PACIFIER STIFFNESS ALTERS THE DYNAMICS OF THE SUCK CENTRAL PATTERN GENERATOR

BY

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Date Approved: April 13, 2007

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ABSTRACT

This study examined the effect of varying pacifier stiffness on non-nutritive suck (NNS) dynamics at the NICU follow-up clinic among infants born prematurely with and without a history of respiratory distress syndrome. Three types of Soothie™ silicone pacifiers used in the NICU were tested for materials stiffness, revealing the Super Soothie™ is 7 times stiffer. No significant between-subjects effects were found for the healthy control infants and the RDS infants. However, Repeated-measures MANOVA within-group subjects effects showed significant differences in NNS cycles/min, NNS amplitude, NNS bursts/min, and NNS cycle periods between the Soothie™ versus Super Soothie™ pacifiers. Infants modify the spatiotemporal output of their suck central pattern generator when presented with pacifiers of different mechanical properties.

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TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

Introduction:

Observation of infant's oromotor patterns during their NICU follow up visit revealed a pacifier preference between two different models of a popular silicone pacifier which have identical mold profile geometries and each has an oral displacement volume of 4 cc. There was a tendency for infants to spit out the blue Super Soothie™ pacifier and infants who did retain the pacifier and latch did not appear to suck in a burst-pause pattern. On the other hand, infants presented with the green Soothie™ silicone pacifier appeared to enjoy the experience and demonstrated the highly organized burst-pause pattern associated with non-nutritive suck. Subjectively, the blue Super Soothie™ pacifier felt stiffer than the green Soothie™ pacifier; however, no objective data on materials stiffness was available from the manufacturer (Children's Medical Ventures, Inc). These observations at the NICU follow-up clinic prompted the following questions: What is the mechanical stiffness of these two popular silicone pacifiers? If significant differences exist in the mechanical properties of the two pacifiers, does this affect infant's preference and alter the central pattern generator for suck (sCPG)?

Non-nutritive suck (NNS) has been widely studied; however, few researchers have examined the physical properties of pacifier nipples such as size and thickness, and none have examined the effects of pacifier stiffness on the sCPG patterning. Given the sensitivity of the sCPG to afferent inputs, it is hypothesized that varying pacifier stiffness will alter the spatiotemporal organization and patterning of the sCPG in human infants.

Background:

Central pattern generators

Three basic forms of neural circuits (dedicated circuits, distributed circuits, reorganizing circuits) produce patterned output (Westberg, Clavelou, Sandstrom & Lund, 1998). Specific to this study, reorganizing circuits associated with ororhythmic activity will be examined closely. Reorganizing circuits generate different patterns when the effectiveness of synaptic connections between members of the total population of neurons changes (Barlow & Estep, 2006). An important concept of these circuits is that not all neurons take part in the full repertoire of behaviors generated by the entire population (Barlow & Estep, 2006). This is just one of the features that characterize CPGs. Consisting primarily of interneurons, CPGs produce a variety of rhythmic motor patterns (ex: walking, breathing, flying, swimming, sucking) in the absence of sensory or descending inputs which conveys specific timing information for motor patterning (Marder & Bucher, 2001). CPGs are found in the cerebral cortex, brainstem, and spinal cord, and generally direct their output to lower motor neurons (LMNs) (Barlow & Estep, 2006). CPGs range from most basic rhythmic movements including respiratory CPGs, which are active throughout life but modulated with changing metabolic demands and further modified during task demands of speech breathing, (Grillner, 2003) to CPGs that are active presumably during a critical period, like the sCPG. Critical Periods are vulnerable epochs in development where the individual is particularly sensitive to harmful external conditions (Jacobsen, 1978). Thus, there is heightened sensitivity to external stimulation. If an individual does not obtain the appropriate stimuli during this period, it may never develop fully.

Suck central pattern generator (sCPG). The neural substrate that regulates the ororythmic motor pattern for suck is driven by a neuronal network called the suck central pattern generator (sCPG) as shown in Figure 1. The sCPG consists of a bilateral circuit of interneurons located in the brainstem reticular formation (Iriki, Nozaki & Nakamura, 1988; Finan & Barlow, 1998). Knowledge of the neural substrate involved in the production of ororythmic motor patterns has been revealed primarily through animal studies. Brain transection studies from an intact guinea pig reveal that the circuitry necessary for production of rhythmic oral-motor movements is located between the trigeminal motor nucleus and the facial nucleus (Chandler & Tal, 1986; Nozaki, Iriki & Nakamura, 1986). In an effort to determine the minimum circuitry necessary to produce rhythmic oral-motor activity, an *in vitro* isolated brainstem was examined from neonatal rat (Tanaka, Kogo, Chandler & Matsuya, 1999). In this study oral-motor activity was recorded from the motor branch of trigeminal by utilizing excitatory amino acid agonists. This study found that the interneurons that compose the rhythm-generating circuits (last-order interneurons and local interneurons) have intrinsic burst generating capabilities (Tanaka et al., 1999; Del Negro, Hsiao, Garfinkel & Chandler, 1998). This study also found that there are separate rythmogenerating circuits that exist within each half of the rostral brainstem and that these circuits are tonically inhibited from lower brainstem sites (Tanaka et al., 1999). Thus, utilizing transection can disinhibit the rhythm generating circuits (Tanaka et al., 1999) revealing that descending inputs play a modulating role in oral rhythmic generation (Barlow & Estep, 2006).

In neonatal guinea pigs, the pontomedullary sCPG is thought to receive descending neuromodulatory inputs from a neocortical region known as the cortical sucking area (CSA) (Iriki, Nozaki & Nakamura, 1988; Nozaki, Iriki & Nakamura, 1986). The CSA has been studied in animal models and further research is required in human studies to match suck to a specific neocortical region. The sCPG is capable of being modulated by descending cortical inputs and sensory signals from the periphery.

Sensory input and its effects on CPGs. Somatic reflexes in the brainstem supply the nervous system with simple patterns of coordination which can be activated by sensory stimuli and descending signals from cerebral cortex (Barlow, Dusick, Finan, Biswas, Coltart & Flaherty, 2000). Sensory signals provided by mechanoreceptors and proprioceptors are utilized to modulate the activity of various CPGs in the mammalian nervous system.

Some sensory experiences begin *in utero* where there are some spontaneous rhythmic movements present before they are needed for the behavior to occur. These early movements are considered important for circuit formation, early pathfinding decisions and cues, terminal phase of motor axon guidance, synaptic tuning and refinement within a nuclear target, and expression of neuronal guidance molecules in locomotor CPGs (Hanson & Landmesser, 2004). This supports the idea of introducing therapeutic interventions early (such as NNS) to restore or develop patterned neural activity when faced with sensory deprivation and restricted motor activity.

Perioral sensory inputs and the sCPG. While sucking on a pacifier, a stream of sensory cues from cutaneous and deep afferents serve to refine the timing and magnitude of the efferent code delivered to lower motor neurons (LMNs) (Barlow & Estep, 2006). The lip vermilion and the tip of the tongue are areas with high densities of low-threshold, rapidly conducting mechanoreceptors and are composed primarily of slowly adapting mechanoreceptors and some rapidly adapting primary afferents (Trulsson & Essick, 2004). Tongue mechanoreceptors have well defined receptive fields and adapt quickly to maintain tissue deformation (Trulsson & Essick, 2004). These oral mechanoreceptors encode important information which is used to modulate sCPG output. This form of neural adaptation plays a critical role in ororythmic behaviors, and is important in the reconfiguration of the sCPG to meet changing task dynamics (Barlow & Finan, 1996). Trigeminal sensory flow modulates the sCPG by fine tuning the sensitivity of orofacial reflexes (Barlow & Estep, 2006). Unexpected disturbances or changes to the environment, such as a stiffer pacifier, is ultimately encoded by trigeminal primary afferents and play a key role in modification of lip and jaw movements for ororhythmic activity (Lund & Kolta, 2006a).

Experience plays a vital role in the sCPG. Experience plays a significant role in modulating sensory signals that influence sCPGs (Estep & Barlow, 2007, under review *Dev Med Child Neurol*; Barlow, Finan & Park, 2004). Frequent exposure to patterned orosensory events generates neural activity which in turn is hypothesized to exert trophic effects on the formation and strengthening of central projections underlying orofacial control (Barlow & Estep, 2006). It has been shown that rats reared in a restricted environment have significantly impaired dendritic development of Purkinje cells, which are a class of GABAergic neurons located in the cerebellum (Pascual, Hervias, Toha, Valero & Figuero, 1998). The reduction of sensory inputs, due to the restricted environment, may produce an imbalance in neurotransmitters which during a critical period may act as a trophic agent (Pascual et al., 1998). Effects of enriched sensorimotor experiences in rats reveal increased dendritic elongation in motor and visual cerebrocortical neurons (Pascual & Figuero, 1996). The impact of sensorimotor manipulation mainly affects immature cortical motor neurons (Pascual & Figuero, 1996). The immature state of neurons is ideal for neural plasticity because the dendrites are more responsive to various environmental stimulations (Pascual & Figuero, 1996) which can result in drastic effects in the structure and function of the brain (Pascual, Fernandez, Ruiz & Kuljis, 1993). There are vast negative effects of environmental deprivation upon cortical differentiation during the early postnatal period, thus environmental enrichment during early life can be very beneficial (Pascual et al., 1996). Therefore, the more experience and exposure to stimuli to the oral mechanism, the more cohesive the neural projections are in the central nervous system (CNS).

Nonnutritive suck (NNS)

The temporal NNS pattern is unique. The nonnutritive suck (NNS) occurs at a frequency of approximately 2 Hz and is organized into bursts, consisting of 6-12 suck cycles, separated by pause periods as shown in Figure 2 (Wolff, 1968; Finan & Barlow, 1996). During NNS, the infant incorporates the burst-pause pattern in accordance with respiration (Goldson, 1987). NNS has a characteristic pattern and is principally controlled by an internuncial brainstem circuit known as the sCPG, therefore, a deviant NNS can provide insight into the CNS.

Maturation and NNS

"Suckling, maintaining the airway, and responding to tactual stimuli are 'mature' neonatal oral functions (Bosma, 1970)." Sucking on a pacifier is one of the first oromotor tasks an infant is asked to perform soon after birth. An infant with a less mature or damaged CNS will consequently have a less developed suck pattern. Sucking ability is presumed to reflect integrity of the central nervous system (CNS) (Mizuno & Ueda, 2005; Barlow & Estep, 2006). A healthy infant begins to suck *in utero* as early as 15-18 weeks gestational age (GA) (Humphrey, 1964; Miller, Sonies, & Macedonia, 2003). As the infant matures, so does the temporal organization of the suck. Sucking becomes more organized and starts to follow the typical burst-pause pattern around 32 weeks GA (Pickler & Reyna, 2004; Wolff, 1968). By 37 weeks GA, the infant is expected to suck at the same rate as a full term infant (Wolff, 1968).

NNS in preterm population compared to full term population.

Preterm infants typically have immature sucking skills (Lau & Schanler, 2000), delayed patterning (Tamura, Horikawa & Yoshida, 1996; Estep & Barlow, 2007, under review *Dev Med Child Neurol*), and generate fewer sucks characterized by shorter bursts, more pauses between bursts, and a lower suck pressure when compared to full term infants (Medoff-Cooper, Weininger & Zukowsky, 1989). Infants who experienced distress exhibit greater variability in sucking patterns when compared to healthy infants (Cowett, Lipsitt, Vohr & Oh, 1978; Dreier & Wolff, 1972; Estep & Barlow, 2007, under review *Dev Med Child Neurol*; Stumm, Barlow et al., 2006, under review *J Clinical Nursing*). This is highlighted by the discrepancy of sick preterm infants' suck abilities compared to healthy term neonate suck abilities. The deviant suck pattern evident among premature infants may be exacerbated by the rate limiting NICU environment.

Noxious stimuli to the perioral region

Premature infants are often exposed to medical devices such as orotracheal tubes, continuous positive airway pressure (CPAP), high-frequency ventilators, nasogastric tubes, orogastric tube tubes, and the tape that holds these devices in place. This alters the expected range of sensory experiences and in some cases, severely restricts orofacial movements resulting in sensorimotor deprivation for the infant. The duration of this maladaptive exposure ranges from a few days to a few months depending on the stability and co-morbidities of the preterm infant. Recurrent oral suctioning, feeding tube placement, tape removal and placement, and other noxious stimuli can irritate sensitive and fragile perioral skin. This can lead to tactile defensiveness and delay the transition to oral feeds presumably because the infant has developed an aversion to oral stimulation and lacks the experience necessary to produce the stereotypic burst-pause pattern (Case-Smith, Cooper & Scala, 1989). Prolonged orotracheal intubation creates a risk for disordered sucking motor patterns (Bier, Ferguson, Cho, Oh & Vohr, 1993; Barlow, Dusick, Finan, Biswas, Coltart & Flaherty, 2000). Premature infants are receiving this noxious stimulus during a critical period where sensorimotor experiences play a vital role in brain development.

RDS and NNS

Respiratory distress syndrome (RDS) is a developmental disorder that is commonly associated with preterm delivery and the more premature the infant, the greater the risk for developing RDS (Avery, 1994). RDS can frequently develop in connection with complications to the CNS such as hemorrhage, patent ductus arteriosus (PDA), air leak and infection (Avery, 1994). These additional CNS insults can attribute to prolonged oxygen requirements. Premature infants who present with RDS typically have poor air exchange and use the accessory muscles for breathe support, nasal flaring, and abnormal patterns of respiration (Avery, 1994). A common treatment for RDS is surfactant replacement therapy, which is provided through an endotracheal tube to allow the inner surface of the lungs to expand properly (Avery, 1994). Many infants with respiratory distress syndrome (RDS) have extensive oxygen histories, often requiring more than 30 days of oxygen therapy via a combination of procedures, including intubation, CPAP, high-frequency ventilation, and nasal cannulation. RDS affects roughly 1% of pregnancies each year. RDS occurs in 60 percent of babies born at less than 28 weeks GA, 30 percent of those born at 28 to 34 weeks GA, and less than 5 percent of those born after 34 weeks GA (American Lung Association, 2006; Avery, 1994). During this period of oxygen dependency, the infant is restricted from autostimulation of the perioral sensorium (Estep & Barlow, 2007, under review *Dev Med Child Neurol).* Infants who experience NNS stimulation daily tend to develop organized sucking behaviors earlier (Bernbaum, Pereira, Watkinsm & Peckhanm, 1983). Consequently infants who lack daily NNS experience have a propensity toward an unorganized NNS pattern. An extended course of oxygen supplementation via intubation, CPAP, and nasal cannulation in infants diagnosed with RDS is associated with a significant decrease in NNS burst amplitude when compared to healthy preterm infants matched for birth age (Stumm, Barlow et al., 2006, under review *J Clinical Nursing*).

Neurological insult and NNS

Depending on the site of lesion, premature infants with a history of periventricular leukomalacia (PVL) or intraventricular hemorrhage (IVH) may show an aberrant or absent suck pattern. Damage to corticobulbar and/or central descending inputs from the neocortex may significantly affect the activity patterns of the sCPG. Recent research has shown that after injury (stroke) to the limb representation in primary motor cortex, post-injury behavioral experience plays a crucial role in mobilizing mechanisms of plasticity to modify the functional organization of the remaining intact cortical area to regain motor control (Nudo, Plautz & Frost, 2001). When considering the brain insults in the premature infant that affect orofacial motor control, the application of neurotherapeutic techniques which can facilitate ororhythmic activity during this critical period of development are essential.

NNS as a diagnostic tool

Sucking is an intricate sensorimotor behavior that can provide valuable information about the integrity of the CNS (Barlow, Finan, Park, 2004; Barlow & Estep, 2006; Mizuno & Ueda, 2005). The spatiotemporal patterning of the suck provides insight into minor CNS disturbances in infants who otherwise show no signs of neurological impairment (Dreier & Wolff, 1972). Thus, utilizing NNS as a diagnostic tool may provide the clinician with a useful index about the infants' CNS and its ability to adapt to diverse local environments. The NNS can also serve as an intervention tool to increase the amount and quality of oral stimulation provided to an infant.

State Regulation and NNS

Infants find the pacifier to be very soothing and take pleasure in the additional oromotor stimulation. When given the opportunity for NNS, the infant benefits immensely from not only the oral stimulation, but also because it improves behavioral state regulation (Kimble & Dempsey, 1992; Pickler, Frankel, Walsh & Thompson, 1999). Behavior maturation mirrors the underlying neurobiology of the infant brain (Parmalee & Stern, 1972). Premature infants typically have a harder time orienting to stimuli and spend more time in non-alert states (Davis & Thoman, 1987). Behavioral improvement in premature infants can lead to better outcomes by improving their neurologic and autonomic organization (Gorski, Davison & Brazelton, 1979). A more alert infant is able to respond to the environment and make the appropriate state modifications. The alert state is ideal for feeding and social interaction. When infants perform NNS prior to the feed, they are better able to maintain an alert quiet state that is essential to the feeding performance (Gill, Behnke, Conlon, McNeely & Anderson, 1988; McCain, 1992) and return to a quiet state sooner after the feeding (Pickler, Higgins & Crummette, 1992).

Since preterm infants are typically less alert, they are less apt to have a typical or satisfying parent-child interaction in the first months of life. Levy (1958) revealed that the state of the infant is a vital predictor of parent-child interaction. Parents interact more when their infant is alert. During presentation of a pacifier, the parent/caretaker is more likely to touch and talk to the infant thus increasing the amount of parent-child interaction. A parent/caretaker providing their preterm infant with a pacifier can be critical because of the already postponed parent-child attachment due to their lengthy hospital stay.

The Newborn Individualized Developmental Care and Assessment Program (NIDCAP, Als et al., 2004) was developed to increase parent-infant interaction and support the infant's development. The NIDCAP program was designed to imitate the support that the child gets in the womb; therefore, it reduces stressful environmental situations while increasing the positive soothing interactions for the infant. One accessory that was utilized with the experimental group included soft, specialized pacifiers. Preterm infants who received the NIDCAP intervention (which incorporated the parents, staff, and developmental specialist) had positive differences in motor systems and self-regulation as well as a number of neurobehavioral aspects involving state stability, intensity, and threshold of response when compared to those infants who did not receive the NIDCAP intervention (Als et al., 2004). Differences were seen in brain structure and brain function between the intervention group and control group (Als et al., 2004). Positive early experiences alter brain function and structure and parental/caretaker involvement in this process creates an enriched bond and promotes a healthy developmental outcome.

Oxygen Benefits and NNS

Another positive effect related to NNS is stable oxygen saturation (Kimble & Dempsey, 1992; Pickler, Frankel, Walsh & Thompson, 1996) and increased transcutaneous oxygen tension ($TcPO_2$) readings, which reflects the amount of oxygen in the bloodstream (Pinelli & Symington, 2000; Burroughs, Asonye, Anderson-Shanklin & Vidyasagar, 1973). Initial concerns about energy expenditure associated with NNS were offset by the positive effects of improved oxygenation associated with sCPG activity (Burroughs et al., 1981). Infants that are able to stabilize their oxygen saturation and increase their $TcPO_2$ are no longer in need of the invasive cannulations or intubations that generally limit infants from enjoying positive orosensory experiences.

Faster feeding and faster discharge as a result of NNS

Poorly developed feeding skills are often what keep premature infants in the hospital for prolonged periods of time, especially those with a history of RDS or brain insult (Comrie & Helm, 1997; Lau & Hurst, 1999; Barlow & Estep, 2006; Barlow & Finan, 2006; Estep & Barlow, 2007, under review *Dev Med Child Neurol*; Lau & Schanler, 2000). When infants experience pre-feeding NNS stimuli, they are more likely to initiate nutritive sucking (NS) faster and maintain the first NS activity for a longer period (Pickler, Frankel, Walsh & Thompson, 1996). Infants that are provided with the rich stimulation of NNS have been shown to be ready for the bottle earlier than other preterm infants and as a result are discharged from the hospital sooner (Segal, Prakash, Gupta, Mohan & Anand, 1990). This is because oral feeding performance has been shown to improve as infants' sucking skills mature (Lau, 1992). Rocha et al., (2006) examined the efficacy of sensory-motor–oral stimulation and NNS in low birth weight infants. They found that infants provided with the additional oral stimulation were able to begin oral diet 8.2 days earlier, suspend the use of gavage 8.6 days earlier, and were discharged from the hospital 10.4 days earlier than the control group of preterm infants that received no additional oral stimulation. Furthermore, NNS encourages an earlier readiness for bottle feeding and enhanced weight gain leading to a decreased length of stay in the NICU by several days (Field, Ignatoff, Stringer, Brennan, Greenberg, Wildmayer & Anderson, 1982; Pinelli & Symington, 2000; Segal, Prakash, Gupta, Mohan & Anand, 1990; Rocha, Moreira, Pimenta, Ramos & Lucena, 2006). Reducing the length of the hospital stay for premature infants saves thousands of dollars per day (~ $4,000/day) for the families and the hospital. When infants leave the hospital earlier it decreases the amount of maternal deprivation and provides the nursing staff with less of a workload. The utilization of NNS as an intervention tool for preterm infants is regarded as a favorable clinical option.

Rationale and Hypotheses

One of the earliest forms of external stimulation that can influence the development and performance of an infant's suck is their pacifier. Infants can encode sensory information about their pacifier and use this experience to develop the ororhythmic patterns of suck. Since the pacifier plays such an integral role in early oromotor stimulation, a key issue to consider is the type of pacifier being used and its effect on the sCPG. A sCPG which operates 'open loop' may show little or no modification with changes in the 'local environment' or pacifier type. However, if the sCPG is responsive to changes in the local environment, then stiffness modifications to the pacifier should induce motor reorganization of the sCPG.

The physical properties of the object (finger, pacifier, breast, etc) placed in a newborn's mouth has noticeable effects on suck patterning. Intraoral stimulation is a significant determinant of sucking development in the newborn. Characteristics of the nipple, such as size, shape, and compressibility, have been shown to influence the frequency of NNS (Lipsitt & Kaye, 1965; Dubignon & Campbell, 1968). In 1968, Wolff found qualitatively that the amplitude of sucking varied with pacifier stiffness.

However, rhythmic features were not influenced by the variation in the shape of the nipple. More research has been completed examining the effects of various pacifiers/nipples on feeding or NS than on NNS.

Infants that are poor feeders might be dealing with a poor pattern of intraoral stimulation (Dubignon & Campbell, 1968). In essence, an infant's poor sucking/feeding performance may be due to the nipple type or pacifier being utilized. Nipple size has been shown to impact NS and in general, infants responded less frequently to a larger nipple (Christensen, Dubignon & Campbell, 1976). This study examined the effects of a larger nipple during feeding and did not examine the effects of a large nipple on NNS. Nowak, Smith, and Erenberg (1994) utilized real-time ultrasonography to visualize four types of artificial feeding nipples *in vivo* during feeding and then compared that with the human nipple during feeding. They found that the four different types of nipples exhibited significantly less elastic deformation than the human nipple. In this study the authors inaccurately utilize the term elasticity. They report that the human nipple is more elastic than the other types of nipples. It is more likely the case that the human nipple is more compliant and thus less elastic, as elasticity is defined as stress divided by strain.

Pacifiers have become an essential part of early oromotor stimulation in preterm infants. However, little is known about the physical properties of pacifiers nor their effect on infants' NNS and the sCPG. One key factor to consider is the stiffness of the silicone pacifier and resultant effects on the infant's sCPG. This study was designed to determine the mechanical stiffness of three popular silicone pacifiers available in most NICUs today and how varying pacifier stiffness on healthy and respiratory distress syndrome (RDS) infants will alter the infant's sCPG.

Given the equivalent bulb volumes for the Soothie™ and Super Soothie™ pacifier, it is hypothesized that preterm infants using the pacifier with the greater stiffness will manifest NNS cycles with decreased amplitude, reduced NNS Cycles/Burst, and reduced NNS Cycles/Minute. It is hypothesized that healthy control infants and RDS infants will show significantly different NNS patterning effects among the 3 dependent measures.

Experiment One: TESTING PACIFIER STIFFNESS

Three popular one-piece silicone pacifiers used in the NICU, including the Wee Soothie™, Soothie™, and Super Soothie™ (Children's Medical Ventures, Inc), were measured for materials stiffness using a linear servo motor programmed to impose step-wise nipple compression in a repeated measures design (Figure 3). Each pacifier was coupled to a Delrin pacifier receiver, vented to atmosphere at room temperature (~72 degrees F), and securely mounted in a vise with the silicone nipple oriented up and positioned against a stationary platform on one side. A custom linear servo motor, operating under position feedback, was positioned on the opposite side of the nipple cylinder and programmed to impose an 8-step sequential compression of the silicone nipple. The resultant force (Newtons) and displacement (millimeters) generated by the linear motor against the pacifier were digitized in real time at 100 samples per second at 16-bits of vertical resolution (+/- 10 volt range). The change in force was divided by the change in displacement at each compression step, $(\Delta\mathbf{F}/\Delta\mathbf{X})_{\text{STEPS 1 thru 7}}$. The resulting stiffness coefficients were plotted as a function of imposed compression (millimeters) (see Figure 4). Stiffness was measured at two locations on each pacifier type, including the cylinder and the nipple bulb.

Results

The results of this experiment revealed that the cylinder of the Super Soothie™ pacifier is approximately 7 times stiffer over the first millimeter of compression than the Wee Soothie™ or Soothie™ pacifiers shown in Figure 4. The Super Soothie™ yielded a stiffness value of nearly 6 N/mm following 1 mm of nipple compression, whereas, the stiffness coefficients for the Wee Soothie™ and Soothie™ pacifiers were only 0.8N/mm at similar compression. Under a full compression load, the difference in stiffness coefficients between the Super Soothie™ and the other two pacifiers is on the order of 7X.

Experiment Two: Pacifier Preference

The study of the effects of pacifier stiffness on the dynamics of the sCPG was completed on 27 infants (11 female:16 male, $\mathbf{MEAN}_{\text{age}}$ = 4 months, 5 days) seen at the University of Kansas Medical Center NICU follow-up Clinic and the Stormont-Vail Regional Medical Center Premature Follow-up Clinic (Table 1). Seven of the 27 infants were healthy controls with an average birth gestational age of 30 weeks and 6 days, average corrected age of 5 months and 28 days at the Follow-up Clinic, and an average of 1.14 days on oxygen. The remaining twenty infants had a history of RDS with an average birth gestational age of 28 weeks and 5 days, average corrected age of 3 months and 4 days at the Follow-up Clinic, and an average of 39.9 days on oxygen. This study was approved by the human subjects committees of the University of Kansas Medical Center (Kansas City, KS) and Stormont-Vail Regional Medical Center (Topeka, KS) and informed consent was obtained from the parents prior to the study.

NNS dynamics were sampled real time from a group of premature infants during their follow-up visits using the ACTIFIER II technology (Figure 5). All pacifiers and receivers were gas sterilized with ethylene oxide (E_tO). Presentation order for pacifier type (Soothie™ versus Super Soothie™) was counterbalanced and a 2-minute sample of NNS behavior was digitized for each infant. Testing was typically completed 10 minutes prior to the NICU Follow-up Clinic ensuring that the family had ample time for the study and was not late for the clinic. During testing, the infant was held in a supportive position either by an experienced member of the Communication Neuroscience Laboratory or the infant's caretaker. The family was provided with a ten dollar gift certificate to Babies "R" Us in appreciation for their time and commitment to the study. Five dependent variables were calculated from 2-minute digital records of ororhythmic activity for each pacifier type using the software algorithm NEOSUCK *RT*. These included Mean NNS Cycle Amplitude (cmH_2O), Mean NNS Cycle Periods (ms), NNS Cycles/Burst, and minute-rates for NNS Burst and NNS Cycle production.

Results

Infant's reorganize their sCPG when faced with silicone pacifiers of varying mechanical properties. An example of this reorganization in NNS is shown in Figure 6. The panels on the left show high levels of NNS behavior for infant T45, an RDS baby tested at 2 months and 23 days corrected age, when presented with the Soothie™ pacifier. The 2 Hz cycling of nipple compression occurs at nearly 40 cmH2O. Switching to the stiffer Super Soothie™ pacifier results in a greatly diminished ororhythmic pattern characterized by low-amplitude, short duration NNS bursts. On average over the 2 minute analysis window, this baby's NNS bursts were only 5 cycles in length compared to the 13 cycles per burst produced on the more compliant Soothie™ pacifier. A new graphical display was developed, termed the NNS spider plot, in order to represent the cumulative NNS burst activity over the 2 minute analysis window. Sample NNS spider plots as a function of the two pacifier types are given for two additional infants in Figure 7. For infant T98, an RDS infant tested at 3 months and 2 days corrected age, the Soothie™ pacifier spider plot reveals a performance total of 19 NNS bursts in 2 minutes with an average amplitude of 20.36 cmH_20, whereas oromotor performance on the Super Soothie™ pacifier reveals 12 NNS burst in 2 minutes at an average amplitude of 6.38 cmH_20. In the lower half of Figure 7, oromotor performance for infant T36 (RDS infant tested at 2 months and 24 days corrected age) when using the Soothie™ pacifier shows that 12 NNS bursts were produced at an average amplitude of 35.31 cmH_20. This is in sharp contrast to the Super Soothie™ pacifier spider plots yielding just 8 NNS burst in 2 minutes at an average amplitude of 7.80 cmH_20. These sample results of oromotor output clearly illustrate the negative performance effect with use of the stiffer Super Soothie™ pacifier.

Repeated-measures MANOVA within-group subjects effects (v. SPSS 14.0) completed on the five dependent variables revealed several significant differences as a function of pacifier type, however, there was no statistical difference between the control infants and the RDS infants, due in large part to the relatively small sample of control infants. The first dependent variable, NNS bursts/min was not significant [F(1,23)=.78, p =.386] with a Soothie™ mean of 5.69 (SE=0.538) bursts/min and a Super Soothie™ mean of 6.26 (SE=.801) bursts/min (Figure 8). Since NNS bursts/min was not a significant measure it shows that infants on both pacifiers initiated similar numbers of NNS burst events in a two minute sample.

NNS cycles/min was a significant main effect [F(1,23)=24.40, p=.0001] with oromotor output on the Soothie™ pacifier yielding an average 70.87 (SE=6.54) cycles/min but only 45.00 (SE=6.96) cycles/min on the Super Soothie™ pacifier (see Figure 9). These finding indicate while the infants are sucking on the Soothie™ pacifier they are able to generate more NNS cycles per minute than when sucking on the Super Soothie™ pacifier.

NNS mean amplitude (Figure 10) was also significantly different for pacifier type [F(1,23)=11.16, p=.003] with use of the Soothie™ yielding a mean of 26.31 (SE=2.36) cmH_20 and Super Soothie™ 15.80 (SE=2.58) cmH_20. While the infants were sucking on the less stiff pacifier, NNS amplitude was increased.

NNS cycles/burst (Figure 11) was significantly different for pacifier type [$F(1,23)=14.86$, $p=.001$] with a mean of 13.52 (SE=1.83) cycles/burst on the Soothie™ pacifier and a mean of 7.01 (SE=1.07) cycles/burst on the Super Soothie™ pacifier. Thus, the complexity of NNS burst structure is greater when infants use the more compliant Soothie™ pacifier.

NNS periods were different depending on pacifier type [$F(1,23)=6.94$, $p=.015$]. As shown in Figure 12, NNS cycle periods resulting from use of the Soothie pacifier averaged 486.84 (SE=10.64) ms and increased significantly when infants switched to the Super Soothie™ to a mean of 544.66 (SE=20.40) ms. This is an interesting finding since it demonstrates that the intrinsic properties and fine structure of the sCPG can be modified by changing the local environment.

No significant between-subjects effects were found for the healthy control infants and the RDS infants; however, a trend was seen between the two infant groups. Although not significant at the alpha level of 0.05, there appears to be an emergent trend on suck compression amplitude [$F(1,23)=3.67$, $p =.068$] with RDS infants showing a lower value of 17.43 (SE=2.02) cmH_20 compared to the healthy control who produced a mean NNS amplitude of 24.68 (SE=3.25) cmH_20. Thus, RDS infants have a tendency to produce a weaker suck.

Discussion

Children's Medical Ventures, the manufacturer of the silicone pacifiers utilized in this study, has never completed an objective examination of the mechanical properties of the pacifiers they sell. This is somewhat surprising since infant's preference will ultimately determine the success of their marketed product. After testing each pacifier for mechanical stiffness and finding that the Super Soothie™ pacifier is 7 times stiffer (over the first millimeter of compression) than the Wee Soothie™ or the Soothie™ pacifiers, it was hypothesized that the NNS dynamics would be altered because of the vastly different mechanical environments presented to the infant's orofacial system. Testing the pacifiers for their stiffness levels only confirmed the need for further, physiological study of sCPG dynamics in the developing infant. There are many different pacifier manufactures and little is known about the mechanical properties of these pacifiers they produce. Similarly, there are many manufacturers producing many different types of feeding nipples which are utilized during nutritive suck, and still, little is known about the mechanics of these nipples and their effect on nutritive suck dynamics. Christensen, Dubignon and Campbell (1976) found that infants respond less frequently to a large nipple but still did not include a complete description of the morphometrics and mechanical properties of this nipple. Mechanical properties are an important piece of information to attain from companies that sell pacifiers and nipples as these factors significantly impact ororhythmic patterning in infants.

The sCPG is an important neural network that is easily modified by local experience. The present study has clearly demonstrated that changing the stiffness environment significantly modifies the NNS dynamics along several dimensions. While sucking on the Soothie™ pacifier infants had more 'burst pause' patterning characterized by more NNS cycles/min and more NNS cycles/burst when compared to the Super Soothie™ pacifier. In 1968, Wolff described NNS as having 6-12 suck cycles per burst. In the present study, the mean NNS cycles/burst for the Soothie™ pacifier was 13.52 cycles/burst, whereas, use of the Super Soothie™ pacifier yielded a mean of 7.01 cycles/burst. Since the shape and displaced volume of the two pacifier nipples are virtually identical (~ 4 cc), we can safely state that the observed difference in ororhythmic output between the two pacifiers (Soothie™ vs. Super Soothie™) was due solely to the large difference in mechanical stiffness.

Wolff (1968) found that the amplitude of sucking varied with pacifier stiffness, however, this variation was not measured objectively. In the present study, NNS amplitude was found to vary with pacifier stiffness. It is logical to assume the infant will have reduced amplitude when sucking on a stiffer pacifier but the question still remains whether or not the same amount of muscle force was used by the infant on both pacifiers. The significant difference between the two pacifiers on amplitude represents the intraluminal pressure between the two pacifiers. More research needs to be done examine the relation between pacifier mechanics and infant applied compression force during suck to better understand the significance of the difference in mean NNS amplitude.

NNS production on the Super Soothie™ pacifier significantly increased within-burst suck cycle periods reflecting a change in the temporal characteristics of the sCPG. Previous research found that rhythmic features were not influenced by the variation in the shape of the nipple (Wolff, 1968). However, the present study reveals that the rhythmic features of NNS do change systematically when nipple stiffness is increased. The infants modulated their sCPG by slowing down the production of nipple compression cycles (increasing cycle periods by 11.87%) to adapt to the stiffer Super Soothie™ pacifier.

While the infant is sucking on the pacifier, mechanoreceptors in the perioral region are encoded by the trigeminal primary afferents which play a key role in modification of lip and jaw movement for ororythmic activity (Lund & Kolta, 2006a). A representation of four CPG circuits known to modulate the activity of orofacial systems along with their relative emergent periods is shown in Figure 13. Evidence from aborted fetuses and contemporary ultrasound imaging has shown the earliest sCPG activity at 15-18 weeks GA (Humprhey, 1964; Miller, Sonies, & Macedonia, 2003). Important features included in the schematic are afferent pathways which can transmit mechanosensory feedback to all levels of the neuraxis, descending neuromodulation, and the hypothesized parallel and shared resource of CPG sub-circuitry involved in the production of speech and voice. The various CPGs are composed of interneurons which effectively serve as premotor inputs to lower motor neurons (LMN), and are thus entry points into the final common pathway for orofacial and chest wall muscle systems active during speech and voice production. This affords the possibility that direct monosynaptic corticomotoneuronal projections, specific to primates and humans, can influence the firing pattern of LMN's directly. Lund and his colleagues have strongly suggested that collaterals and/or direct descending inputs are likely to take advantage of ororhythmic CPGs through circuit fractionation to achieve synergistic control of opening and closing muscles of the jaw and mouth (Lund & Kolta, 2006a). Mechanoreceptors in the perioral region likely encode salient sensory features from any given pacifier type and convey this rich stream of information along primary and lemniscal trigeminal projections to modulate the sCPG. Infants with a significant history of RDS may have reduced trigeminal lemniscal integration and sensory gating functions due to the negative effects of sensory deprivation and motor restriction associated with lung disease and mechanical ventilation. These alterations to the developing nervous system have been shown to negatively influence the pyramidal dendritic field development in motor cortex, and Purkinje cell dendritic arborization in the cerebellum of the rodent model (Pascual et al, 1993; Pascual & Figuero, 1996; Pascual et al., 1998)

It was hypothesized that the control infants would show a significant difference in the dependent variables when compared to the infants from the RDS group; however no significant group effect was found. This is mainly due to the reduced number of healthy control infants in the study. Univariate tests reveal that there is an effect between the two groups on some measures but that the overall effect did not reach statistical significance. Of experimental significance was the emergent difference between the two groups on the mean NNS amplitude dependent measure. The control infants had higher amplitudes on average than infants with RDS. This group difference could be due to the difference in muscle force that the infant is using on the two different pacifiers. Since experience plays a significant role in modulating sensory signals that influence sCPGs (Estep & Barlow, 2006) the healthy control infants most likely have more experience and thus generated greater compression forces on the stiffer pacifier. Control infants typically have a more appropriate set of perioral experiences which are presumed to lead to better pathway formation and synaptogenesis. Ultimately this provides the infant with a more secure sCPG network to support neural encoding of oromechanosensory events and improved sensorimotor reorganization in the presence of complex local environments to maintain and elaborate ororhythmic control.

In summary, the results of the present investigation show that young infants modify the spatiotemporal dynamics of the sCPG as a function of changes in local oral environment (i.e., changes in nipple stiffness with shape/size held constant). The activity encoded by peri- and intraoral mechanoreceptors is central to modulation of the sCPG in the time and frequency domain. Based on the current findings, pacifier/nipple manufacturers should pay special attention to the mechanical properties of their products and carefully monitor the influence of these properties on infant oromotor behavior. Further research in the area of pacifier mechanics and their effect on NNS dynamics and the spatiotemporal characteristics of the sCPG is needed.

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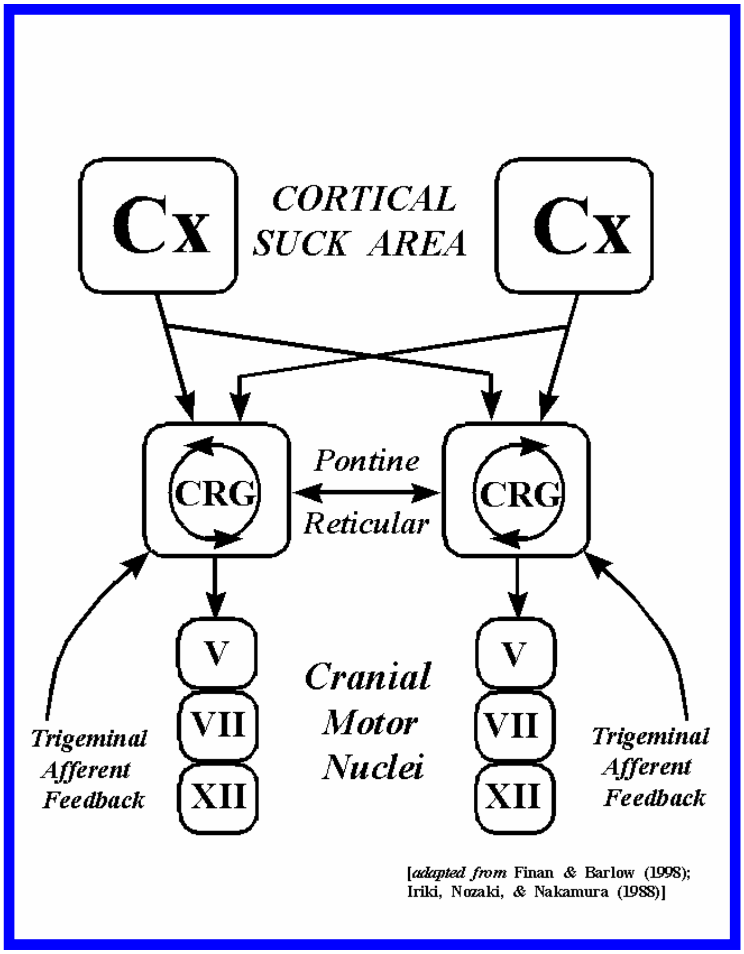


Figure 1. A schematic of the suck central pattern generating system in the pontine reticular formation in the mammalian brainstem with descending cortical inputs and peripheral feedback from trigeminal mechanoreceptive afferents (adapted from Finan & Barlow, 1988; Iriki, Nozaki, Nakamura, 1998). Cx – cerebral cortex, CRG – central rhythm generator circuit.

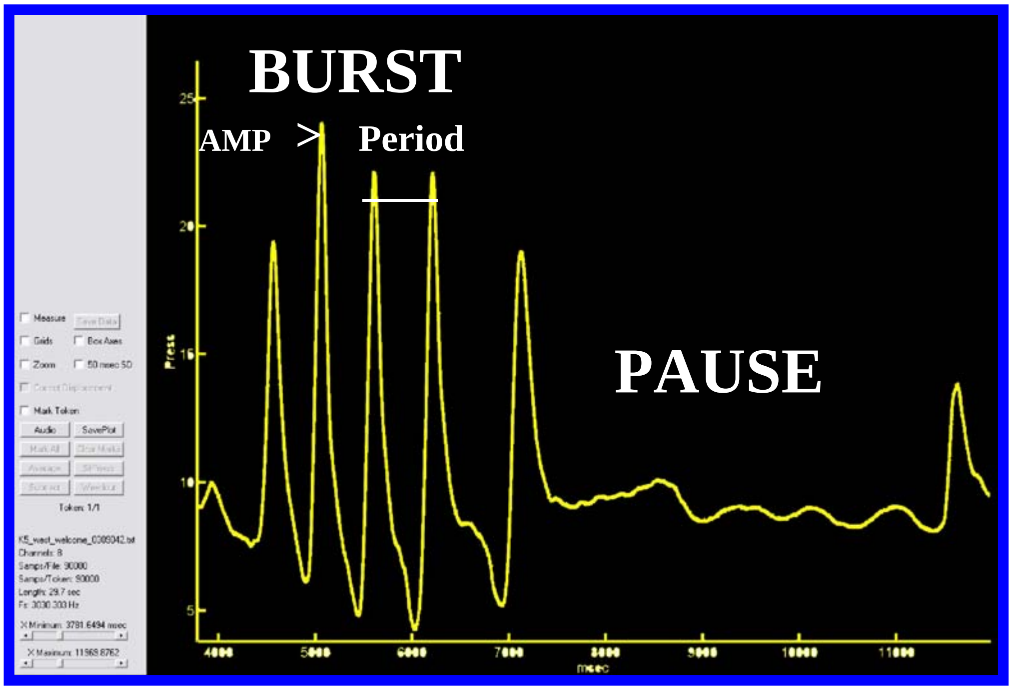


Figure 2. An example of NNS patterning characterized by the burst-pause relation.

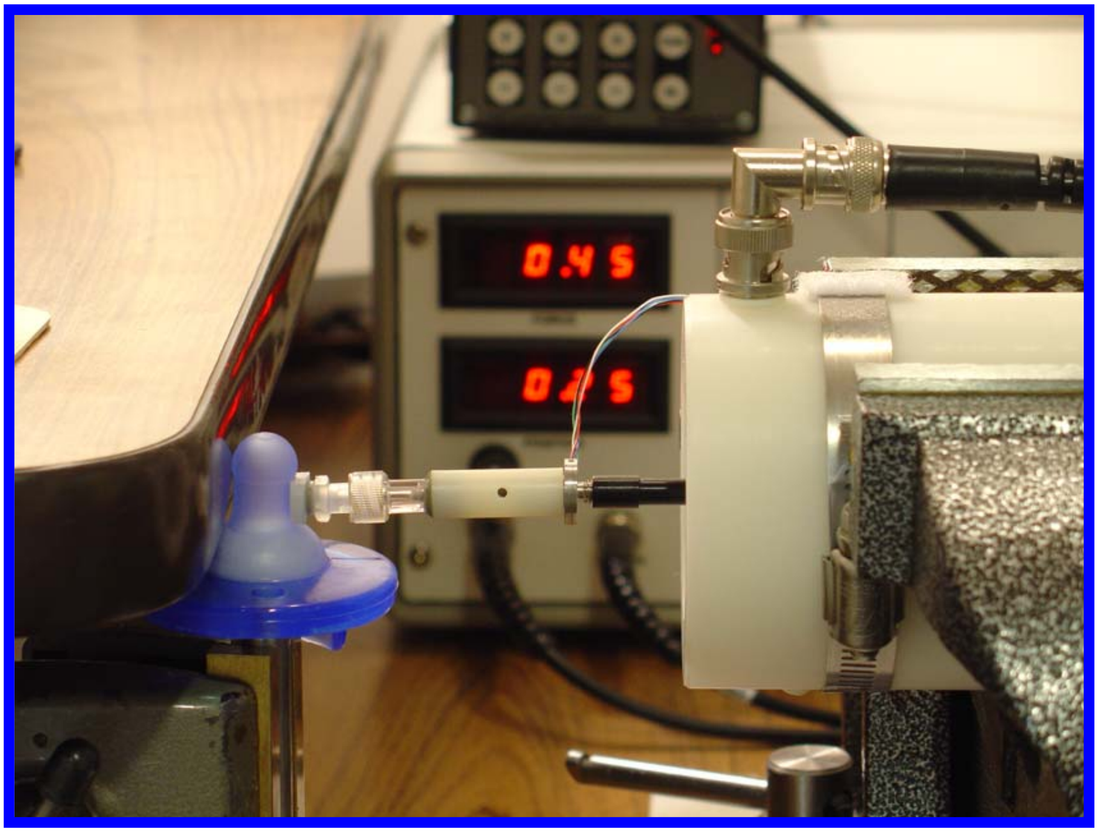


Figure 3. The linear servo motor that introduced step-wise nipple compressions in a repeated measures design to estimate materials stiffness of each pacifier type.

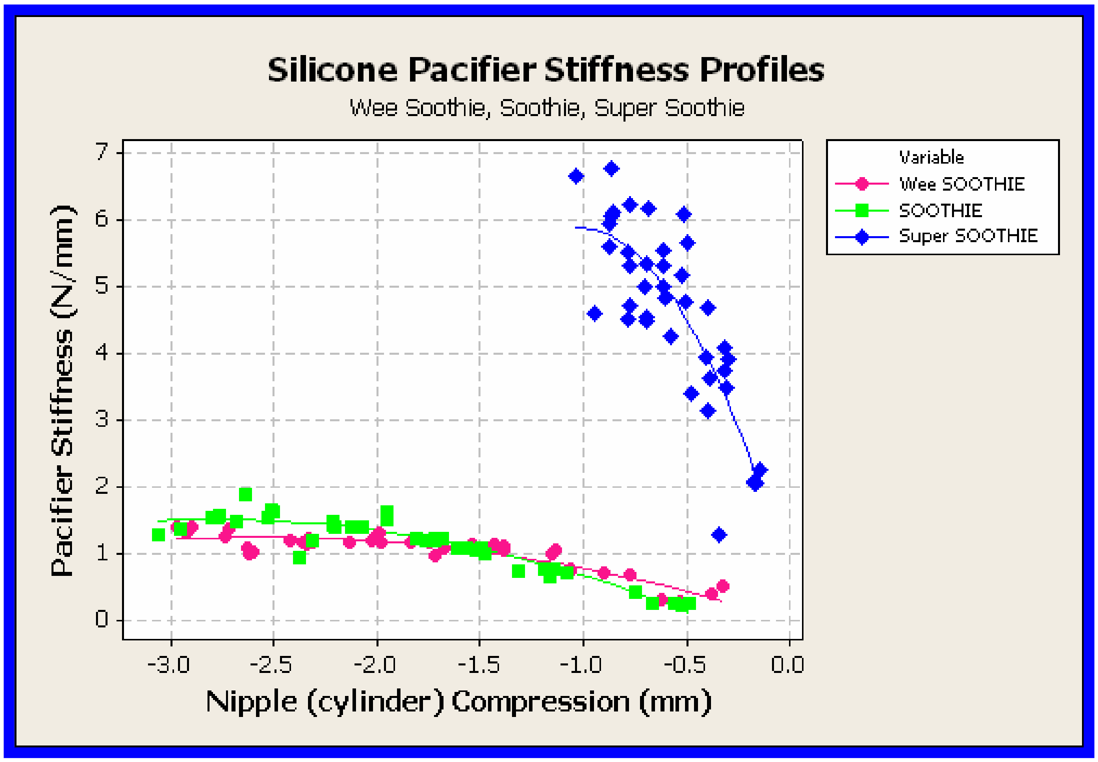


Figure 4. Automated signal processing completed in a custom MatLAB© digital signal processing routine to calculate pacifier stiffness.

Figure 5. An infant producing non-nutritive suck on the ACTIFIER and digitized in real time using *Neosuck RT* technology.

Same Baby, Different Pacifier

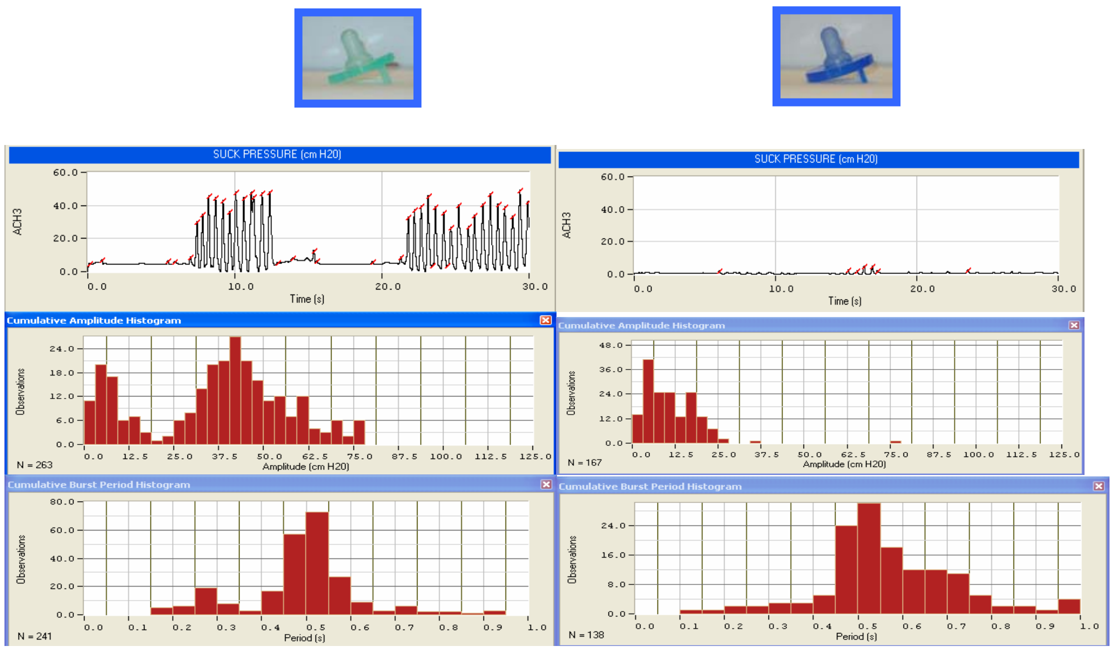
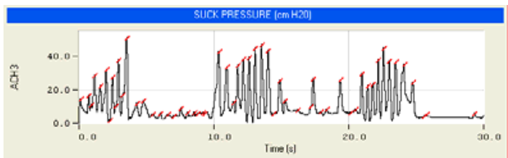


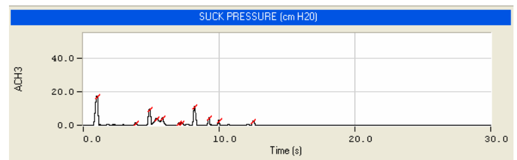
Figure 6. An example from *Neosuck RT* digital signal processing display of the same infant (T45) sucking on the Soothie™ (left) and Super Soothie™ (right) pacifiers. NNS amplitude and cycle period histograms are also given.

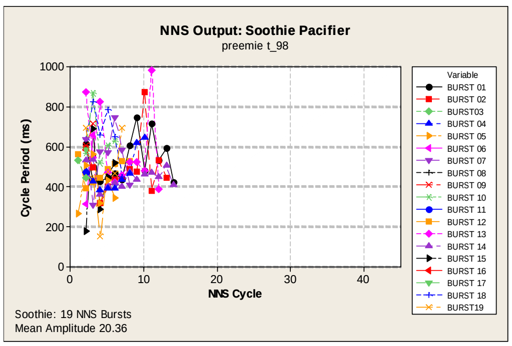
Soothie™

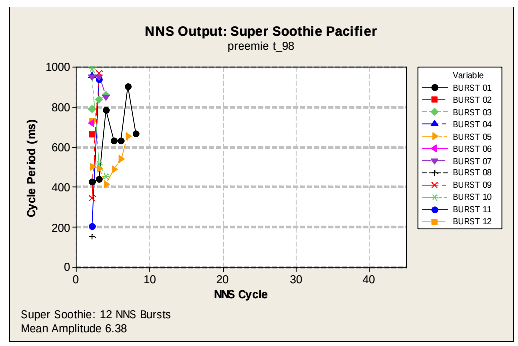
Super Soothie™

T98 (RDS)

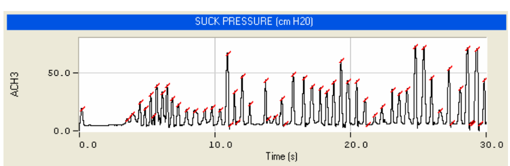


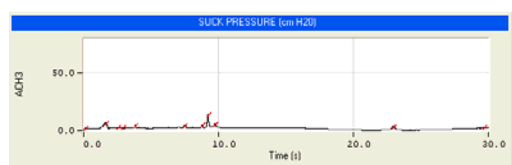


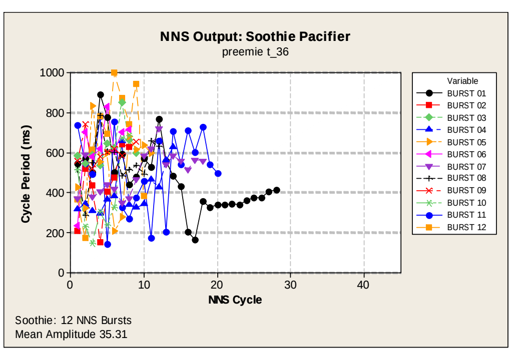




T36 (RDS)







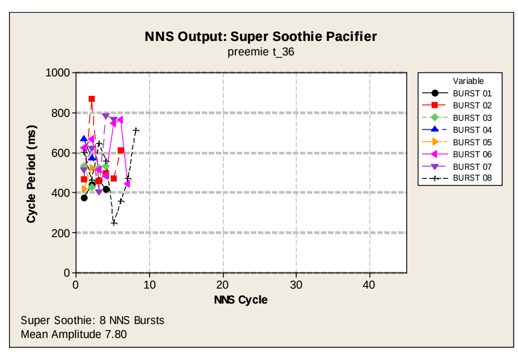


Figure 7. NNS Spider plot burst profiles for two different infants for each pacifier. A sample NNS compression waveform from *Neosuck RT* is given above each spider plot.

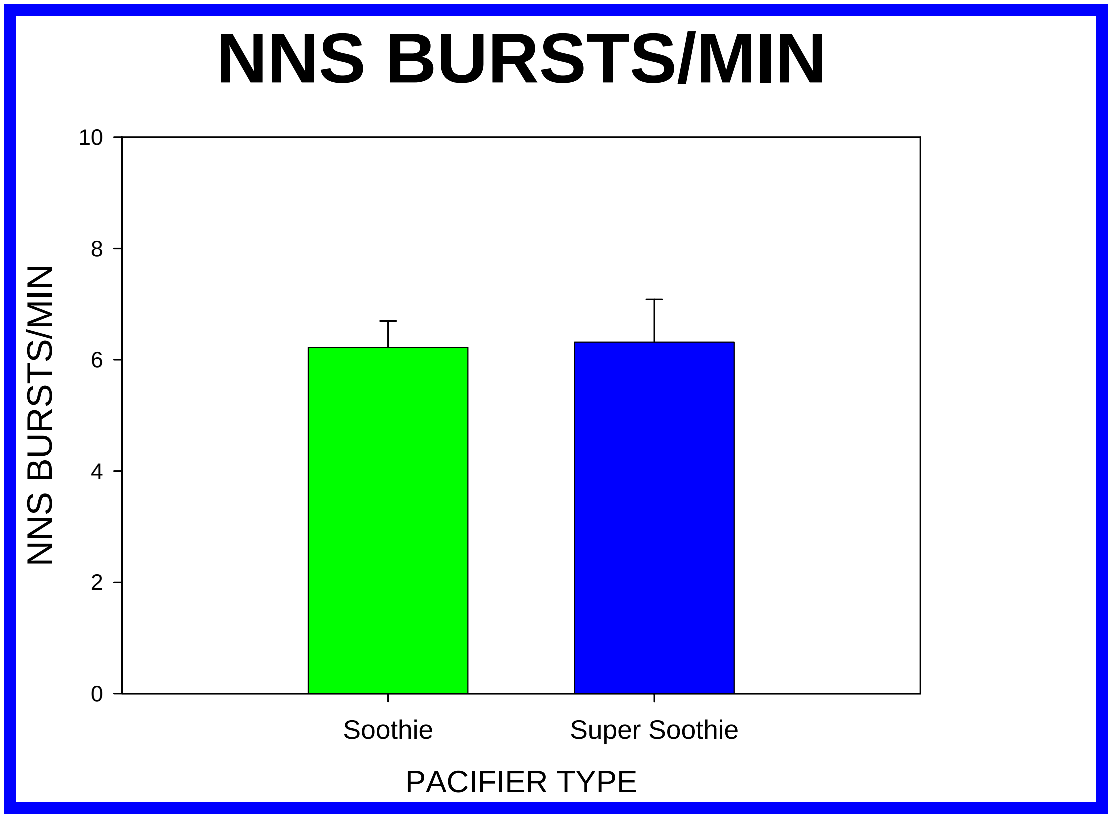


Figure 8. Mean NNS BURSTS/MIN among preterm infants was not significantly different between the two pacifier types (p =.386). Vertical bars represent the standard error of the mean.

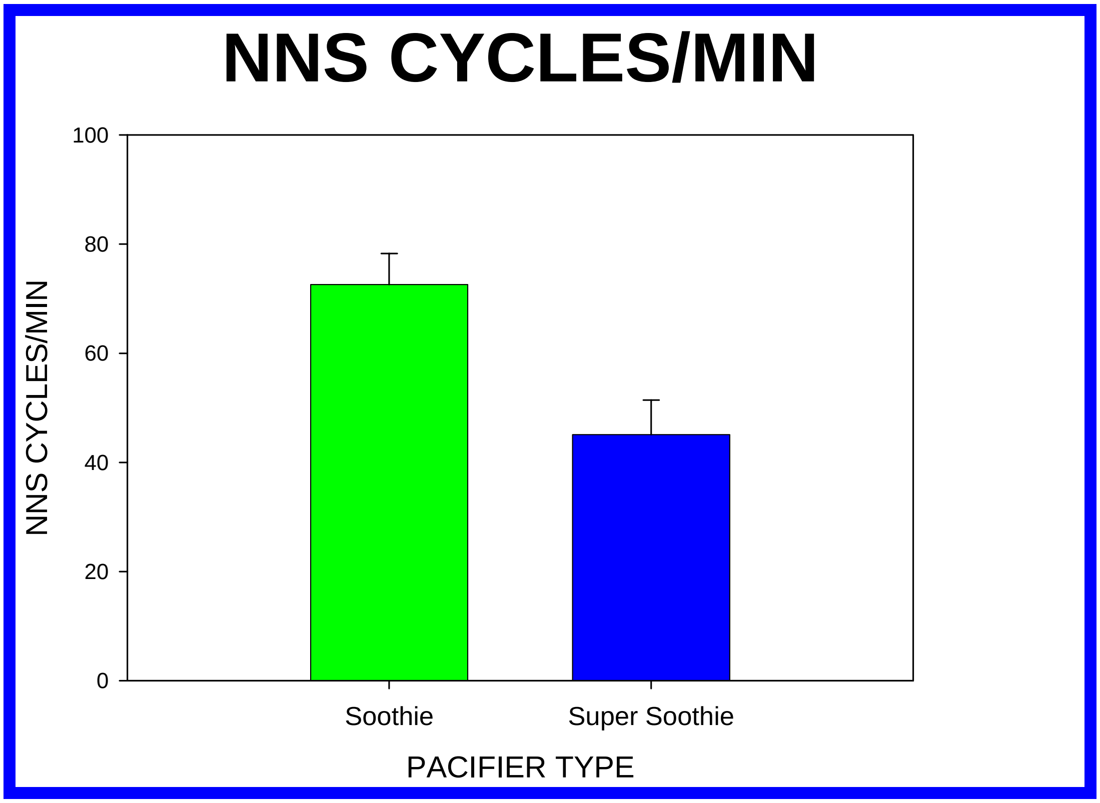


Figure 9. Mean NNS CYCLES/MIN among preterm infants was significantly different between the two pacifier types ($p < .0001$). Vertical bars represent the standard error of the mean.

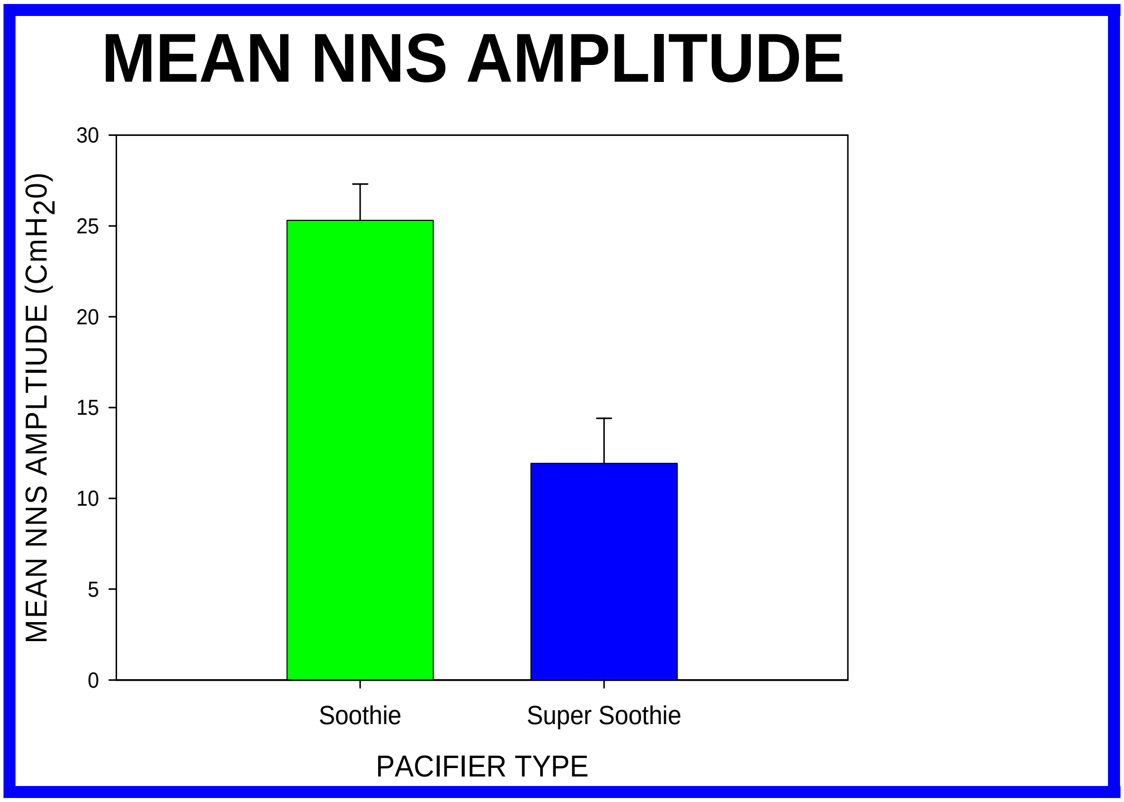


Figure 10. Mean NNS AMPLITUDE among preterm infants was significantly different between the two pacifier types ($p = .003$). Vertical bars represent the standard error of the mean.

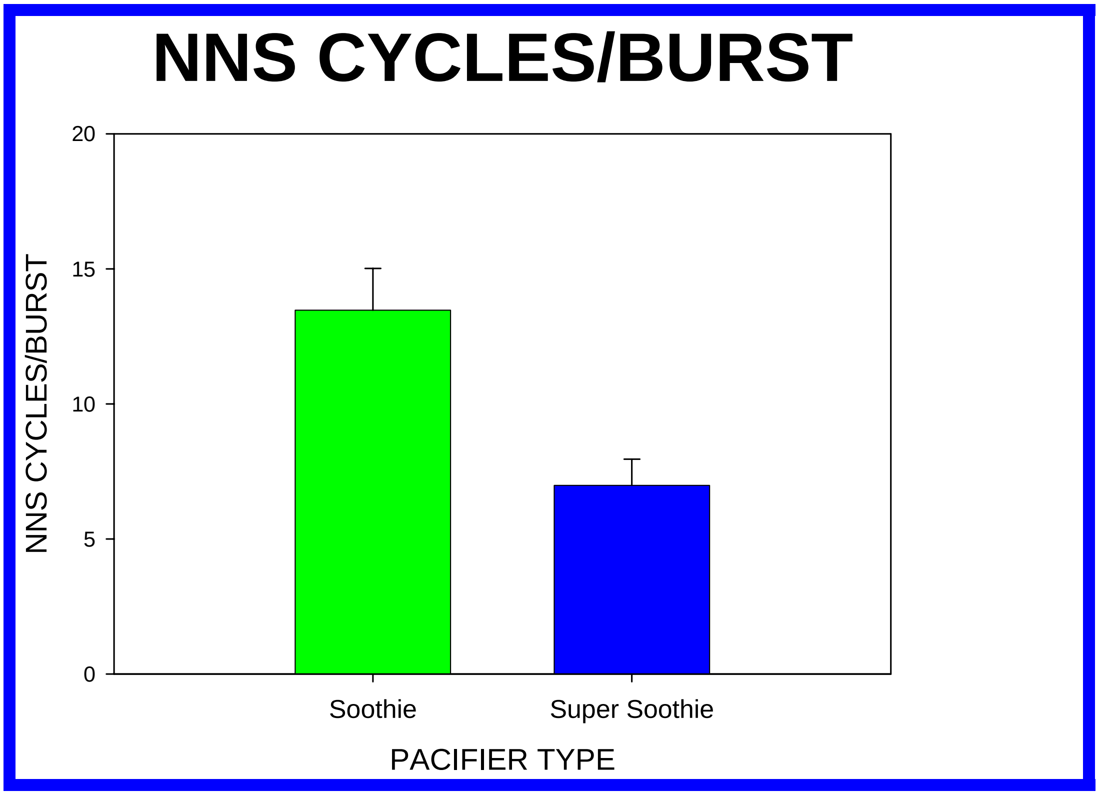


Figure 11. Mean NNS CYCLES/BURST among preterm infants was significantly different between the two pacifier types ($p < .001$). Vertical bars represent the standard error of the mean.

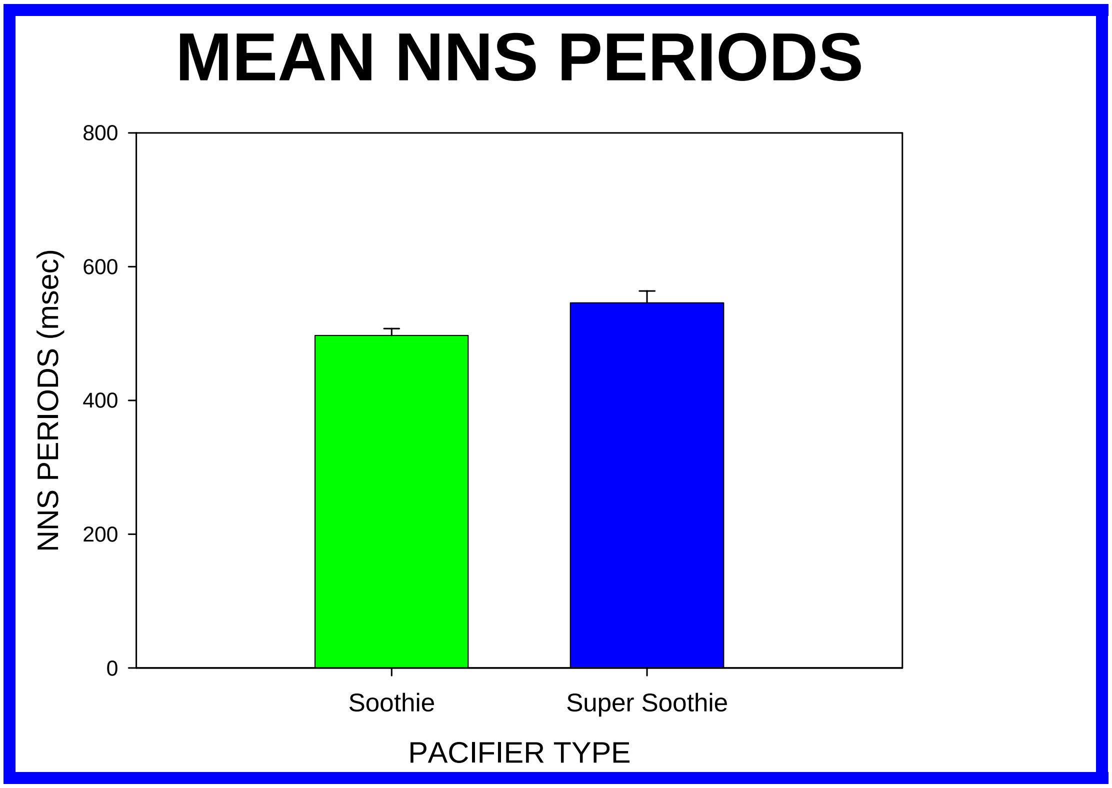


Figure 12. Mean NNS cycle PERIODS among preterm infants was significantly different between the two pacifier types ($p = .015$). Vertical bars represent the standard error of the mean.

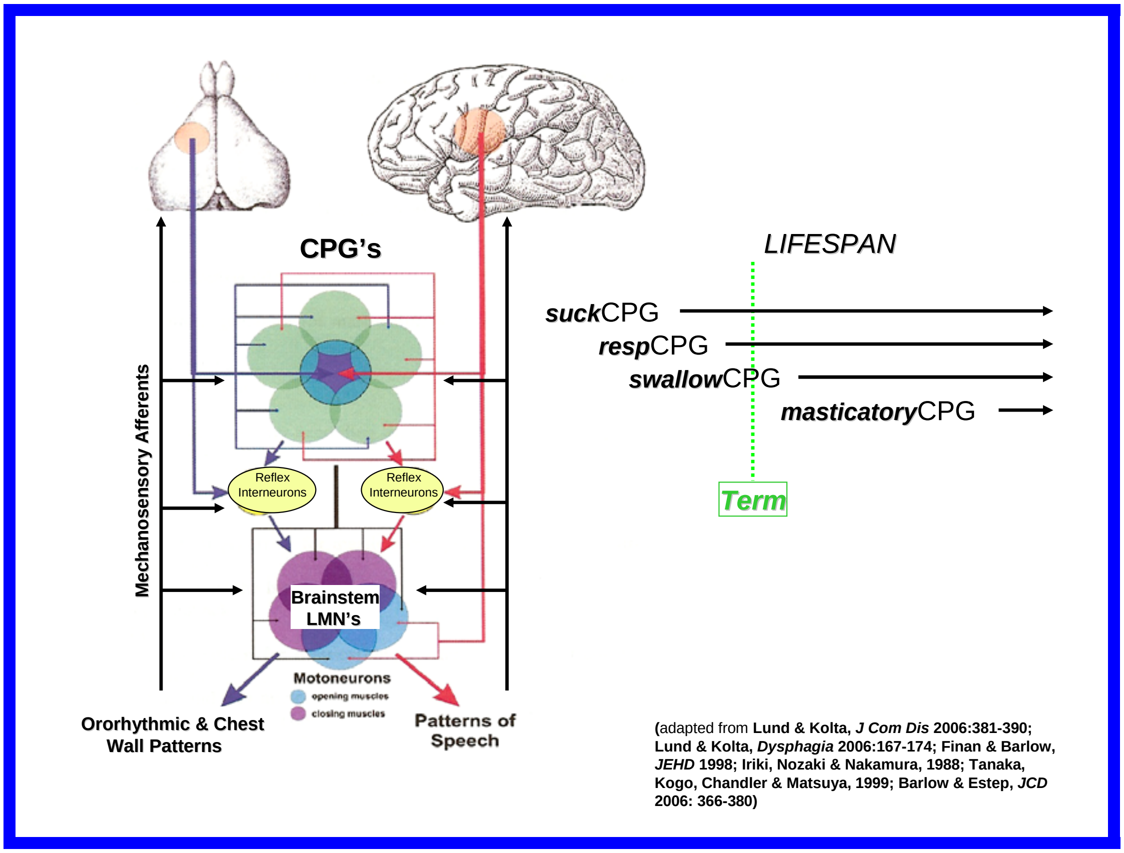


Figure 13: A schematic of ororhythmic and chest wall CPGs and their relative activation timeline. An important feature included in this diagram is the availability of mechanosensory feedback to all levels of the neuraxis, descending neuromodulation, and the hypothesized parallel and shared resource of CPG sub-circuitry involved in the production of speech and voice.

Infant	Sex	GA @ birth (wks;days)	Birthweight (gms)	Corrected Age @ Study (months;days)	Baby Group	O_2 Hx (days)	Medical comments
T19	M	31;1	1800	9;7	RDS	3	
T36	M	29;0	1305	2;24	RDS	3	
T45	M	31;0	1725	2;23	RDS	4	
T46	F	28;1	1125	3;7	RDS	23	Maternal substance abuse
T63	F	2;5	765	2;28	RDS	86	
T66	M	29;5	610	3;9	RDS	91	
T64	F	24;6	735	2;7	RDS	35	
T51	M	29;0	1178	2;23	RDS	56	Twin
T61	F	27;5	1232	2;24	RDS	18	
T50	F	29;0	1150	2;23	RDS	44	Twin
T54	F	31;1	1290	2;18	RDS	12	R. Choroid plexus cyst
T98	M	30;0	1190	3;2	RDS	13	
T93	M	26;6	918	2;24	RDS	64	
T60	M	30;1	1085	3;16	RDS	54	
T102	M	31;3	1685	2;28	RDS	6	
T57	F	31;1	1405	2;18	RDS	15	hx PDA
T59	F	26;3	1070	2;24	RDS	69	
T90	M	26;6	795	2;21	RDS	94	BPD
T89	F	27;1	750	2;24	RDS	43	
T47	M	27;5	765	2;19	RDS	65	
K16	M	30;7	1701	8;22	HEALTHY	3	
T21	M	31;1	1580	6;8	HEALTHY	0	
T30	M	33;0	1780	11;23	HEALTHY	0	
T44	F	31;4	1510	4;23	HEALTHY	0	
T38	M	31;4	1090	2;24	HEALTHY	0	triplets
T91	F	26;6	1485	2;18	HEALTHY	4	
T39	M	31;4	1090	4;23	HEALTHY	1	
MEAN		29;2	1215.33	4;5		30	
Standard Deviation		2;.1	355.59	2;11		32	

Table 1. Infant profiles.