceleration). Overall, coherence outcomes were very low ($\leq$.023) providing little evidence for entrainment between the glider and abdominal wall motion.

Figure 64: Coherence plot from the glider vs. abdomen for stimulus 7.



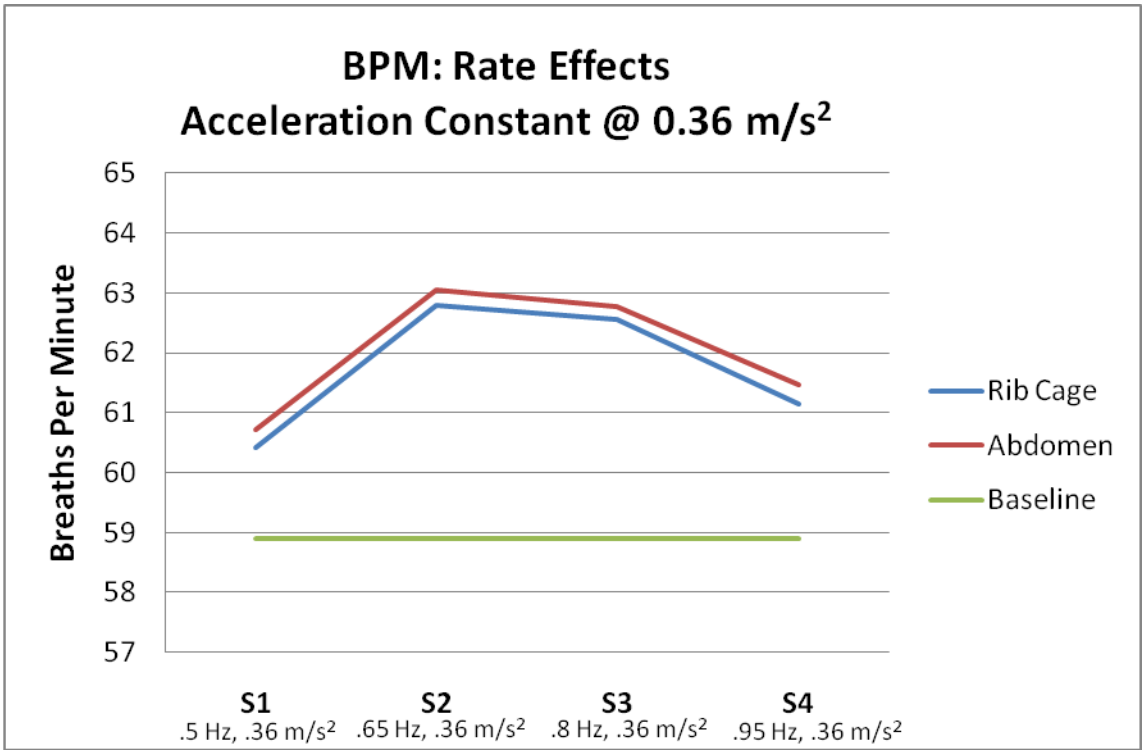
CHAPTER FOUR: DISCUSSION

SPECIFIC AIMS DISCUSSION

Specific Aim #1: To examine the role of vestibular stimulus rate on chest wall motor patterning (movement) in preterm infants.

Vestibular stimulus rate did not significantly alter chest wall motor patterning in preterm infants. However, there were some variations in chest wall kinematics seen across the four different rates, but these differences did not reach statistical significance after Bonferroni-correction. Infants had the slowest BPM in responses to stimulus 1 with an average of 60.42 ($\pm$2.28) for the rib cage and 60.72 ($\pm$2.32) for the abdomen. Infants had the fastest BPM in response to stimulus 2 with an average of 62.80 ($\pm$2.28) for the rib cage and 63.05($\pm$2.32) for the abdomen. All of the stimulus conditions, except stimulus 1, had significantly higher BPM than the baseline average (Figure 65). This means that infants increased their BPM during the stimulus conditions compared to the baseline conditions. More data is needed to have these differences across the four rates reach significance.

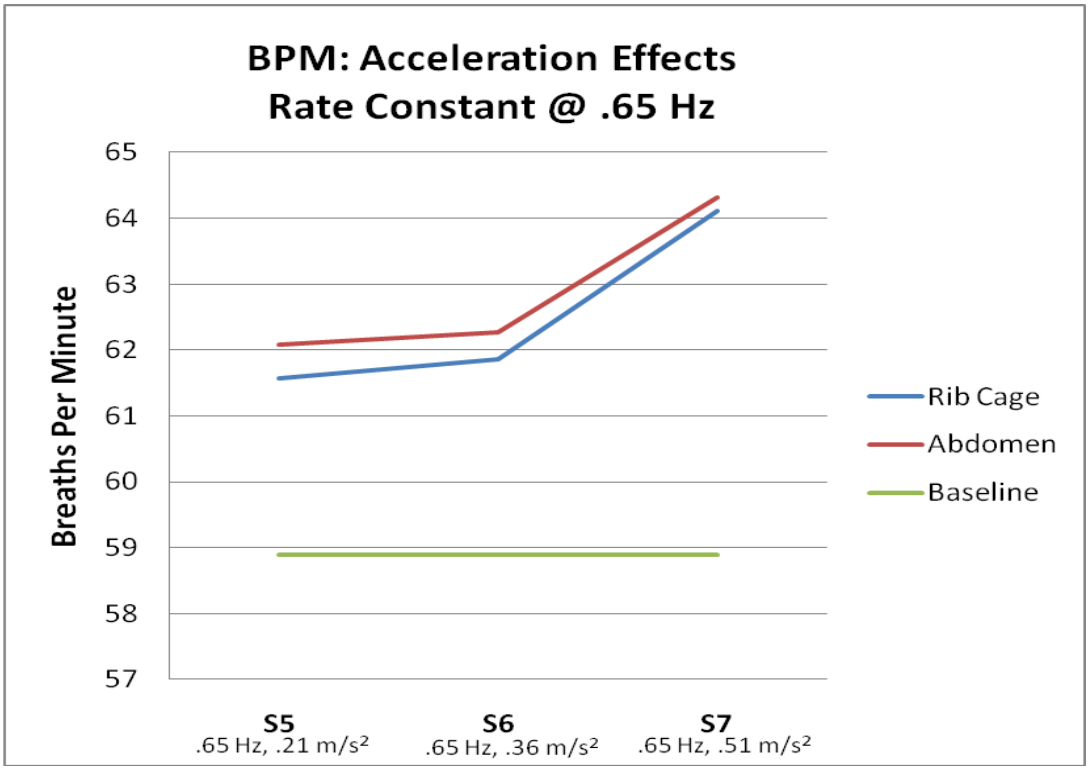
Figure 65: Rate changes in BPM for the first four stimulus conditions (S1, S2, S3, and S4).



Specific Aim #2: To test the effect of vestibular stimulus acceleration on chest wall motor patterning (movement) in preterm infants.

Vestibular stimulus acceleration had a significant effect on chest wall motor patterning in preterm infants. Stimulus 7 provided the fastest acceleration to the infant and induced significantly higher BPM than stimuli 1, 4, and 5 for the rib cage and stimuli 1 and 4 for the abdomen. As acceleration increased from stimulus 5 to 7 so did the BPM, see Figure 66. There was a small difference in BPM between stimulus 5 and 6 but the largest difference in BPM is evident in stimulus 7.

Figure 66. Acceleration changes in BPM for the last three stimulus conditions (S5, S6, and S7).



It is clear that acceleration has the largest influence over the rCPG and is capable of inducing significant changes in chest wall kinematics. Vestibular otoliths respond best to linear acceleration; therefore, the highest peak acceleration provided by stimulus 7 increases otolith stimulation resulting in strengthened sensorimotor connectivity between the vestibular apparatus and the rCPG.

Sensory signals, such as linear acceleration, serve to regulate the magnitude of ongoing motor activity and dynamically adjust the sensitivity of reflexes, thereby providing an adaptive and flexible neural substrate with changes in task dynamics and environmental conditions (Barlow & Estep, 2006). Infants that are able to modify their chest wall kinematics to linear acceleration are at an advantage for rapid control of their breathing mechanism. This type of

adaptive response is vital for adapting to various task demands, such as feeding and early vocalizations.

The increase neural integrity afforded by gliding reduces the intensity on internal needs and allows the focus to be more on external needs, such as responding to one's local environment (Korner, et al., 1982). Adapting to one's environment is a critical component for early learning. The richness of sensory experience offered by the VestibuGlide stimulation offers a new and exciting neurotherpeutic application for habilitation of the rCPG in preterm infants.

Specific Aim #3: To examine the efficacy of vestibular stimulation on the attainment of oral feed in preterm infants.

There was no significant difference in the attainment of oral feeds in the infants who received the vestibular stimulation compared to an age-matched control group who did not.The American Academy of Pediatrics suggests that premature infants should demonstrate feeding competency prior to hospital discharge ("Guidelines for developing admission and discharge policies for the pediatric intensive care unit. Pediatric Section Task Force on Admission and Discharge Criteria, Society of Critical Care Medicine in conjunction with the American College of Critical Care Medicine and the Committee on Hospital Care of the American Academy of Pediatrics," 1999). When comparing the length of stay between the VestibuGlide treatment infants and the age-matched controls, there was a 12 day difference. Considering that feeding competency is a requirement prior to discharge, it is clear that infants in the VestibuGlide study demonstrated adequate feeding competency earlier as they were able to discharge sooner from the NICU. The NICU costs approximately $3,500 dollars a day, therefore, coming home 12 days

earlier results in saving $42,000dollars. Not only do parents who had their infants enrolled in the study decrease their medical bill, they also get to have their baby home sooner.

Parent attachment to their infant is a large issue in the NICU. When parents give birth to a premature infant they feel guilt, sadness, and worry on a day–to–day basis (Stjernqvist, 1988). Separation from their child was found to be the most difficult aspect for mothers when their infant was in the NICU (Nystrom & Axelsson, 2002; Wereszczak, Miles, & Holditch-Davis, 1997). If parents are able to have their infants discharge sooner from the NICU, they will have reduced stress and be able to attain the necessary parent-child attachment sooner.

Specific Aim #4: To examine the efficacy of vestibular stimulation on non-nutritive suck development in preterm infants.

Overall, vestibular stimulation had no significant effect on NNS development when compared to the baseline conditions. Only one dependent measure (mean interburst NNS period) had a significant stimulus condition effect therefore infants sucked the same whether or not the chair was in a stimulus or baseline condition.

Seven out of the ten suck dependent variables significantly changed across days. NNS STI did not significant change across days but there were some striking differences between conditions. NNS STI measures suck pattern stability and the lower the STI number, the better the suck pattern stability. Figure 55 shows the estimated STI output across days and it is clear that the average baseline condition has the highest STI values (less stable suck pattern) and stimulus 7 with the highest acceleration had the lowest STI value.

In order to fully explore how the VestibuGlide stimulus alters suck, a larger sample size is needed. In addition, the suck dependent variables need to be matched to control infants who

are given a sham stimulation condition. In the sham stimulation condition, the infants will be held in the VestibuGlide chair, offered the pacifier, and the chair will remain stationary. A sham stimulation would reveal if the VestibuGlide stimulus improves suck above and beyond normal maturation.

ADDITIONAL FINDINGS

Oxygen Saturation and Pulse

In spite of the increases in BPM during vestibular stimulation, infants maintained stable oxygen saturation (SpO_2) and pulse rate throughout the VestibuGlide study. In fact, infants often had more oxygen saturation during the stimulus conditions compared to baseline, see Tables 6, 7. This finding is not suprising as vestibular stimulation can elicit respiratory changes that provide for stable blood oxygenation during movements and changes in posture (Yates & Miller, 1998).

Many previous rocking studies have shown that rocking stimulus can prevent apneic attacks and decrease the need for respiratory therapies (Farrimond, 1990; Korner, et al., 1975; Tuck, et al., 1982). Infants in the VestibuGlide study were able to modify the rCPG in response to vestibular stimulation and produce a stable and effective respiratory response. Apnea is the result of non-integrated inputs to/from the rCPG.

Apnea of prematurity is the most common problem in preterm infants with 70% of infants born less than 34 weeks GA having significant apnea, bradycardia, or O_2 desaturations during their hospital stay (Finer, Higgins, Kattwinkel, & Martin, 2006). Immaturity and depression of the rCPG drive to respiratory musculature are key factors in the pathogenesis of apnea of prematurity (Darnall, Ariagno, & Kinney, 2006). A neurally intact rCPG is essential for optimal respiration during the neonatal period. Therefore, therapeutic programs, like the

VestibuGlide system, aimed at accelerating the development of the rCPG are vital for this population.

Power Spectrum Analysis

The power analysis shows that the first baseline condition has more energy than the post-baseline and stimulus conditions. There are a few possible explanations for this occurrence. First, the infant's stimulus breathing pattern persisted into the post-baseline conditions making the power spectra for these conditions similar. Second, the increase in energy seen in the first baseline condition likely emerges from larger chest wall amplitudes and depth of chest wall cycles. It is possible that the decrease in energy evident in the stimulus and post-baseline conditions may be due to the infant stiffening his/her chest wall in response to the gliding movement, thereby resulting in smaller excursion of the Respitrace™ bands. Future studies need to be completed to fully understand the difference between the first baseline condition compared to the stimulus and post-baseline conditions.

Coherence Analysis

The coherence values remained under .02, indicating a very weak coupling between the abdomen and glider chair. This finding sharply contradicts the report by Sammon and Darnall (1994) who reported strong coherence(>.8) between the glider and abdomen motions. There are several reasons for the discrepancies between the two studies. When completing the coherence analysis Sammon and Darnall picked the best 164-second breathing window, removed the first and last 15-seconds, and further divided the data into four 41-second windows for analysis, thereby, largely manipulating the raw data. They also used a nonlinear (arc) displacement

trajectory under manual control with unspecified parameters for stimulus control and data analysis; whereas, the present study used highly controlled horizontal displacements with clearly defined stimulation and analysis parameters.

Subject enrollment and exposure to vestibular stimulation was very different between the two studies. Sammon and Darnall enrolled infants born between 28-34 weeks GA and provided vestibular stimulation two-to-eight weeks later. Three of the infants enrolled in their study had BPD and one was on nasal CPAP during the stimulus. Each infant was held by an investigator, parent, or volunteer and received one session of vestibular stimulation lasting anywhere from 30-90 minutes. There was no consistency in how the infants were held in the study—3/18 infants were held in a head-to-shoulder orientation and the remainder of the infants were cradled during the stimulus. In contrast, this dissertation study included only healthy preterm infants (28-34 weeks GA), vestibular stimulation was initiated at 32 weeks PMA, infants received vestibular stimulation for 15 minutes 3x/day for 10 days, and all infants were held in the same orientation each session and by the same investigator.

Vestibular Apparatus and its Connectivity

Based on the findings of the current study, it is clear that there is connectivity between the vestibular apparatus and the rCPG. The lack of entrainment between the glider and the abdomen reveals this connectivity is probably not direct, rather it is likely polysynaptic and indirect, possibly via reticular formation in brain stem and spinal cord. Other studies have shown that multiple populations of neurons are likely to participate in producing vestibulo-respiratory responses (Anker, Sadacca, & Yates, 2006).

Natural vestibular stimulation, like gliding, reveals the widest distribution within the vestibular nuclei (Wilson, 1978). Therefore, the VestibuGlide stimulus likely results in the activation of vestibular efferents that project to numerous areas within the CNS including the following cranial and spinal nerves, cranial nerves V, VII, IX, X, and XII, and cervical and thoracic intermediate and ventral horn cells projecting to the rib cage and abdominal muscles.

The masseter muscle, controlled by CN V, has connectivity with the vestibular system (Cuccurazzu, et al., 2007; Tolu & Pugliatti, 1993). The vestibular apparatus also has potent connectivity to the intrinsic and extrinsic tongue musculature (Anker, et al., 2003; Cotter, et al., 2004; Elmund, et al., 1983), which is controlled by CN XII. Vestibular connectivity to the tongue and jaw is essential in maintaining the patency of the airway during postural changes. Vestibular stimulation has been shown to influence upper airway musculature (Siniaia & Miller, 1996), controlled by CNs IX and X. Short trains of current pulses to the vestibular nerve in cats has been shown to evoke reflex reponses in the following nerves: recurrent and superior laryngeal (CN X), pharyngeal branch of the vagus (CN X), glossopharyngeal (CN IX), and hypoglossal (XII) (Siniaia & Miller, 1996). Not only does vestibular stimulation evoke responses in many cranial nerves, but sensory signals from the upper airway enter the CNS by CNs V,VI,IX, X, and XI and these signals can also alter respiratory rate and rhythm (Harding, 1984).

Exactly how the vestibular apparatus connects to all of these brainstem areas is unknown. However, early understanding of the pattern-generating circuitry for suck, respiration, and mastication suggests multiple loci in brainstem and motor cortex with a significant role for integration among subsystems that occur within the periaqueductal gray (Barlow, Lund, Estep, & Kolta, 2009). More research is needed regarding the vestibular apparatus and its connectivity.

Subjective Observations

Respiratory Re-setting Events

Preliminary data on full-term infant W4 revealed respiratory re-set events during transition periods between baseline and stimulus conditions. These re-set events were also evident in preterm infants, see Figures 67 and 68. Sten Grillner (1991) has demonstrated CPG re-setting events where the sensory stimulation results in a reassembly of the neuronal networks that compose the rCPG, and therefore produces new motor forms. These events provide evidence that vestibular stimulation alters the rCPG and in turn produce new respiratory patterns.

Figure 67: Entire gliding protocol for infant W9, trial 16, sequence 1

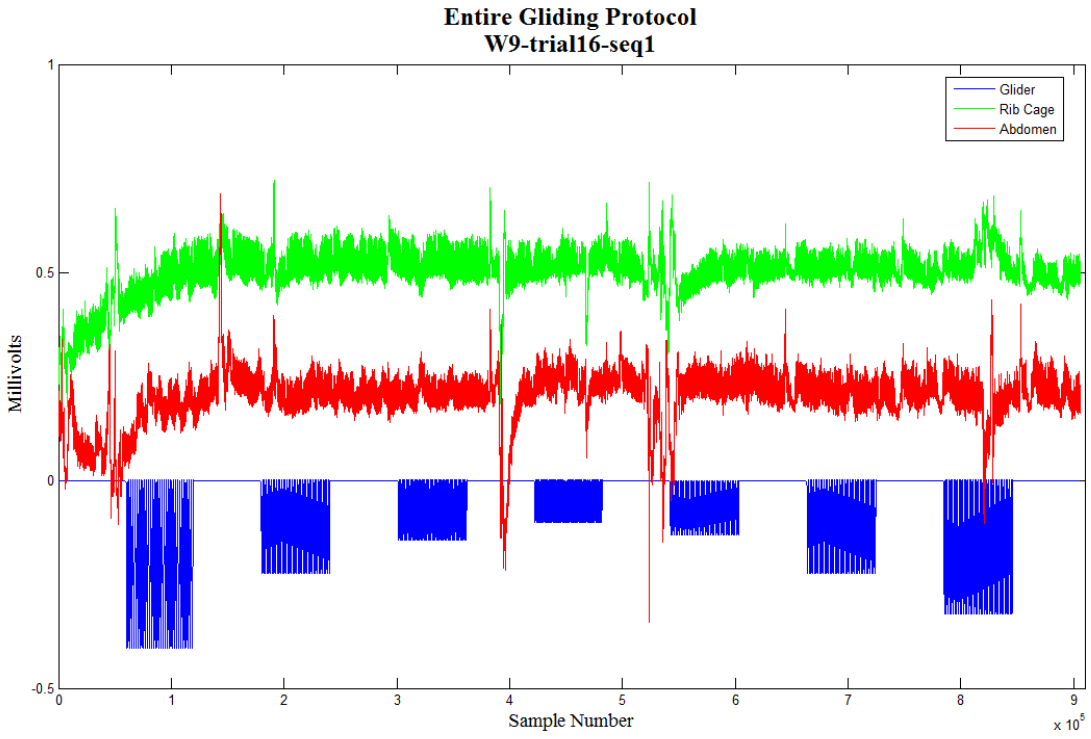
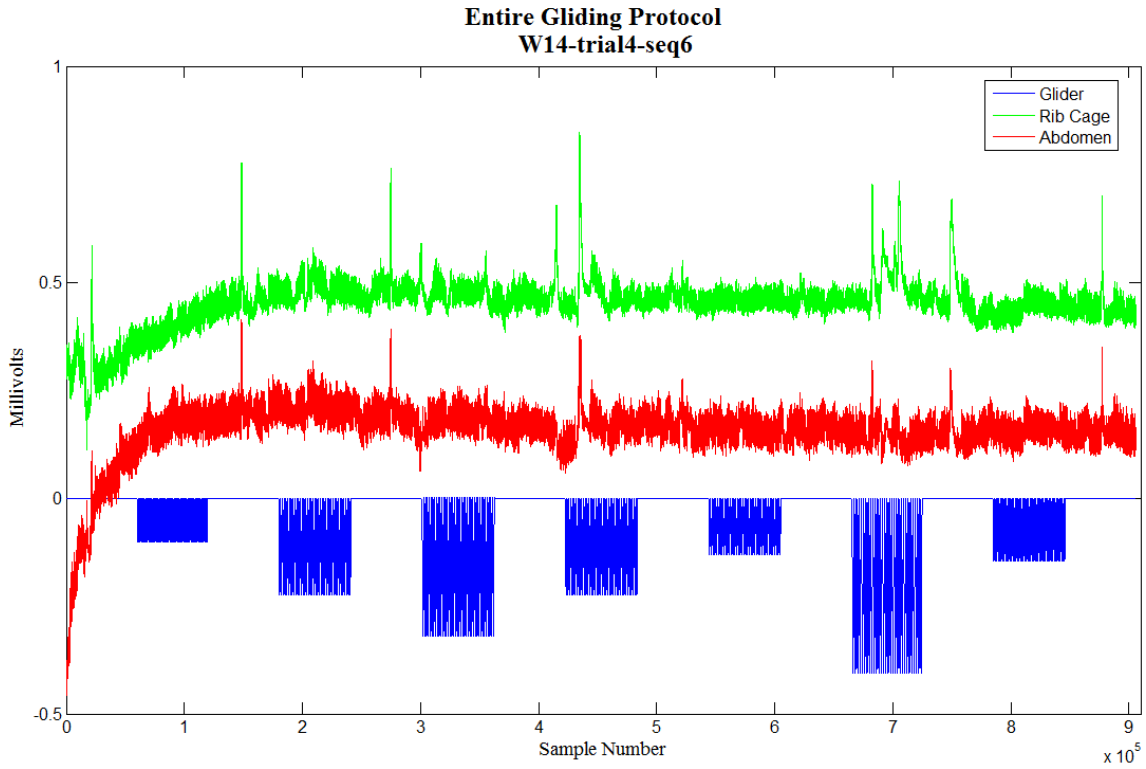


Figure 69: Entire gliding protocol for infant W14, trial 4, sequence 6.



Infants Enjoyed the Stimulus

Infants appeared to enjoy the VestibuGlide stimulus. There were no abnormal or adverse events that occurred during the gliding protocol. All infants had stable oxygen saturation and pulse, which indicates that the stimulus did not cause the infant stress. There were no episodes of emesis during- or after- any of the VestibuGlide sessions.

Eye Movements

Infants often increased their eye movements during the stimulus conditions. These movements consisted of vertical, horizontal, and saccade-like eye movements. The increase in eye movements associated with the stimulus conditions was not surprising considering the rich

connectivity between the vestibular apparatus and the eye musculature, specifically the extrinsic eye muscles (Cohen, 1974; Precht, 1977; Raphan, 1985; Robinson, 1985).

Vestibular stimulation has been shown to encourage later emerging sensory modalities including more accurate visual and auditory pursuits (Korner, et al., 1975; Korner, et al., 1983; Neal, 1968). It is vital to follow these infants long-term and asses their visual and auditory pursuits compared to a cohort of control infants who did not receive the stimulus.

Infant State

Vestibular stimulation has a large influence over behavioral states (Balaban, 2002; Korner, et al., 1983; Kramer & Pierpont, 1976; White & Labarba, 1976). In fact, one study showed that vestibular stimulation reduced crying in normal and excessive criers (Elliot, et al., 1988). None of the infants cried during the VestibuGlide stimulus. Infants were often in a quiet-to-active alert state throughout the stimulus and maintained their active-alert state post-gliding stimulus, which is the ideal state for feeding.

The VestibuGlide stimulus provided infants with the opportunity to reach an active-alert state. Often, infants in the study were placed on cue-based feeding. This meant that prior to their feed; their nurse would look for feeding cues (e.g. rooting, infant state, etc.) and then either offer them a bottle or gavage feed based on these cues. Typically, as the infant was being fitted with the Respitrace™ bands, they would be in a drowsy state and if the nurse were to assess the feeding cues at this point, the infant would receive a gavage feed. However, after the VestibuGlide stimulus, these infants would show feeding-ready cues. This finding was consistent with another study that showed vestibular stimulation facilitated arousal following cessation of the intervention (White-Traut, Nelson, Silvestri, Cunningham, & Patel, 1997).

Gastric Emptying

Gastric motility and muscle tone are decreased and emptying time is delayed in preterm infants (Blackburn Tucker, 2007). Infants enrolled in the study often completed gastric emptying during- or soon after- the VestibuGlide stimulus. An infant's body position affects gastric emptying (Cohen, Mandel, Mimouni, Solovkin, & Dollberg, 2004; Victor, 1975). It is likely that the VestibuGlide stimulation has a positive effect on gastric emptying by increasing gastric motility.

Parental Response to the VestibuGlide System

Parents were asked to describe the experience of having their infant enrolled in the VestibuGlide study and if they thought s/he enjoyed it?

The parents of infant W7 stated, "Our daughter was enrolled in the VestibuGlide program while staying in the NICU. While we had some early hesitations about enrolling our child into a research program these worries were quickly erased when we saw the 'chair' and the care that Emily took with our daughter. Our daughter seemed to enjoy the interactions and she still completed all of her feedings during this time. Overall, the program was terrific and we would happily repeat the experience."

The parents of infant W9 were initially anxious that the VestibuGlide stimulus was making their infant too tired for his feeds. This initial fatigue appeared to be more closely related to the infant completing his first bottle rather than the chair stimulus. After the initial hesitancy, the mom thought the chair stimulus was very beneficial and made the following statement: "The VestibuGlide study was very beneficial to my son. He was born 9 weeks premature making him 31 weeks at the time of birth, and they did not believe he would take a bottle or pacifier as soon

as he did. When his feedings increased his ability to finish his bottle declined. Once he started the glide study, he slowly began to finish more bottles. By day 6 of the study, his skills took off and he became more alert and continuously progressed in suck-swallow-breath techniques. My son physically enjoyed the study he was alert and maintained eye contact during his 15-minute glide session. The study also gave him the opportunity to be held more and receive more contact, which I feel helped him to stay awake better/longer during his afternoon feeds. I enjoyed watching the excitement on his face while the transitions of the chair stopped and started. I appreciate the study because I truly believe it made my son be available to leave the NICU sooner."

No parents responded negatively to the study. In fact, several parents purchased glider chairs to have at home to continue the gliding stimulus post-discharge.

Nursing Staff Response to the VestibuGlide System

Prior to the start of the study, the nursing staff was emailed a Microsoft PowerPoint presentation on the VestibuGlide system and informed that it would be coming soon to the NICU. Therefore, most of the nursing staff was aware that a new study was starting prior to data collection. However, it did take a few months before the nursing staff was familiar with the entire gliding protocol.

Over the five months of data collection, nurses would request that the infants they were caring for be enrolled in the study. Nurses would report that they saw improvements in the VestibuGlide infants. One nurse, who has worked in the NICU for over 20 years, said the following: "The infants who were enrolled in the VestibuGlide study had no negative response to the study. From observation, they had a couple of days of adjustment to the motion, and then did

extremely well with feedings. Parents were pleased with the infant's positive response. Nursing staff positively participated and were pleased with the positive results."

Another nurse, who specializes in development, stated "I definitely think the babies and the families benefited from the study. The babies that were enrolled seemed calmer and more organized. Additionally, it appeared that these babies progressed more quickly, were more organized with feedings and were discharged sooner. The parents seemed so happy to see something additional that could be helpful to their babies, and all I saw were eager participants... Another benefit of the study is that it models to the parent a developmentally appropriate, gentle manner of interacting with their babe that presumably would continue at home.
I think your hypothesis makes a lot of sense from a developmental standpoint. Babies born early miss out on months or weeks of uterine nurturing, sound, motion and tactile feedback. The VestibuGlide is an opportunity to replace that loss and provide a nurturing environment."

Study Limitations

NICU Setting

The NICU is a very difficult setting to get a homogenous sample size due to the following variables: birth GA, birth weight, amount/ type of oxygen hx, PMA at the start of study, and co-morbidities that are often associated with preterm birth. Not only does the investigator deal with a heterogeneous sample but also various day-to-day variables that can influences the outcomes of a study. These include medical procedures (e.g., eye exams, circumcision, etc), various nursing practices, various levels of parental involvement, and various feeding schedules. All of these variables had the capability of altering how the infant responded to the VestibuGlide system. For example, if an infant took his/her entire bottle after the first

morning VestibuGlide session, he/she would likely be more fatigued for the next VestibuGlide session in the afternoon.

Sample Size:

This study had as sample size of 24 (12 VestibuGlide infants/12 preterm controls), which is an adequate number to start with for NICU research; however, in order for some of the dependent variables to reach significance, a bigger sample size is needed.

Control Group:

This study had no control group for the respiratory, SpO_2, pulse, and suck outcomes. In order to ensure that the main outcomes are due to the VestibuGlide stimulus and not the infants being held by a consistent caregiver 3x/10 days, a sham treatment paradigm needs to be created. In the sham treatment paradigm, infants would be fitted with the Respitrace™ bands and neonatal oxygen sensor, placed against the bobby pillow, offered the pacifier, and the glider chair would remain stationary for 15 minutes.

Parental Involvement:

While many parents were excited to enroll their infants in the study, several parents wanted to sit in the chair and glide their own infant. Unfortunately, this was not possible due to the need for constant monitoring of the infant's physiology and the need for tester consistency across babies and days. Eventually, having a more user-friendly VestibuGlide system—where the parents/caregivers can provide the gliding stimulus is ideal. Having the parents glide the infants will likely reduce stress and increase parent-child attachment. The next VestibuGlide

model should make it possible for parents to glide their own infants and be an active participant in their care.

Missing Data:

Missing data occurred throughout data collection due to hardware/software issues. Oftentimes the Respitrace™ bands would come apart and either needed to be re-sown or replaced. At one point, the Respitrace™ output cord needed to be re-soldered. With approximately one month left of data collection, the NELLCOR OxiMAX™ N-600 pulse oximeter sensor broke and the entire unit was replaced. A software bug occurred twice in the study where the chair skipped the first baseline condition and went immediately to stimulus 1.

Although there was occasionally missing data throughout data collection, the mixed model analysis used in this study ensured that missing data had no effect on other scores from that same subject.

Stomach Contents and VestibuGlide Movement:

As the infants were glided, their stomach contents were also being accelerated. Because the stomach is a bolus-filled chamber, the inertial forces exerted by the stomach contents could possibly account for some small portion of the kinematic signals sampled during respiration.

Length of the Baseline:

Power spectrum analysis revealed that the infant's stimulus breathing persisted well into the subsequent one-minute baseline condition. This means that the post-stimulus baseline conditions are not long enough to get a true baseline condition measure—where the infant goes

back to his/her optimal breathing rate. Another study needs to be completed to assess the length of persistence and then modify the time of the baseline accordingly.

VestibuGlide System and Other NICU Populations

Knowledge of chest wall modulation in response to linear acceleration is critical for disease/illness prevention. Considering that the VestibuGlide system is capable of modifying the rCPG and increasing oxygen saturation during the stimulus conditions, it would likely benefits many populations in the NICU, including respiratory distress syndrome (RDS) and chronic lung disease (CLD) infants.

Infants with RDS and CLD have had invasive oxygen therapies trussed to the face that alter the expected range of sensory experiences necessary for well-integrated to/from the rCPG and sCPG. Using the VestibuGlide system with these populations will likely enhance their respiratory/suck patterning and oxygen saturation.

Future VestibuGlide Studies

A subsequent study to this dissertation project would be to increase the sample size, focus on only few of the salient stimulus conditions (e.g., stimuli 2, 6, and 7), and increase the time of the baseline conditions.

It is necessary to have one- and three- year follow up studies with the VestibuGlide infants. These follow up studies will assess speech-language, cognition, and motor ability. Additional tests including vision, auditory, vestibular-ocular reflex (VOR), and vestibular evoked myogenic potential testing (Vemp) would show the long-term effects of vestibular stimulation.

Pairing the VestibuGlide stimulation with other potent forms of sensory stimulation, such as the NTrainer™ stimulus, auditory, and/or olfactory cues, will provide potent multi-modal stimulation to the infant. Multi-modal stimulation often results in neural facilitation/summation; therefore, it is likely that multi-modal forms of sensory stimulation increase the behavioral outcomes (respiratory patterning, sucking, feeding, and speech skills) above and beyond only stimulating one sensory system.

Examining the link between the vestibular apparatus and the activity patterns of the masseter and rectus abdominis muscles is a natural next step. This will be accomplished by placing surface EMG electrodes on the infant's masseter and rectus abdominis muscles and recording muscle activation pre-, during-, and post- the VestibuGlide stimulus. This experiment will reveal more details on the connectivity between the vestibular apparatus and the masseter muscles as well as further explore the relation between vestibular stimulation and gastric emptying.

Examine if the VestibuGlide stimulus reduces stress level in the infant by measuring salivary cortisol levels pre-, during-, and post- VestibuGlide stimulus. It would be beneficial to provide the infant's parents with a stress level survey to examine if having their infant enrolled in the study reduces their stress level as well. It is hypothesized that the VestibuGlide system reduces infant and parent stress levels.

CONCLUSIONS

Results of this study increased our understanding of the salient operating range for vestibular stimulation rate and acceleration and provided new information on the role linear acceleration plays in modifying the rCPG. This information will be used to inform the

development of new therapeutic interventions aimed at enhancing chest wall control to support respiration and oral feeding in preterm infants. Overall, vestibular stimulation delivered to the preterm infants between 32 and 34 weeks PMA effectively modulates respiratory rate and resets the rCPG.

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APPENDIX

Stimulus Sequence

Stimulus Sequence 1	**Stimulus Sequence 2**	**Stimulus Sequence 3**	**Stimulus Sequence 4**	**Stimulus Sequence 5**	**Stimulus Sequence 6**	**Stimulus Sequence 7**	**Stimulus Sequence 8**
1	6	2	3	1	4	6	3
2	3	7	5	3	6	5	2
3	7	6	1	6	7	2	7
4	4	1	6	7	2	4	4
5	2	3	4	5	5	1	6
6	1	5	7	2	1	7	1
7	5	4	2	4	3	3	5

Stimulus Sequence 9	**Stimulus Sequence 10**	**Stimulus Sequence 11**	**Stimulus Sequence 12**	**Stimulus Sequence 13**	**Stimulus Sequence 14**	**Stimulus Sequence 15**
7	6	4	3	1	3	5
3	4	7	2	4	2	7
6	1	3	1	5	5	3
5	3	6	4	7	4	4
4	5	1	7	6	6	6
1	7	2	5	3	7	2
2	2	5	6	2	1	1