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An exploration of swallowing stimulation in the infant

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An Exploration of Swallowing Stimulation in the Infant

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Dedication

I dedicate this dissertation to my wonderful family, my inspiration in reaching for the stars and my anchor in being able to achieve this goal. A special word of gratitude goes to my loving parents, Steve and Katherine, my role models for hard work, perseverance, and unconditional love, as well as to my sister, Laura, for her amazing friendship, support, and encouragement. I could not have completed this process without the endless support and love from my family. You have made all of this possible—I will always appreciate and cherish your strength and encouragement.

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Abstract

        The purpose of this study was twofold: to determine the effects of two types of non-invasive, peripheral sensory stimulation on the frequency of infant swallowing and to explore the cortical activation patterns in response to stimulation in the somatosensory and motor regions of the brain during infancy, between 2-4 months and 7-9 months of age. The two different forms of mechanical stimulation investigated include pacifier stimulation to the lips and oral cavity and vibrotactile stimulation via the external throat area to the laryngeal tissues. The study represents a prospective, repeated experimental research design. Investigators utilized an accelerometer and an inductive plethysmography system to identify swallowing events and functional near-infrared spectroscopy (NIRS), a non-invasive cortical optical-imaging technique, to cortical responses to the peripheral stimulation conditions by measuring the hemodynamic responses in cortical oral-motor and sensorimotor regions. A repeated-measures ANOVA was performed on the participants' swallowing frequency data with and without the stimulation conditions. The results indicated a significant difference ($p < .001$) among the three conditions (no stimulation, pacifier stimulation, and vibrotactile stimulation), with pairwise comparisons indicating that the pacifier and vibrotactile conditions significantly ($p < .001$) increased the infants' swallowing frequency compared to swallowing frequency without stimulation. Swallowing frequency did not differ between the pacifier and vibrotactile conditions ($p > .05$). NIRS recordings were obtained on only a few subjects for technical reasons. NIRS pilot data changes in blood flow occurred during the pacifier and vibrotactile stimulation conditions in a few infants. Overall findings suggest that both pacifier and vibrotactile stimulation can serve to up-regulate the frequency of swallowing in normal infants. Non-nutritive pacifier stimulation may be beneficial for increasing the frequency of swallowing in infants in addition to the known benefits of aiding in sucking skills development. Vibrotactile stimulation represents an alternative or complementary intervention for increasing the frequency of swallowing in infants that may not interfere with the process of oral intake. The current study continues to collect data for normal infants and should be explored in infants with disordered swallowing, particularly in the neonatal intensive care unit.

Introduction

Background of the Study – Normal and Disordered Swallowing

Dysphagia is the term used to describe a swallowing problem. Swallowing begins during the fetal stage of development, emerging *in utero* around 12-14 weeks of gestation, but can appear as early as 10 weeks and matures significantly during the period of neonatal maturation (Bosma, 1985; Bulock, Woolridge, & Baum, 1990; Devries, Visser, & Prechtl, 1982; Humphrey, 1967; Jadcherla, Gupta, Stoner, Fernandez, & Shaker, 2007; Lopez Ramon y Cajal, 1996; Petrikovsky, Kaplan, & Pestrak, 1995). Swallowing involves an extensive control system, ranging from areas of the cortex down to the cervical spinal cord (A. J. Miller, 1999). Swallowing is largely mediated through bilateral brainstem neural pathways, involving central pattern generators (CPGs) that produce stereotypical and rhythmic motor activity (Jean, 1972, 1984a, 1990, 2001; A. J. Miller, 1993). The swallowing CPGs are composed of afferent and efferent neural networks within the nucleus tractus solitarius (NTS), the dorsal medullar region of the reticular formation, and the dorsal and ventral medullar areas surrounding the NTS and the nucleus ambiguus, respectively. These swallowing CPG networks are composed of two primary groups of neurons. A system of interneurons organizes and programs the motor patterning for swallowing (Jean, 2001). The first group of swallowing of neurons, named the dorsal swallowing group, is positioned in the nucleus tractus solitarius in the dorsal medulla. These neurons are responsible for producing, molding, and organizing the timing of the swallow. The second group, or the ventral swallowing group, are positioned in the ventrolateral medulla and act as "switching neurons," in that they distribute the programmed swallowing drive to the motoneuron pools responsible for swallowing. The primary cranial nerves that carry sensory and/or motor

information involved in deglutition include the Trigeminal (V), Facial (VII), Glossopharyngeal (IX), Vagus (X), and the Hypoglossal (XII) cranial nerves.

A growing base of research also indicates increasing cortical involvement and modulation of swallowing throughout development. Research primarily involving electrophysiological methods with primates and functional magnetic resonance imaging (MRI) with humans have identified an extensive network of cortical areas of activation during swallowing. Such areas include the primary sensorimotor cortex, sensorimotor integration areas, premotor cortex, supplementary motor areas, insula, frontal operculum, anterior cingulate cortex, and the left pericentral and anterior parietal cortex (Hamdy, Mikulis, et al., 1999; Hamdy, Rothwell, et al., 1999; Kern, Jaradeh, Arndorfer, & Shaker, 2001; Kern & Shaker, 2002; Malandraki, Sutton, Perlman, Karampinos, & Conway, 2009; R. E. Martin, Goodyear, Gati, & Menon, 2001; R. E. Martin et al., 1999; R. E. Martin et al., 2004; R. E. Martin & Sessle, 1993; Michou & Hamdy, 2009; A. J. Miller, 2008; Mistry & Hamdy, 2008; K. Mosier & Bereznaya, 2001; K. Mosier et al., 1999; K. M. Mosier, Liu, Maldjian, Shah, & Modi, 1999; Toogood et al., 2005).

Swallowing represents one of the most complex sensorimotor acts of the human body (Jean, 2001; A. J. Miller, 1993). Swallowing disorders can manifest in difficulties with one or more phases of the swallow: oral phase, pharyngeal phase, and the esophageal phase. The oral phase (generally divided into a separate oral preparatory and oral phases for adults) involves formation of the bolus and oral transit of the bolus posteriorly towards the pharynx, and pharyngeal swallow initiation. The pharyngeal phase involves the movement of the bolus through the pharynx, with protective mechanisms engaged to allow for safe transit past the entrance to the larynx. Airway protection mechanisms include closure due to hyolaryngeal excursion, laryngeal vestibule closure with the arytenoids to the epiglottis, and

vocal fold closure. Normally swallowing does not involve aspiration, when food, liquid, or saliva travels below the vocal folds, en route to the trachea. Reflexive relaxation of the cricopharyngeus muscle, one part of the upper esophageal sphincter (UES), occurs due to suppression of motor neuron activity for the cricopharyngeus and inferior pharyngeal muscles. Finally, active pull with the hyolaryngeal excursion aids UES opening and bolus propulsion through the sphincter into the esophagus. The esophageal phase involves passage of the bolus down the esophagus pushed by a series of peristaltic waves, and entry into the stomach through the lower esophageal sphincter (Bosma, 1957; Doty, 1968; A. J. Miller, 1982). Precise timing and coordination of swallowing and respiration are essential for a safe swallow, to prevent material from reaching the lungs (Bosma, 1985; Thach & Menon, 1985). Malandraki et al. (2009) demonstrated that the oral phase involves more cortical control, whereas the pharyngeal phase may be more reflexive and involve brainstem control to a greater degree (Ertekin & Aydogdu, 2003).

Infants are primarily breast or bottle feeders for the first six months of life. Early infant feeding is characterized by a suck-swallow-breathing pattern. Infants are faced with the task of coordinating this sucking, swallowing, and breathing pattern while feeding after birth. Full-term, healthy infants are expected to successfully execute this coordination pattern at their first oral feeding. Coordinating the infant feeding pattern is often difficult for preterm infants in the neonatal intensive care unit (NICU) due to neurological immaturity (Bingham, 2009). Around 40% of preterm infants that experience deficits in oral feeding are considered to stem primarily from their neurologic and physiologic immaturity (Simpson, Schanler, & Lau, 2002). Other medical conditions that may result in dysphagia in infants include congenital and craniofacial anomalies, respiratory disorders, gastrointestinal disorders, cardiovascular disorders, neurological conditions, and neuromuscular disorders (J.

C. Arvedson, 2008; C. K. Miller, 2009; Newman, Keckley, Petersen, & Hamner, 2001; Sheppard & Fletcher, 2007). High percentage of infants under one year of age with neurologic abnormalities, genetic syndromes, congenital heart disease, and premature birth, including those with a history of bronchopulmonary dysplasia have swallowing dysfunction (Mercado-Deane et al., (2001).

The swallowing motor program is present early in the gestational period and fetuses nearing term-birth swallow around 500-1,000 mL of amniotic fluid each day (Mizuno & Ueda, 2003; Ross & Nijland, 1998). Despite the swallowing that the fetus experiences *in utero*, the coordination of swallowing, sucking, and breathing may not be efficient enough for successful oral feeding with the preterm infant after birth. The general consensus is that premature infants are not capable of coordinating the suck and swallow with breathing for successful and efficient total oral feeding until around week 34 of gestation (Bauer, Prade, Keske-Soares, Haeffner, & Weinmann, 2008; Da Nobrega, Boiron, Henrot, & Saliba, 2004; Lau & Schanler, 1996; Matthews, 1994; McCain, Gartside, Greenberg, & Lott, 2001). This age also corresponds with the time period of maximum synaptogenesis of the medulla (Rogers & Arvedson, 2005; Takashima, Mito, & Becker, 1985). Therefore, preterm infants in the NICU often require gastric feeding tubes to meet growth and nutritional needs until their feeding skills mature and improve (Bauer, et al., 2008; Boiron, da Nobrega, Roux, & Saliba, 2009). Infants with dysphagia may demonstrate difficulties with sucking, swallowing, respiration, or a combination of all three. Expanding our knowledge base of normal infant swallowing patterns is needed.

Pediatric feeding disorders (which may or may not include a swallowing disorder) occur in approximately 25-45% of children considered to be developing normally and up to 80% of non-typically developing children (J. C. Arvedson, 2008; Bell & Alper, 2007;

Burklow, Phelps, Schultz, McConnell, & Rudolph, 1998; Lefton-Greif & Arvedson, 2007;

Linscheid, 2006; Manikam & Perman, 2000). Within the broader category of feeding

disorders, the precise incidence rate of pediatric swallowing disorders is unknown (Lefton-

Greif & Arvedson, 2007; Loughlin & Lefton-Greif, 1994). Jadcherla et al. (2009) report that

26% of infants born prematurely experience dysphagia. Based on parent-report, 12% of

infants who were preterm displayed swallowing problems when assessed at 30 months of age

(Wood et al., (2003). The incidence of swallowing disorders appears to be growing as the

survival rate of premature infants with complex medical conditions continues to increase due

to advanced medical technology and knowledge and the improved professional identification

of children with dysphagia (Ancel et al., 2006; J. C. Arvedson, 2008; Burklow, et al., 1998;

Hawdon, Beauregard, Slattery, & Kennedy, 2000; Lefton-Greif & Arvedson, 2007; Marlow,

2004; Newman, et al., 2001).

Statement of the Problem

Although swallowing difficulty is not uncommon in preterm and early infancy,

limited literature is available on infant swallowing in contrast with research on infant sucking

(Lau, Smith, & Schanler, 2003; Rogers & Arvedson, 2005). In healthy preterm and term

infants oral feeding performance improvement relies on sucking skills, increased swallowing

frequency, and the ability to handle larger boluses (Lau, (2003). The approach to swallowing

intervention with infants differs from that of adult swallowing rehabilitation. First, the

anatomical differences and immature neurological systems result in biomechanical

differences in the swallow for infants and young children (Newman, et al., 2001). The

anatomical structures involved with the swallowing mechanism develop as the infant grows,

reaching adult-like approximation around age six years (J. C. Arvedson & Brodsky, 2002).

Secondly, some intervention techniques do not transfer in application to the pediatric

population, due to infants' and young childrens' inability to verbalize needs or follow

instructions (Kramer & Eicher, 1993). Many of the current interventions for dysphagia in the

NICU are targeted toward environmental modifications (feeding schedules, nipple selection,

thickening agents, positioning, chin and cheek support, and external pacing. Interventions

also target oral and labial stimulation via non-nutritive sucking on a pacifier. A full

understanding of how such orally-centered treatments influence the remainder of the

swallowing motor act, such as the pharyngeal component is lacking (Sheppard & Fletcher,

2007). Some of the interventions although commonly used in practice have not been shown

to directly affect the swallowing component of the suck-swallow-breathe patterning during

infancy. Legislative intiatives have increased the access that the pediatric population has to

dysphagia services, but scientific bases for guiding services to this population are limited

(Bell & Alper, 2007). The incidence of pediatric swallowing disorders may be increasing and

an improved understanding of normal infant swallowing patterns and development of

cortical response to swallowing stimulation is warranted. Such knowledge is needed to

inform future intervention techniques targeting infant swallowing disorders.

Statement of the Need

The American Academy of Pediatrics hospital discharge criteria for the high-risk

neonate require safe and efficient oral feeding is a prerequisite for discharge from the NICU

(Committee on Fetus and Newborn, 1998; Lau, 2006). Successful oral feeding often

represents the final milestone that a preterm infant in the NICU must master. A lack of oral

feeding can increase hospital stay by an average of 9.3 days (Bingham, 2009; Bragelien,

Rokke, & Markestad, 2007; Poore, Barlow, Wang, Estep, & Lee, 2008). Hospitalization in

the NICU is expensive, costing around $1,000 per day. More than 500,000 infants are born

prematurely each year in the United States. The first year of tube feeding costs approximately

$46,875 and can cost up to approximately $180,000 across the first five years of tube feeding (Jadcherla, et al., 2009; Piazza & Carroll-Hernandez, 2004). Immature oral feeding among NICU babies may cost around 4.5 billion dollars each year (Bingham, 2009). Furthermore, it appears that the number of previously preterm infants returning for feeding services is at least 40% of those patients seen in feeding clinics (Lau, 2006).

Persisting neurodevelopmental sequelae associated with NICU infants have been established (Hawdon, et al., 2000). Specifically related to feeding skills, neurodevelopmental outcomes at 18 months has been correlated with neonatal feeding performance (Mizuno & Ueda, 2003). Hawdon et al. (2000) discovered that neonates with feeding disorders are more prone to vomiting and coughing when presented with solid food at six months, and not as likely to tolerate lumpy food textures or experience pleasurable mealtimes at 12 months of age. Persisting transitional feeding complications are not uncommon with infants who experience feeding difficulties early in life (Emond, Drewett, Blair, & Emmett, 2007).

In a longitudinal study, Palmer and Heyman (1999) observed developmental delays on the Denver Developmental, Vineland Social Maturity Scale, and the Bayley Scales of Infant Development) at two to three years of age in children who had a dysfunctional suck as neonates. Of the infants previously found to have a disorganized suck, 44% demonstrated developmental delays at 2 years of age. The two infant with a normal suck did not have developmental delay during later assessment. Medoff-Cooper (2005) presented study findings demonstrating a strong relationship between characteristics of sucking in very low birth weight infants at 40 weeks gestation and their score on the Bayley Scales of Infant Development at six months of age. Finally, problems with feeding early in life may also represent a factor in the delay of other motor behaviors involving the shared aerodigestive tract, such as babbling and speech production (Adams-Chapman, 2006; Ballantyne, Frisk, &

Green, 2006; Barlow, 2009c; McFarland & Tremblay, 2006; Mizuno & Ueda, 2005).

Therefore, intervention for feeding and swallowing deficits at an early age that can be

implemented in the NICU, may contribute to improved developmental outcomes (e.g.,

cognitive and motor outcomes) in addition to facilitation of safe and efficient oral feeding.

In addition, research is needed to understand the influence of sensory input on

swallowing for all ages (Logemann, 1996). Based on what Bingham (2009) calls the

"deprivation model of dysphagia in premature infants," sensory interventions to encourage

appropriate feeding development within the pediatric population are needed. (p. 744)

Specifically, knowledge of the influence of such stimulation "on the rhythmicity and

frequency of ingestive behaviors" is needed to augment current intervention techniques. (p.

747) Opportunity exists to explore the influence of sensory stimulation on the frequency of

swallowing in infants, which could capitalize on the role of experience-dependent sensory

stimulation in central pattern generator and neocortex pathway formation (Barlow, Finan,

Lee, & Chu, 2008).

Specific Aims:

- Determine the effect of pacifier stimulation on the frequency of infant swallowing.

- Determine the effect of vibrotactile stimulation on the frequency of infant

  swallowing.

- Determine if cortical activation occurs with stimulation in the somatosensory and

  motor regions of the brain in early infancy between 2-4 months and 7-9 months of

  age.

Research Questions

The purpose of this study is twofold: to determine the effects of two different stimuli on the frequency of swallowing and to determine if cortical activation occurs in response to swallowing stimulation in early infancy. Specifically, this study aims to address the following questions:

1. Does the presence of a pacifier increase the frequency of swallowing in normal infants at 2-4 and 7-9 months of age?

2. Does the presence of vibrotactile stimulation increase the frequency of swallowing in normal infants at 2-4 and 7-9 months of age?

3. Does cortical activation with stimulation increase in the somatosensory and motor regions of the brain between 2-4 and 7-9 months of age?

It is hypothesized that:

1. The presence of a pacifier will increase the frequency of swallowing.

2. The presence of vibrotactile stimulation will increase the frequency of swallowing.

3. Cortical activation with stimulation occurs in the somatosensory and motor regions of the brain in the 7-9 month group and will be greater than in the same regions of the 2-4 month old infants.

Limitations

The present research begins an investigation of the infant swallow in healthy, typically developing, full-term infants. An understanding of whether particular stimuli affect the frequency of swallowing in a typically developing, healthy infant is important before studying the techniques with a medically fragile and disordered infant population. Due to the nature of the medical conditions associated with prematurity and the environment of the neonatal intensive care unit, preterm infants are already subjected to numerous aberrant

sensory experiences. Therefore, the present research targeted healthy infants without swallowing disorders as the participants, with hope of transferring the focus of this research to infants experiencing dysphagia in the NICU in the future, once the knowledge base of normal infant swallowing stimulation is expanded.

An additional limitation of the present research includes a small sample size. The present research represents preliminary exploration of infant swallowing stimulation using the pacifier and vibrotactile stimulation and the related brain activation patterns. However, interventional studies in preterm NICU infants would be optimal future studies.

Limitations are also involved in the determination of cortical activation by stimulation using near-infrared spectroscopy (NIRS) with infants. For adults, the placement of NIRS probes over specific, targeted brain regions is accomplished using a structural magnetic resonance image (MRI) to ensure consistent positioning of the NIRS probes for each adult participant, as anatomical landmarks in the brain are individualized. For safety considerations, a structural MRI for neuronavigation with the infants, especially healthy infants with no other medical need for a MRI, was not considered (Aslin & Mehler, 2005). Safety considerations involve the requirement that infants remain still in the MRI tunnel in order to avoid motion artifact, which often involves sedation. Exposure to high magnetic fields and the loud noise level that occurs with the radiofrequency (RF) gradient changes may be a risk to the infant during MRI. Therefore, NIRS probe placements on the infant participants in this study may not represent exact positioning over the somatosensory or motor brain regions. Rather, the positioning was estimated based upon atlases displaying average infant brain anatomical landmarks and the 10-20 International System of Electrode Placement for Electroencephalograpy (Jasper, 1958). Therefore, variation in the targeted

underlying neural regions during NIRS probe positioning may have occurred in the present study.

Finally, the use of near-infrared spectroscopy limits the current study's infant participants to those without highly-pigmented skin color. NIRS involves the measurement of the degree of absorption by hemoglobin chromophores by different wavelengths of near-infrared light as the light is reflected back through the scalp. Wassenaar and Van den Brand (2005) found that the high levels of melanin, which are greater in individuals with dark skin color, interfere with wavelength transmission, making the measurement of changes in absorption inaccurate. The authors suggested that NIRS measurements involving participants with highly-pigmented skin should be interpreted with caution. Therefore, in an effort to collect reliable NIRS measurements, we excluded participants with highly-pigmented skin.

<center>**Review of the Literature**</center>

Infant swallowing frequency

       Infant swallowing frequency has been researched using both animal models as well as preterm and full-term infants. However, the frequency of swallowing in the infant population has not been investigated extensively.

Animal research pertinent to infant swallowing frequency

       Ross (1998) found that a spontaneous swallowing frequency of 43 swallows per hour (around 0.72/min) in near-term ovine fetuses was similar to the swallowing frequency of preterm ovine fetuses. However, the volume intake differed, with the near-term ovine fetuses displaying an increased volume intake per swallow as compared to the preterm counterparts.

       In an investigation of swallowing and respiration coordination in full-term lambs, a mean non-nutritive swallowing frequency of $121 \pm 9 \, h^{-1}$ (around 2.02/min) during wakefulness was observed (Reix et al., 2003). A mean non-nutritive swallowing frequency of $57 \pm 10 \, h^{-1}$ (around 0.95/min) during wakefulness was observed in preterm lambs (Reix, Arsenault, Langlois, Niyonsenga, & Praud, 2004). The frequency of isolated, non-nutritive swallowing in preterm lambs during periods of wakefulness was lower as compared to full-term lambs.

Human infant non-nutritive and nutritive swallowing frequency research

Non-nutritive swallowing

       Menon, Schefft, and Thach (1984) report that during a control period, which did not include any apneic spells or the presence of pharyngeal devices, preterm infants with diagnosed idiopathic apnea demonstrated an average of 0.69 ± 0.16 swallows per minute. Thach and Menon (1985) report that infants (preterm and older infants) complete around six

swallows per minute during wakefulness. In a study involving both healthy full-term infants and infants born prematurely, but having reached term gestational age at the time of the study, Jeffery, Ius, and Page (2000) report a mean spontaneous swallowing frequency of 1.6 swallows per minute with the term infants. The infants born prematurely demonstrated a mean spontaneous swallowing frequency of 1.3 swallows per minute. Statistical analysis indicated no statistically significant difference between the spontaneous swallowing frequencies for term and prematurely-born infants. Nixon, Charbonneau, Kermack, Brouillette, and McFarland (2008) report non-nutritive swallowing frequency for infants born prematurely, but near full-term in age at the time of the study of 47 swallows per hour (around 0.78/min) during wakefulness. Koenig, Davies, and Thach (1990) report an infrequent swallowing frequency of 0.10 ± 0.03 swallows per second during non-nutritive sucking and indicated similar frequencies for both term and preterm infants. Kramer (1993, 1985, 1989) indicates that pharyngeal swallows may occur more frequently and at faster speeds in the infant as compared to the pharyngeal phase of an adult swallow. Furthermore, Kelly, Huckabee, Frampton, and Jones (2008) report an informal observation during a longitudinal study with 10 term, healthy infants that swallowing frequencies declined as age increased.

Nutritive swallowing

Adult humans swallow an average of around 580 times per day (around 0.40/min), with swallowing becoming more frequent during activities such as eating (Lear, Flanagan, & Moorrees, 1965; Logemann, 1998). da Costa, van den Engel-Hoek, & Bos (2008) state that infants typically swallow as often as 60 times a minute (around 1 per s) while feeding. Bamford, Taciak, & Gewolb (1992) report that an infant swallowing frequency of 1 Hertz or more (around 1 per s) during periods of rapid feeding may function to protect the airway

(Daniels et al., 1988; Koenig, et al., 1990; Mathew & Bhatia, 1989). The swallowing

frequency during feeding appears to be rapid at the onset of feeding, with one suck per

swallow initially, but the frequency of swallows decreases after the first several swallows

(Koenig, et al., 1990; Matthew, 1991; Thach, 1992b).

Swallowing during sleep

In contrast to swallowing during wakefulness, the frequency of infant swallowing

decreases during sleep. In a group of 10 preterm infants diagnosed with idiopathic apnea,

Pickens et al. (1988) observed an average of 0.94 $\pm$ 0.25 swallows per minute during sleep.

An average swallow frequency of 23.3 $\pm$ 2.1 swallows per hour (around 0.39/min), was

observed during a sleep study involving infants between one and 34 weeks of age (Don &

Waters, 2003). Although the frequency of non-nutritive swallowing tends to decrease during

periods of sleep, the frequency of non-nutritive swallowing during infant sleep is more rapid

than the swallow frequency for adult mammals during sleep (Jeffery, et al., 2000; Nixon, et

al., 2008; Reix, et al., 2003; Thach & Menon, 1985). Nixon and colleagues' 2008 study

confirmed earlier findings of more swallowing events during respiratory pauses, as compared

to swallowing during continuous breathing while infants slept (Don & Waters, 2003; Menon,

et al., 1984; Pickens, Schefft, & Thach, 1988; Pickens, Schefft, & Thach, 1989). Frequent

non-nutritive swallowing during periods of respiratory pause may serve as a protective

mechanism for airway safety, in order to escape apnea or aspiration caused by gastric reflux

or other secretions (Nixon, et al., 2008; Praud & Reix, 2005; Reix, et al., 2004; Thach, 1992a).

Premature infant swallowing characterized by decreased frequency

Premature infants demonstrate a decreased frequency of swallowing compared to

their full-term counterparts and this may be associated with persistent tube feeding. In a

study of 20 neonates with dysphagia, (Jadcherla, et al., 2009) found that a subset of five

infants with dysphagia who required chronic gavage feeding displayed unique characteristics during pharyngoesophageal motility studies. The researchers observed that the five subjects who did not achieve oral feeding success, among other characteristics not pertinent to the present study, displayed an infrequency of swallows. The majority of the infants with dysphagia achieved oral feeding and displayed a mean swallowing frequency of 2.4 ± 0.3 swallows per minute, whereas the five neonates who remained on tube feedings at the follow-up evaluation demonstrated a mean swallowing frequency of 0.4 ± 0.2 swallows per minute.

Using audiosignal recordings with premature infants at the level of the cricoid cartilage in the neck, Da Nobrega et al. (2004) observed a swallowing frequency of 13.1 ± 4.7 swallows per minute during the tube-bottle feeding period in which the infants were transitioning toward full oral feeding, and a swallowing frequency of 22.2 ± 6.8 swallows per minute in the premature infants who had advanced to full bottle-feedings. The frequency of swallowing increased for all infants advancing from tube-bottle feeds to full oral feeds. However, the results of this study should be interpreted with caution, as the researchers utilized a microphone placed in front of the cricoid cartilage to record swallowing patterns. Cervical auscultation has not recognized as a valid diagnostic tool for measuring swallowing in clinical practice. Rather, clinicians are encouraged to use cervical auscultation only as a supplemental tool during swallowing evaluation. Furthermore, the researchers placed the microphone in front of the cricoid cartilage, which may not represent the optimal location during cervical auscultation. The lateral portion of the larynx may represent the best placement site for a microphone or stethoscope during cervical auscultation (Vice, Heinz, Giuriati, Hood, & Bosma, 1990). Lau et al. (2003) also observed an increased swallowing frequency during oral feedings between preterm and full-term newborn infants, suggesting

that the increase is mediated by maturation of the swallowing reflex. Twelve healthy preterm infants displayed 45 $\pm$ 14 swallows per minute, while the eight healthy full-term infants displayed a swallowing frequency of 55 $\pm$ 15 swallows per minute. In summary, swallowing frequencies of premature and term infants increase with the development of stable sucking and swallowing motor activity (Gewolb, Vice, Schwietzer-Kenney, Taciak, & Bosma, 2001).

Critical periods – why early intervention is important

The first research aim of the present study is to determine if stimulation can increase the frequency of infant swallowing through peripheral, mechanical sensory input. Keeping in mind that the ultimate application for this research is geared toward the neonatal intensive care unit population, the concept of a "critical period" is crucial to the timing of intervention.

Experience aids the development of neuronal circuitry during early postnatal life (Hensch, 2004). Around 28 weeks of gestation in the human fetus, synchrony of cell wave signals between sensory and central brain systems begins, creating a foundation for neurosensory connections between the periphery and central systems before the influence of sensory input external to the central nervous system (W. F. Liu et al., 2007; Penn & Shatz, 1999). In addition to the intrinsic neural development just described, external, or activity-dependent sensory stimulation, is also essential during critical periods for normal development of neuronal connectivity (W. F. Liu, et al., 2007). Extrinsic stimulation, specific to various sensory networks, signals arrangement of neurons in the cerebral cortex into unique, functional sensory systems. Central pattern generators for motoric movement involve an inherent network that is modulated through activity-dependent sensory experience. For movements such as swallowing, such motor experiences begin *in utero* and mark the beginning of early sensory experience that aids in circuit formation and tuning

(Barlow 2006). Critical periods, or windows of time in which developing systems are vulnerable to certain types of sensory input, coincide with a period of rapid synaptogenesis (cortical growth) in which environmental factors may advantageously shape or disrupt development and mapping of the immature brain (Barlow, Finan, Lee, et al., 2008; Beradi, Pizzorusso, & Maffei, 2000; Bosma, 1970; Bourgeois, 1997; Hensch, 2004; Hubel & Wiesel, 1970; Huttenlocher & Dabholkar, 1997; W. F. Liu, et al., 2007; Mrzlajk, Uylings, Kostovic, & Van Eden, 1990; Pomeroy & Volpe, 1992; Wiesel, 1982; Wiesel & Hubel, 1965). The pattern of rapidly increasing myelination within the central nervous system occurs during the first eight months after birth and represents a vulnerable window of time of high sensitivity to environmental experiences (Kinney, Brody, Kloman, & Gilles, 1988). Specifically related to deglutition, the nucleus tractus solitarius region of the reticular formation and nucleus ambiguus myelination begins around the 40th week of gestation and persists through early postnatal development (Takashima, et al., 1985).

Animal research regarding critical periods

Animal research first perpetuated the concept of critical periods early in life, in which an organism's system is "primed" to collect sensory information from the environment (J.C. Arvedson, 2006; Lorenz, 1965). Animal model studies have demonstrated the disturbance in the developing brain structures engaged in sensorimotor functions as a result of sensory deprivation and motor constraints (Pascual, Fernandez, Ruiz, & Kuljis, 1993; Pascual & Figueroa, 1996; Pascual, Hervias, Toha, Valero, & Figueroa, 1998; Poore, Barlow, et al., 2008). Due to sensory deprivation, the cerebral cortex in animal models displays a reduced number of dendritic spines (Takashima, et al., 1985; Valverde, 1967)

On the other hand, specialization and diversification of the early postnatal neocortex in rats has been observed to develop at an increased rate following different forms of

sensorimotor stimulation, suggesting that sensorimotor experiences can modulate brain structure and function during the period sensitive to plasticity in early postnatal life (Pascual, et al., 1993; Pascual & Figueroa, 1996; Poore, Barlow, et al., 2008). Further, it has been demonstrated in animal models that early, enhanced sensory experience is capable of augmenting the number of dendritic spines (Globus & Scheibel, 1967; Schapiro & Vukovich, 1970; Takashima, et al., 1985).

Critical periods and deglutition

The critical period represents the window of opportunity for optimizing pattern formation in the sensory-driven neuronal system for functional and proficient swallowing, along with other processes involved in deglutition (Barlow, 2009a; Hensch, 2004; McFarland & Tremblay, 2006; Penn & Shatz, 1999). Sensory input may aid in tuning the central pattern generators involved in deglutition (Bingham, 2009). Aberrant or a lack of external sensory stimulation during critical periods may disrupt the normal course of neuronal maturation, subsequently delaying appropriate development of a sensory system (Beradi, et al., 2000; W. F. Liu, et al., 2007).

Infant volitional feeding is a learned motor behavior, and the lack of adequate sensory learning experiences may, in turn, affect normal brain development for feeding and swallowing proficiency, as sensory stimulation affects the motoric swallowing response (Bingham, 2009; McFarland & Tremblay, 2006). A lack of experience-dependent sensory stimulation events in the NICU due to prolonged tube-feeding can lead to oral aversions, an aberrant gag reflex (oversensitive, elicited by non-oral stimulation) and continued dysphagia (J. C. Arvedson & Brodsky, 2002; Barlow, Finan, Lee, et al., 2008; Bingham, 2009; Comrie & Helm, 1997; Scarborough & Isaacson, 2006). Additionally, Samson et al. (2005) found that the presence of continuous positive airway pressure (CPAP) decreased the frequency of non-

nutritive swallowing in full-term lambs. Many preterm infants undergo CPAP administration and the potential inhibitory effects on swallowing frequency could also possibly contribute to delay in swallowing maturation.

It is hypothesized that prolonged dependence on tube feedings and oxygen administration, which many premature infants experience, and the subsequent sensory and motor deprivation to the oral-facial region disrupts the "critical period" during the first two months of life in which sensory stimulation maximally aids in neural pathway development within the developing cortex and brainstem central pattern generators for the suck, swallow, and respiration (Barlow, 2009a, 2009c; Bingham, 2009; Hensch, 2004; Illingworth & Lister, 1964; Kelly, Huckabee, Jones, & Frampton, 2007a; McFarland & Tremblay, 2006; Penn & Shatz, 1999; Poore, Barlow, et al., 2008; Stevenson & Allaire, 1991). Scarborough and colleagues found that infants experiencing oral deprivation, due to continued gavage feeding as the primary means of nutrition, displayed a persisting abnormal gag reflex (Scarborough, Isaacson, & Wiley, 2005). A critical period is also believed to be involved in the transition to solid foods. Children delayed in the transition to solid foods have been observed to display food refusal and emesis (J.C. Arvedson, 2006; Illingworth & Lister, 1964). Experimentally delayed transitions to solid food in rats have demonstrated a cortical decrease in synapse development (Lorenz, 1965).

Prompting the development of sensory receptors in a system via peripheral stimulation may aid in the developing sensory network connections (Bradley, 1975). Early tactile sensory stimulation to the oral and pharyngeal regions that occurs during the act of swallowing is essential during the first few months of life to foster appropriate pathway connections for swallowing within the nucleus tractus solitarius of the brainstem (Scarborough, et al., 2005).

Entrainment of the infant suck

In line with early sensory stimulation experiences, a logical research extension may be to apply the idea of entrainment of the infant suck to infant swallowing, through presumed targeting of glossopharyngeal, vagus, and potentially trigeminal cranial nerve sensory input pathways. Sucking and swallowing behaviors observed *in utero* with co-occurring oral-facial self-stimulation have served as guidance for appropriate sensory stimulation postnatal interventions in the NICU (J. L. Miller, Sonies, & Macedonia, 2003). Research indicates that oral stimulation programs and non-nutritive suck (NNS - sucking for reasons other than nutritional intake, e.g., on a pacifier) entrainment through trigeminal cranial nerve sensory input may result in earlier attainment of efficient oral feeding, increased volume intake, weight gain, and decreased hospitalization (Barlow, 2009c; Bingham, 2009; Fucile, Gisel, & Lau, 2002; Fucile, Gisel, & Lau, 2005; Poore, Barlow, et al., 2008; Rocha, Moreira, Pimenta, Ramos, & Lucena, 2007; Sheppard & Fletcher, 2007). Liu et al. (2007), Delaney & Arvedson (2008), and Arvedson, Clark, Lazarus, Schooling, & Frymark (2010) provide detailed information regarding studies exploring the benefits of interventions involving oral stimulation and NNS. Barlow and colleagues have enhanced the approach of NNS in training the development of sucking skills for tube-fed infants with the use of a new device, the NTrainer (Barlow, Finan, Lee, et al., 2008; Poore, Zimmerman, Barlow, & al., 2008).

The NTrainer device takes advantage of the extensive supply of mechanoreceptors in orofacial tissues (Finan & Barlow, 1996). Their innovation is a motorized, pulsating servomotor pacifier designed to match the natural temporal characteristics of the non-nutritive sucking pattern. Six to 12 sucking cycles occurring at a frequency of around two Hz, followed by a pause for respiration, is characteristic of an infant's non-nutritive sucking pattern (Barlow, Finan, Lee, et al., 2008; Wolff, 1968). Therefore the NTrainer was designed

to pulsate in a pattern of six bursts, at an individual frequency of 1.8 Hz within bursts, with two seconds of pause over three minutes. The intervention protocol was administered three to four times a day. Results of the Barlow et al. (2008) intervention protocol illustrate the effectiveness of the NTrainer in assisting tube-fed premature infants with no or inefficient sucking skills in the accelerated development of an organized non-nutritive suck, which in turn, increased oral feeding success. Premature infants in the NTrainer experimental group demonstrated greater oral intake amounts (total oral intake percentage per day) sooner than their control-group counterparts.

Barlow and colleagues' (2008) research illustrates the potential for aiding and strengthening the developing neuronal pathways of the brainstem and cerebral cortex via mechanical sensory stimulation. The infant sucking control center is receptive to peripheral input (Barlow, Finan, Chu, & Lee, 2008; Finan & Barlow, 1996, 1998; Poore, Zimmerman, et al., 2008; Rocha, et al., 2007). The NTrainer entrains the ororhythmic sucking behavior through sensory input to mechanoreceptors in the orofacial region to the sucking central pattern generator. In other words, mechanoreceptor afferent activity is entrained which, subsequently, modulates firing patterns of the lower motor neurons involved in the motor activity (Barlow, 2009b). That is, "neurons that fire together will wire together" (S. Lowell & Singer, 1992). Descending inputs may shape the firing patterns of motoneurons involved in trigeminal, facial, and hypoglossal cranial nerve motoric functions (Barlow, 2009c). Animal research using neonatal guinea pigs and neonatal rats has indicated the sucking central pattern generator is housed bilaterally within the reticular formation at the levels of the pons and medulla (Iriki, Nozaki, & Nakamura, 1988; Tanaka, Kogo, Chandler, & Matsuya, 1999). Motor nuclei of the trigeminal, facial, and hypoglossal cranial nerves are all involved in producing sucking activity and likely operate in a coordinated fashion, however the

trigeminal nuclei may play a principal role (Tanaka, et al., 1999). Again, animal research has indicated that the sucking central pattern generator can be modulated via inputs traveling down to the brainstem from a sucking region within the motor cortex (Iriki, et al., 1988; Nozaki, Iriki, & Nakamura, 1986). Such neural network entrainment parallels current proposals concerning the role of sensory experiences in pathway emergence (Hensch, 2004; Marder & Rehm, 2005; Penn & Shatz, 1999).

Entrainment of the infant swallow?

Many of the current intervention techniques, including behavioral and environmental modifications as well as oral-motor stimulation and non-nutritive suck promotion, practiced with infants with dysphagia are implemented without evidence-based data of how such interventions affect the entire feeding process. In particular, how do such interventions affect the pharyngeal component of a swallowing event? Our field needs a better understanding of the underlying anatomic and neurophysiologic underpinnings of the functions we are attempting to change during therapy.

In an effort to address the pivotal need for new knowledge of infant swallowing patterns, the present research aimed to investigate mechanisms which may lower the threshold for swallowing by providing external sensory input to elicit swallowing. This basic level, mechanism research may lead to potential clinical techniques to enhance facilitation of efficiency in sucking, swallowing, and breathing coordination. Emergent research suggests that entrainment of feeding central pattern generators can be accomplished via tactile, kinesthetic, auditory, and chemosensory stimuli (Bingham, 2009). Sensory input not only aids in the initiation of a swallow, but also in modification of the swallowing threshold (Mistry & Hamdy, 2008). In an effort to investigate mechanisms involved for swallowing among two sensorimotor intervention techniques commonly used in the neonatal intensive care unit,

Boiron, da Nobrega, Roux, and Saliba (2009) used acoustic signal analysis. Results indicate that an oral support protocol, involving jaw and cheek stabilization and external pacing, yielded the greatest increase in the number of swallows during feeding compared to an oral stimulation protocol and control group in 43 preterm infants. Very little literature exists concerning the effect of intervention techniques currently practiced with the infant population for feeding and swallowing difficulties on the frequency of swallowing.

Sensory input from the oral and pharyngeal regions due to food, liquid, or saliva are essential for swallowing, and activates afferents within the trigeminal, glossopharyngeal, and vagal (superior laryngeal) nerves (Jean, 1984b, 2001; S. Y. Lowell et al., 2008; Shaker & Hogan, 2000). Early animal research indicates that stimulation of the pharynx can elicit closure and rising of the larynx for swallowing, and that stimulation of the larynx can initiate swallowing (Jean, 1984b; Nishino, Tagaito, & Isono, 1996). The internal branch of the superior laryngeal nerve (iSLN) has been identified as a potent afferent for pharyngeal swallow initiation (Doty, 1968; Jean, 1972, 2001; A. J. Miller, 1972a, 1999; Mistry & Hamdy, 2008; Storey, 1968b). Jafari, Prince, Kim, & Paydarfar (2003) confirmed the importance of the iSLN for safe deglutition in adults, as afferent signals from this nerve facilitate complete closure of the larynx, preventing penetration and aspiration. Findings indicate that interference with sensory reception disrupts swallowing initiation and movement patterning important for preventing penetration and aspiration.

However, researchers have illustrated that the pharyngeal branch of the glossopharyngeal nerve also plays an important role in the reflexive pharyngeal swallow in rats (Kitagawa, Shingai, Takahashi, & Yamada, 2002). Mechanical stimulation of pharyngeal mucosa effectively elicits swallowing (Doty, 1968; F. R. Miller & Sherrington, 1916; Sinclair, 1970). Whereas the superior laryngeal nerve primarily supplies sensory pathways from

laryngeal mucosa, the pharyngeal plexus (pharyngeal branch of the vagus nerve and pharyngeal branch of the glossopharyngeal nerve) supplies the mucosae of the pharynx. Kitagawa and colleagues' de-nervation experiments in rats referenced above demonstrate that mechanical stimulation of pharyngeal regions using a von Frey hair effectively elicited a swallow, but that the reflexive activity was innervated by the pharyngeal branch of the glossopharyngeal nerve. Stimulation of the pharyngeal branch of the vagus nerve was not involved in swallow initiation in the rat. The involvement of the pharyngeal branch of the vagus nerve may be in the efferent output of a swallow pharyngeal reflex. The study also illustrated that the pharyngeal branch of the glossopharyngeal nerve may be just as successful in eliciting a swallow as the superior laryngeal nerve. It is clear that the pharyngeal and laryngeal areas are highly sensitive to stimulation of the pharyngeal swallow reflex.

Research concerning increasing the frequency of the swallowing via peripheral, mechanical sensory input has been investigated in the healthy adult population (Theurer, Bihari, Barr, & Martin, 2005; Theurer, Czachorowski, Martin, & Martin, 2009). Stimulation of oropharyngeal regions via sensory input has been shown to increase cortical activation of areas involved in swallowing (Fraser et al., 2003; Hamdy et al., 2003; Power et al., 2004). Lowell et al. (2008) also observed in adults that oral air pulse stimulation resulted in activation of both bilateral subcortical and cortical swallowing areas, as well as both sensory and motor areas involved in swallowing. Furthermore, the air pulse stimulation resulted in brain activation similar to subjects who were asked to produce a volitional swallow. Results indicate that peripheral sensory stimulation is capable of initiating the brainstem and cerebral swallowing network in the adult human.

Therefore, animal and human research has indicated the ability of peripheral sensory stimulation to elicit swallowing and research in the adult human population has indicated

that mechanical sensory input can facilitate an increased frequency of swallowing. Furthermore, such swallowing stimulation has been demonstrated to increase both subcortical and cortical activation for areas involved in swallowing. Similar investigations with the infant population are needed in order to gain a better understanding of swallowing patterns earlier in life. The present study aims to explore mechanisms that might be used not only to elicit swallowing, but also serve to increase the frequency of swallowing in young infants with swallowing difficulties or those born prematurely, whose central pattern generators are still maturing and primed to collect sensory information - those who are still learning to efficiently coordinate sucking, swallowing, and breathing. However, application of the present research to such disordered or premature populations will depend upon future investigation regarding the ability of infants with neurological immaturity or damage to respond to the sensory stimulation utilized in this research.

Eliciting the infant swallow – current knowledge base

German, Crompton, Owerkowicz, & Thexton (2004) state that limited knowledge exists regarding initiation of the pharyngeal swallow in the infant population. Orenstein and colleagues found that perioral stimulation in the form of an air puff administered to the face at a distance of 30 centimeters consistently and immediately induced the infant swallow, likely influencing afferents of maxillary and manibular branches of the trigeminal nerve (Orenstein, Bergman, Proujansky, Kocoshis, & Giarrusso, 1992; Orenstein, Giarrusso, Proujansky, & Kocoshis, 1988). This technique to elicit a swallow in the infant, coined the "Santmyer swallow," is dependent on the infant's behavior state. The swallowing reflex, using the Santmyer swallow technique, could not be elicited during deep sleep without the infant waking, and was also difficult to elicit during crying. The response to this form of stimulation was found to disappear between 11 and 24 months of age (Orenstein, et al.,

1992). Additionaly, the behavioral shaping of light tactile stimulation applied to the posterior

tongue, and removed immediately to avoid a gag, consistently elicits a swallow in infants and

children with dysphagia (N. Lamm & Greer, 1988; N. C. Lamm, De Felice, & Cargan, 2005).

Specifically, Lamm and colleagues describe their participants as infants and children with

lingual disorders and underlying causes of the dysphagia due to genetic, gastrointestinal,

neuromuscular disorders, or cancer.

Jadcherla et al. (2007) explored two forms of pharyngeal stimulation (air and water

infusions) utilizing pneumohydraulic micromanometry within a sample of healthy, but

premature neonates. The researchers hypothesized that both forms of pharyngeal

stimulation would generate specific neuromotor behavioral outputs, including the pharyngeal

reflexive swallowing (PRS) event. The pharyngeal swallows were confirmed using submental

electromyography (EMG). PRS frequency was found to be greater with the water stimulus

condition as compared to the air stimulus condition. PRS was elicited 22% of the time in

response to air stimulation, whereas PRS was elicited 69% of the time in response to water

stimulation. This study suggests that water is the more reliable form of direct pharyngeal

stimulation to evoke a pharyngeal swallow in healthy, premature neonates. Furthermore, the

frequency of swallowing increased as the volume of water infusions increased. Although

mechanoreceptor and osmoreceptor stimulation in infant development is not fully

recognized, this study demonstrates that such stimulation does elicit PRS responses.

Jadcherla et al. (2007) suggest that their approach using pneumohydraulic

micromanometry represents a safe and reliable instrumental method for evaluating

sensorimotor and physiologic characteristics of the neonatal swallow. However, pharyngeal

stimulation with the administration of water is invasive and requires costly instrumentation.

Potentially, other forms of pharyngeal stimulation may similarly influence glossopharyngeal

and laryngeal nerve afferents, leading to neural activation responsible for swallowing. Many infants in the NICU are already exposed to abnormal sensory expereiences due to the nature of their medical conditions, which emphasizes the importance of considering less intrusive swallow stimulation methods for dealing with the NICU population.

The present study aims to study the effects of two different, non-invasive forms of mechanical, or tactile, stimulation to elicit swallowing in the infant. Tactile input may serve as a robust type of sensory input with infants, as tactile sensory tracts represent one of the first sensory pathways to develop, beginning during the early fetal period (Garcia & White-Traut, 1993). In fact, initial reaction to tactile stimulation *in utero* can be observed shortly following the eighth week of gestation (Hooker, 1942). Due to the early development of tactile sensory tracts, tactile stimulation has traditionally been utilized with infants, who following birth, are experiencing apnea as a method to trigger respiration (Garcia & White-Traut, 1993).

Pacifier and swallowing

A mechanical stimulus is recognized in many regions of the oral cavity, as a large region of mechanoreceptors are on the tongue (A. J. Miller, 1999). In addition to the Santmyer swallow elicited by facial stimulation, perioral and intraoral stimulation to the lips and oral cavity also elicits the sucking reflex (Orenstein, et al., 1992). Different stimuli to the same perioral area elicit different reflexes, thus a close relationship between the suck and swallow is evident (Barlow, 2009c; Lau, 2006; Orenstein, et al., 1992). In 1988, Orenstein and colleagues reported that a pacifier dipped in a sweet substance such as jelly (infants demonstrate an early preference of sweet tastes) only initiates swallows infrequently and inconsistently (Mennella & Beauchamp, 1998). German, Crompton, Owerkowicz, & Thexton (2004) highlight the lack of data concerning how oral sensation influences the

elicitation of swallows in infants. German and colleagues have used infant pigs as the animal model to explore questions surrounding infant feeding behaviors. The researchers investigated how various sensory inputs (frequency and volume of milk delivery) influenced feeding behavior in this animal model. The volume of the milk bolus delivered did not influence the feeding swallow frequency, which is fairly constant at 1.5 swallows per second. However, the increased frequency of milk delivery, particularly in younger infant pigs, increased the swallow frequency to around two swallows per second at higher frequencies of delivery. Therefore, results from their study referenced above demonstrate an increased motor response in the pharynx was observed subsequent to oral stimulation of the anterior oral cavity of infant pigs. This suggests that sucking activity may serve to increase the frequency of swallowing however, the relationship between the suck and elicitation of the swallow is not fully understood. The German, Crompton, Owerkowicz, & Thexton (2004) study illustrates a potential connection between stimulation of trigeminal afferents in the intra-oral region and the posterior glossopharyngeal afferents during feeding with the onset of increased swallowing in the infant animal model.

Suggestions that the maxillary branch of the trigeminal nerve may carry sensory fibers involved in pharyngeal swallowing stimulation have been offered (Doty, 1968; Dubner, Sessle, & Storey, 1978; Jean, 2001; A. J. Miller, 1972b, 1982, 1999). These may or may not be positioned in the optimal location for stimulation of pharyngeal swallowing. Initiation of pharyngeal swallowing via trigeminal sensory fibers may depend on the location of fibers stimulated within the oral cavity. Mechanoreceptors of the anterior tongue involve neuronal connections in the pons region, as opposed to mechanosensitive sensory fibers located in the posterior oral area that involve synapses in the nucleus tractus solitarius. Therefore, the latter may prove better positioned for eliciting pharyngeal swallowing (A. J.

Miller, 1999). Swallowing may be initiated or modified by exciting intraoral and pharyngeal afferents innervated by the trigeminal and glossopharyngeal networks during sucking activity (Barlow, 2009a, 2009c; Jean, 1990; Mistry & Hamdy, 2008). Furthermore, with neuromuscular development, increased tongue force used in driving the bolus toward the pharynx may aid in eliciting the swallow (Barlow, 2009c; Lau, 2006). Lau, Smith, Schanler (2003) found a close relationship between the frequency of swallowing and sucking during oral feeding. However, Lau (2006) suggests that swallowing may not be frequent during non-nutritive sucking since it only involves management of an infant's secretions. Koenig (1990) reports that swallowing was not frequent during non-nutritive sucking activity for a group of term and preterm infants. A close connection between sucking and swallowing is evident, but the precise relationship remains unclear. Thus, the present study aimed to determine the influence of non-nutritive sucking on a pacifier on the frequency of swallowing in the infant. If non-nutritive sucking does not serve as an effective form of entrainment for mechanoreceptors involved in swallowing elicitation, vibrotactile stimulation may represent an alternative, or complementary, habilitation strategy for infants with swallowing disorders.

Vibrotactile device and swallowing

To our knowledge, vibrotactile stimulation and swallowing has not been investigated in the infant population. Previous research suggests that sensory stimulation of the exterior throat region at the laryngeal level is effective in improving swallowing function in adults (Ludlow et al., 2007). In 2007, Ludlow and colleagues devleoped a vibrotactile device that administers mechanical sensory input to the exterior throat area. The vibrotactile sensory input is transmitted via tissue vibration to mechanoreceptors in the laryngeal mucosa via the thyroid cartilage and musculature in the larynx and pharynx.

The two main cranial nerves involved in initiation of the pharyngeal phase of swallowing include the glossopharyngeal and the internal superior laryngeal nerve (iSLN) of the vagus. The glossopharyngeal nerve innervates the posterior region of the tongue and the upper portion of the pharynx. The iSLN innervates the lower portion of the pharynx, down to the level of the true vocal cords. Stimulation of the glossopharyngeal nerve and iSLN can elicit initiation of pharyngeal swallowing. However, as mentioned earlier, stimulation of the iSLN appears to be the most potent pathway in eliciting pharyngeal swallowing. Sensory fibers of the iSLN contain receptors sensitive to tactile stimulation of the mucosa in different regions of the larynx (A. J. Miller, 1999).

Superficial mucosa and laryngeal joints in the laryngeal and pharyngeal regions contain mechanorecepors (Bradley, 2000). Stimulation of pharyngeal and laryngeal mucosa induces various reflexes, including swallowing, for airway protection (Mathew & Sant'Ambrogio, 1990; Storey, 1968a, 1968b; Widdicombe, 1986). Mucosa and joints in the larynx contain both superficial and deep mechanoreceptors (Bradley, 2000). Afferents in the superior laryngeal nerve are primarily rapidly adapting and some slowly adapting to pressure and vibratory stimuli (Boushey, Richardson, Widdicombe, & Wise, 1974; Davis & Nail, 1988). Merkel cell and Meisnner corpuscle receptors likely respond to tactile stimulation in the laryngeal and pharyngeal region (Bradley, 2000).

The vibrotacile device may lower the threshold for swallowing by deliverying sensory input that stimulates superior laryngeal nerve and glossopharyngaeal afferents, which may enhance activation of brainstem and cortical neural networks that control swallowing. Vibratory stimulus applied to the exterior throat region activates mechanoreceptors in the mucosa in the around the glottis and pharyngeal regions. Sensory information involved in the innervations of the pharynx and larynx, likely primarily carried via the iSLN, is carried to

the nucleus tractus solitarius (NTS) and surrounding reticular formation in the dorsal

medullary area of the brainstem. The NTS serves as an elongated relay nucleus that stretches

from the area of the facial motor nucleus down to the level of the cervical spinal cord. The

interstitial subnucleus of the NTS represents the primary area for synaptic terminals of the

glossopharyngeal and iSLN nerves. The dorsal swallowing group interneurons will then

organize and shape the timing for the pharyngeal phase of swallowing. The program is

distributed to the ventral swallowing group of interneurons, which then communicates the

swallowing drive to the various motoneuron pools. The motoneuron pools include the cell

bodies of neurons that innervate skeletal muscles of the head and neck involved in

swallowing, and are located in the longitudinal nucleus ambiguus (NA), which lies ventrally

to the nucleus tractus solitarius in the brainstem, and the dorsal motor nucleus of the vagus.

The semicompact region of the NA receives projections from the NTS innervating

pharyngeal muscles, while the loose area of the NA contains motoneurons specific to

innervations of laryngeal muscles. Motoneuron pools for innervations of muscles important

to pharyngeal swallowing are also located in the trigeminal motor nucleus, the facial motor

nucleus, the hypoglossal nucleus, and at the level of C1-C3 of the cervical spinal cord. (Jean,

2001; A. J. Miller, 1999)

In the present study, vibrotactile senosry stimulation was delivered to the participants

at a low frequency of stimulation. When turned on, the vibrotactile device is programmed to

deliver a four Hz vibration (150 ms on, 100 ms off). The vibration can be heard during

voicing in adults. Vibration, or a moving and dynamic mechanical stimulus, appears to be

more effective in stimulation of sensory fibers sensitive to mechanical stimulation (Davis &

Nail, 1988; A. J. Miller, 1999). Furthermore, these fibers and their synaptic connections on

neurons in the NTS appear to respond to low frequency stimulation. Mechanoreceptors

responding to stimulation of pharyngeal and laryngeal mucosal vibratory stimulation may be significant in activating the pathways involved in pharyngeal swallowing (A. J. Miller, 1999). Additionally, second order neurons are selectively activated at certain frequencies (Mifflin, 1997). Data regarding the appropriate intensity (e.g., frequency of vibrotactile stimulation) for various types of sensory stimulation have not been fully indentified for the human newborn population (W. F. Liu, et al., 2007). Therefore, administration of vibrotactile stimulation to infants at an extremely low frequency marks a safe starting point. Further studies investigating the optimal frequency of delivery in the infant population would be beneficial.

Cortical activation for swallowing in infants – reflexive to volitional

The second aim of the present study is to determine if cortical involvement in response to swallowing stimulation increases over time in early infancy, specifically from two-four months of age to seven-nine months of age. The neonatal phase marks a period in which volitional swallowing is lacking (Jadcherla, et al., 2007). Infants gradually transition from a reflexive, brainstem-mediated suck-swallow-breathe pattern to increasingly include a volitional swallowing component as cortical pathways develop via transitional feeding learning experiences (Jadcherla, et al., 2009; Loughlin & Lefton-Greif, 1994; Stevenson & Allaire, 1991). However, this presumed period of increasing cortical modulation has not been thoroughly documented and the growing suprabulbar influence during the first year remains unclear (Barlow, 2009c; Kelly, et al., 2008).

Research in both animals and humans indicates that breathing-swallowing coordination is mainly brainstem-controlled (Dick, Oku, Romaniuk, & Cherniack, 1993; Feroah et al., 2002; Kelly, et al., 2008; Lewis, Bachoo, Polosa, & Glass, 1990; F. R. Miller & Sherrington, 1916; Saito, Ezure, & Tanaka, 2002; Smith, Wolkove, Colacone, & Kreisman,

1989). However, over the course of development in the first couple years of life, synaptogenesis and cortex and corticobulbar tract myelination occurs, suggesting an increase in suprabulbar control (Gibson, 1991; Huttenlocher & Dabholkar, 1997; Kelly, et al., 2008; Sarnat, 1989). Furthermore, neonates experiencing damage to suprabulbar structures can exhibit swallowing disorders (Sarnat, 1989). Interestingly, developing cortical influence may differ between nutritive suck-swallow-breathe coordination and non-nutritive breathing and swallowing coordination, in that the former may involve growing cortical influence over the first year of life, while non-nutritive coordination may be solely under brainstem control during the first year of life (Kelly, et al., 2008; Kelly, Huckabee, Jones, & Frampton, 2007b). Further investigation is needed. In other sensory domains, using near infrared spectroscopy, findings include different cortical activation patterns between two and three-month old infants for visual perception (Watanabe, Homae, & Taga, 2010). The present study aimed to determine cortical activation patterns over time for non-nutritive swallowing using near infrared spectroscopy.

Bosma (1986) introduced the idea of encephalization in describing the maturation from a reflexive feeding process to one with increasing cortical modulation (Rogers & Arvedson, 2005; Stevenson & Allaire, 1991). The pattern of gradual suprabulbar contribution is suggested through examination of infant feeding reflexes. Infant primitive reflexes related to swallowing, such as rooting and suckling (an immature version of sucking), disappear around 6 months (J. C. Arvedson & Brodsky, 2002). Volitional control of the infant suck has been reported to emerge at 3 months, but more research is needed (Reynolds & Fletcher-Janzen, 2008). It appears as though the evolution of volitional oral-preparatory and oral-phase motor skills begins around 6 months of age and continues for several years (Kramer & Eicher, 1993; Stevenson & Allaire, 1991).

Near-infrared Spectroscopy

Near-infrared spectroscopy (NIRS), an optical imaging technique, has been utilized in infant studies in the assessment of motor, visual, cognitive, auditory, and language domains (Aslin & Mehler, 2005; Isobe et al., 2001; J. Meek, 2002). This optical imaging technique was first implemented with adult humans and reported in 1977 (D. Boas & Franceschini, 2009; Jobsis, 1977). Near infrared spectroscopy was first developed for use in infants to screen for brain function abnormalities in the nursery. NIRS is a safe, non-invasive technique for clinical and research purposes with infants and has been utilized with premature, medically-fragile infants (Cerussi, Van Woerkom, Waffarn, & Tromberg, 2005; Liston et al., 2002; Pichler et al., 2008; Zotter et al., 2007).

Optical imaging utilizes absorption spectroscopy as a measure of relative blood oxygenation in the brain via measurements of hemoglobin concentration, as near-infrared light in the 650-950 nm wavelength range is capable of penetrating hemoglobin, with low absorption by cerebral tissues (D. Boas & Franceschini, 2009; Bortfeld, Wruck, & Boas, 2007; J. Meek, 2002). Wavelengths of light beyond the 950 nm range are greatly absorbed by water (D. Boas & Franceschini, 2009). Within this "optical window," near-infrared light is emitted through the scalp and brain tissue and is differentially absorbed by oxygenated and deoxygenated hemoglobin in the blood (Gratton, Sarno, Maclin, Corballis, & Fabiani, 2000; Villringer & Chance, 1997). One of the chief limitations with NIRS is the quantification of hemoglobin concentration changes (Hoshi, 2003). The path-length of light transmission cannot be precisely quantified due to the scattering of light as it traverses through the scalp and outer cortex tissue (D. Boas & Franceschini, 2009). However, a reliable amount of light travels through the cortical mantle in a banana-shaped pathway back through the scalp and is measured by photodetectors (Gratton, Maier,

Fabiani, Mantulin, & Gratton, 1994). Two wavelengths of near-infrared light are used in order to maximize the relative quantifications of hemoglobin concentration changes (D. A. Boas, Dale, & Franceschini, 2004). The TechEn, Inc. system (Milford, MA, model CW6) used in the present study emits two wavelengths of near-infrared light: 690 nm (more sensitive to deoxygenated hemoglobin) and 830 nm (more sensitive to oxygenated hemoglobin). Changes in local oxygenated hemoglobin and deoxygenated hemoglobin (relative to a control period) are measured in a region of interest, and contribute to the computation of a total hemoglobin measurement. The absorption changes are quantified via a modified Beer-Lambert Law (Cope et al., 1988).

In reaction to a stimulus event, neural activation typically results in an increase of oxygenated hemoglobin in the area of interest, while local concentrations of deoxygenated hemoglobin decrease. Total hemoglobin is also found to increase (Bartocci et al., 2000; Bortfeld, et al., 2007; Hoshi & Tamura, 1993; Jasdzewski et al., 2003; Obrig et al., 1996; Strangman, Franceschini, & Boas, 2003). The term coined, "neurovascular coupling," describes the physiological changes in the relationship between neural and vascular responses to brain activation. Cerebral blood flow increases to the local region of interest due to an increase of oxygen consumption resulting from neural activation. This hemodynamic response is utilized as an index of cortical activation and research indicates a link between hemodynamics and neural activity (Bortfeld, et al., 2007; Gratton, Goodman-Wood, & Fabiani, 2001; Grinvald et al., 1991; J. Meek, 2002; Obrig et al., 2000; Seiyama et al., 2004; Strangman, Boas, & Sutton, 2002; Villringer & Chance, 1997; Villringer & Dirnagl, 1995; Watanabe, et al., 2010). The hemodynamic response is slow, typically peaking 6-8 seconds after the stimulus event (Irani, Platek, Bunce, Ruocco, & Chute, 2007; J. Meek, 2002).

Literature points to considerable variation in the infant oxygenated- and deoxygenated hemoglobin response during optical imaging (Karen et al., 2008). Studies have indicated that infants may demonstrate increases in both oxygenated and deoxygenated hemoglobin, contributing to the increased total hemoglobin (Bortfeld, et al., 2007; J. Meek, 2002; J. H. Meek et al., 1998). The rise in deoxygenated hemoglobin, an opposite response compared to adults, may be due to an immature infant brain (Bortfeld, et al., 2007; J. Meek, 2002). Findings from other research indicate an increase in oxygenated-hemoglobin, with a varying deoxygenated-hemoglobin response (Hoshi et al., 2000; Taga, Asakawa, Hirasawa, & Konishi, 2003). Other infant research has found a decrease in both oxygenated- and deoxygenated-hemoglobin (Kusaka et al., 2004). Some exceptions to the above variation include NIRS studies in which infants were sedated (Isobe, et al., 2001). In these cases, the typical adult hemodynamic response pattern was observed, with a local increase of oxygenated hemoglobin concentration and decrease of deoxygenated hemoglobin concentration in the region of interest. Thus, behavioral state may affect the infant hemodynamic response (Karen, et al., 2008).

Aslin & Mehler (2005) report that studies with infants have not been conducted to determine if neural tissue damage occurs from the transmission of infrared-light through the scalp and brain tissues. With the infant brain, general consensus suggests that between 0.3 mW and 5.0 mW of near-infrared light intensity is safe.

10-20 International System for Electrode Placement with Electroenchephalography

The 10-20 system of electroencephalography (EEG) electrode placement, as delineated in 1957 in the Report of the Committee on Methods of Clinical Examination in EEG, is currently the most reliable technique for positioning the NIRS probes with the infant population (Jasper, 1958; Wilcox, Bortfeld, Woods, Wruck, & Boas, 2008).

Neuronavigation to locate the precise underlying neural areas of interest is not typically

performed with infants due to the safety considerations with magnetic resonance imaging

(MRI) (Aslin & Mehler, 2005). In the current study, NIRS probe positioning for the brain

regions of interest for swallowing used external anatomical landmarks of the infant skull (i.e.,

nasion, inion, external auditory canals) and averaged infant atlas MRI templates, accessed

from Dr. Richards' at the University of South Carolina Neurodevelopmental MRI database

(Almli, Rivkin, & McKinstry, 2007; Evans, 2006; Fu, Fonov, Pike, Evans, & Collins, 2006;

Karama et al., in press; Leppert et al., in press; A. K. Liu et al., 2007; Richards, 2010, 2009;

Sanchez, Richards, & Almli, 2011; Waber et al., 2007; Wilke, Holland, Altaye, & Gaser,

2008). The 10-20 system assumes a reliable relationship between the external scalp

landmarks and the underlying neural substrates, although individual variation does exist

(Blume, Buza, & Okazaki, 1974; Homan, Herman, & Purdy, 1987; Jasper, 1958; Okamoto et

al., 2004).

Methods

Participants

Subjects were recruited by a recruitment pamphlet (see Appendix A) placed in local hospital's birthing center, local obstetrician and pediatrician offices, the local community health center, and local retail and professional organizations.

A power analysis was performed before participant enrollment using data on the mean spontaneous swallowing frequency in infants with dysphagia who had achieved oral feeding (Jadcherla, et al., 2009). The independent variable was the type of feeding group and the outcome variable was the swallowing frequency of infants with dysphagia. The number of subjects required in each age group was determined using a power analysis performed using Systat13 software and yielded the following results, as outlined in Table 1 below.

Table 1

A Priori Power Analysis

_____

Expected difference	Standard deviation of difference	Effect size	Alpha	Power	No. of subjects
0.400	0.300	1.333	0.05	0.80	7 per group

_____

Infant exclusionary criteria were determined through parent/caregiver-report:

- History of feeding or swallowing problems
- Currently being treated for a diagnosed reflux
- Never been exposed to either a bottle or a pacifier
- Born prematurely (before 37 weeks gestation)
- Fails the Ages & Stages-3 developmental screening
- Unable to maintain a quiet, calm behavior state for less than 5 minutes at a time
- History of seizures
- History of neurological or neurodevelopmental abnormalities
- Congenital anomalies or craniofacial malformation

Additional exclusionary criteria regarding the use of near-infrared spectroscopy (NIRS)

included:

- Highly-pigmented (dark) skin color
- Known cardiovascular disorders or neuropathies
- Unable to maintain a quiet, calm behavior state for less than 5 minutes at a time
- Broken skin in the area of the head that NIRS probes will be placed on the scalp

As all of the researchers involved use English as their primary mode of

communication, participants of the current study were limited to parents/caregivers able to

proficiently speak, read, and understand English. Data collected from the infants tested

during the pilot phase was used in the final study if their data was valid and reliable.

Equipment and Software

All study equipment was used in the Neural Bases of Communication and

Swallowing Laboratory at James Madison University.

Pacifier Stimulation

Parents/caregivers were instructed to bring a familiar pacifier that their infant used

consistently at home for the portion of the study utilizing pacifier stimulation.

Vibrotactile Stimulation

Vibrotactile stimulation was delivered via a small flat motor (size of a dime) attached

to the outside of the throat, laterally to the thyroid cartilage, with medical or double-sided

adhesive tape.

Accelerometers

Two 0.4 gram Kistler accelerometers (Amherst, New York, model 8778A500) were

used in an attempt to measure swallowing and sucking movements. The first accelerometer

was secured using tape on the infant's external throat area, laterally to the thyroid cartilage,

to detect movement of the hyolaryngeal elevation during swallows. This was used to indicate

a swallow had occurred. Pharyngeal swallows are regularly identified by the characteristic

hyoid and laryngeal elevation (Amaizu, Shulman, Schanler, & Lau, 2008; Bulock, et al., 1990;

Logemann et al., 1992). A second accelerometer was positioned with tape in the infant's

facial region in an attempt to detect and confirm sucking movement.

Inductotrace

The Inductotrace System (Ambulatory Monitoring, Inc., Ardsley, NY, model

10.9000), inductive plethysmography, was used to record the transient suppression of

respiration, or apneic moment, associated with a swallowing event for both adults and

infants (Ardran, Kemp, & Lind, 1958; Bamford, et al., 1992; Clark, 1920; Curtis, Cruess,

Dachman, & Maso, 1984; Gryboski, 1969; Koenig, et al., 1990; Logan & Bosma, 1967;

Loughlin & Lefton-Greif, 1994; B. Martin, Logemann, Shaker, & Dodds, 1994; Mathew,

1991; Nishino, Yonezawa, & Honda, 1985; Preiksaitis, Mayrand, Robins, & Daimant, 1992;

Selley, Flack, Ellis, & Brooks, 1989a, 1989b; Thach & Menon, 1985; Wilson, Thach,

Brouillette, & Abu-Osba, 1981). Two elastic transducer bands (Ambulatory Monitoring, Inc.,

Ardsley, NY), which contain insulated wires and are made specifically for infants within the

current study's age range, were used to record the respiratory patterns of the participant.

One elastic band was placed around the infant's rib cage and one elastic band around the

abdomen. Inductive plethysmography is regularly used to record respiratory measurements

in humans, even during infancy (Martinot-Lagarde, Sartene, Mathieu, & Durand, 1988;

Semienchuk, Motto, Galiana, Kearney, & Brown, 2005). Abdominal, rib cage, and sum

motion signals were not calibrated for volume. Rather, the amplifiers were set at 1.0 for the

abdominal and rib cage signals and 2.0 for the sum signal. The inductive plethysmography

has been used previously with infants for measurement of respiratory movements related to swallowing (Goldfield, Richardson, Lee, & Margetts, 2006; Nixon, et al., 2008).

Near-Infrared Spectroscopy (NIRS)

Near-infrared spectroscopy (TechEn, Inc., Milford, MA, model CW6) was used to quantify the percent change in deoxygenated hemoglobin and percent change in oxygenated hemoglobin in response swallowing stimulation. Using the International 10-20 system of electrode placement for electroencephalography, this study placed NIRS probes bilaterally on the scalp over the somatosensory and motor areas of the infant brain. Probe configuration consisted of an emitter placed bilaterally over the primary motor region (M1) of the brain, with two detectors in the post-central sensory region and two detectors in the pre-central motor planning region (see Figure 1 below). Emitters and detectors were separated by a distance of 2 cm (Taga, Homae, & Watanabe, 2007). Thus, for each hemisphere, data was collected from four sampling areas (the region between each of the 4 detectors and the central emitter). Probes were housed in an elastic headband. The intensity of the laser light hitting the scalp was between 3-3.5 mW for the 830 nm wavelengths and around 5 mW for the 690 nm wavelengths.
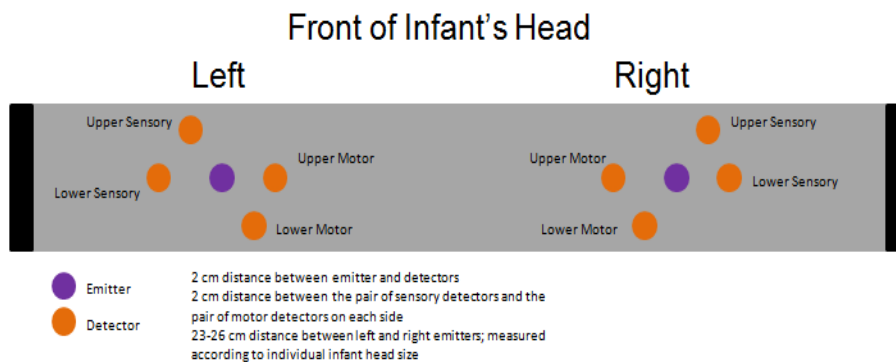
Figure 1. Near-infrared spectroscopy headband probe configuration. The lower sensory and upper motor detectors were on a 180° angle relative to the emitter on either side, while the upper sensory and lower motor detectors were positioned at 10° angles from relative to the emitters.

Brainsight v2.0 (Rogue Research Inc., Montreal, QC) was used to view and navigate averaged infant atlas MRI templates, accessed from Dr. Richards' at the University of South Carolina Neurodevelopmental MRI database (Almli, et al., 2007; Evans, 2006; Fu, et al., 2006; Karama, et al., in press; Leppert, et al., in press; A. K. Liu, et al., 2007; Richards, 2010, 2009; Sanchez, et al., 2011; Waber, et al., 2007; Wilke, et al., 2008). An atlas for infants aged 3 months, 6 months, and 9 months of age were used in order confirm that probe configuration (see Figure 2 below) targeted the same underlying neural areas for the entire age range of the present study. Brainsight neuronavigation also facilitated determination of emitter placement three inches above T3 and T4 along the lateral Cz to T3/T4 line of the International 10-20 system. The lower region of the primary motor area (M1) was consistently located three centimeters above T3/T4 for our age range.

Figure 2. Near-infrared spectroscopy probe configuration as determined using Brainsight. The letter "e" represents an emitter and the letter "d" represents a detector. Probes were placed bilaterally.

Specifically, for each of the three infant brain atlases utilized (3 months, 6 months, and 9 months), the files was opened in Brainsight using the 3x1 layout. Under the "MNI

tab," the Anterior Commissure-Posterior Commissure line (AC-PC line) was manually set, using an online AC-PC line figure for visual guidance in marking the AC and PC points. Visual observation confirmed that the line was oriented in a midline position. No bounding box or overlay adjustments were made. Under the "ROIs Tab," a new region of interest (ROI) was selected from region paint. The sagittal view was selected for the main window. The "+" marker was then moved to the right edge in the coronal view. The pen diameter was set to 10 mm (1 cm). The emitter and detectors distances were then measured and marked in the appropriate motor or somatosensory area of the brain. The detectors were placed at a 2 centimeter distance from the emitter.

Data collection and analysis

An ADInstruments, Inc. PowerLab 16/30 (Colorado Springs, CO, model ML880) data acquisition unit was used to collect and synchronize all signals described above, as well as amplify and digitize the signals for data analysis. E-Prime v2.0 (Psychology Software Tools, Inc., Sharpsburg, PA) was used to control (run) the vibrotactile stimulation, while LabChart v7.1 (ADInstruments, Colorado Springs, CO) with PowerLab was used to collect, display, and analyze the digitally acquired signals from the various measurement methods being used in this study. HomER (Hemodynamic Evoked Response) software was used for NIRS data analysis (Huppert & Boas, 2005). Systat 13 and SPSS 18.0.0 were used for statistical analyses. Figure 3 below provides visual mapping of the equipment set-up for the overall experiment.
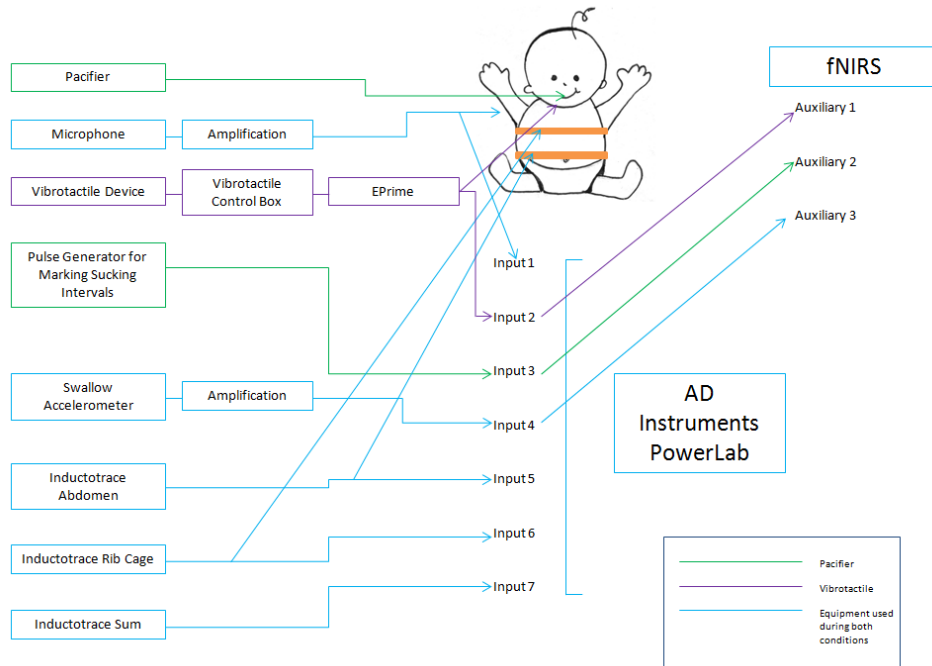
Figure 3. Equipment flowchart for overall experiment.

Experimental Design

This study was a prospective, repeated design. Outcome measures were within-subjects (effect of stimulation) and between-subjects (age). All infants in this study were to receive pacifier and vibrotactile stimulation, with a corresponding period of no stimulation. The independent variables were the stimulus conditions (no stimulation, pacifier stimulation, and vibrotactile stimulation) and age group. The dependent variables were the frequency of swallowing and the NIRS measures of changes in percent oxygenation hemoglobin in the somatosensory and motor regions of the infant brain.

The pacifier stimulation, vibrotactile stimulation, and no stimulation conditions were presented in a counter-balanced order. Each condition was presented for an accrued time of 5-10 minutes. For the pacifier stimulation period, the infant was offered a pacifier for non-nutritive sucking, which was recorded for up to 10 minutes. Vibrotactile stimulation was also presented for up to 10 minutes. For the present study, the vibrotactile motor ran at 100 Hz

and was programmed, via an E-Prime script, to be on for 150 ms of vibration followed by 100 ms quiet intervals, resulting in 4 Hz modulation. Each vibrotactile stimulation epoch was presented for 10 seconds at a time, with randomized inter-stimulus periods of no stimulation for 18-28 seconds between each stimulus presentation (see Figures 4, 5 below). Up to 18 stimulus epochs were presented within a 10 minute timeframe. Infants were allowed to feed during the session, pending individual hunger demands.
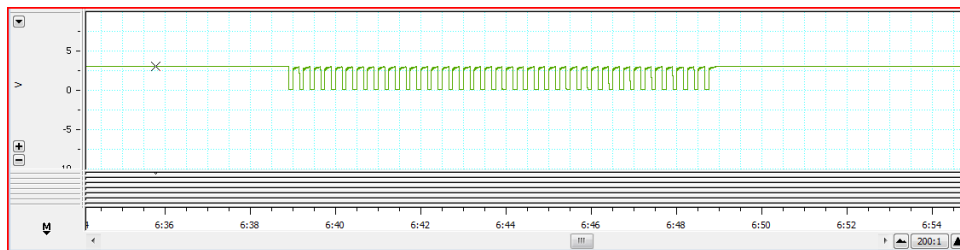
Figure 4. Single, 10s vibrotactile stimulation epoch as displayed in LabChart.
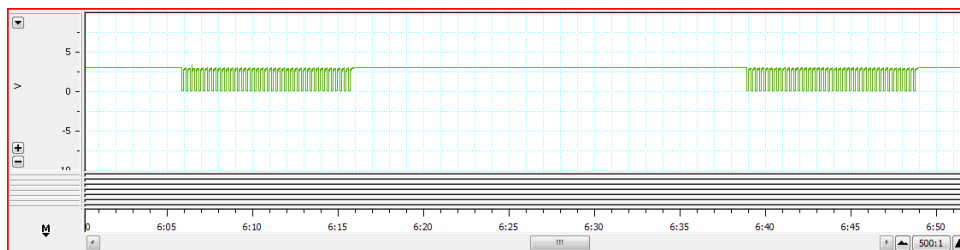
Figure 5. Two, 10s vibrotactile stimulation epochs separated by a randomized non-stimulation interval of 23s as displayed in LabChart.

Procedures

Consent Process

Interested parents/caregivers were instructed to call the Neural Bases of Communication and Swallowing Laboratory (NBCSL) at James Madison University to participate in the telephone screening in order to determine whether or not the infant was eligible to participate (see Appendix B). If the infant was determined eligible, the investigator scheduled an appointment with the parent/caregiver to discuss the informed consent form and begin the experimental session. A letter of invitation to participate in the study, a copy of the parental informed consent form (see Appendix C), a JMU parking

pass, and the Ages & Stages-3 developmental screening parent questionnaire were mailed to the parent/caregiver (Dionne, Squires, & Leclerc, 2004; Pizur-Barnekow et al. 2010). The caregiver was asked to bring the completed questionnaire to the scheduled appointment. If the caregiver did not complete the questionnaire prior to the scheduled appointment, it was completed at the time of the appointment. During the scheduled appointment, parents/caregivers of the eligible infants read and reviewed the informed consent form with the investigators. After all parent/caregiver questions were answered and the parent/caregiver displayed full understanding of the consent form and agreed to allow the infant to participate in the study, the consent form was signed. Additional release forms involving permission to use data for educational purposes and permission to contact the parent/caregiver for future studies were presented and signed.

Caregivers/parents could elect or decline to have their infant participate in using near-infrared spectroscopy to measure brain activity in response to stimuli. Once the consent process was complete, the participants spent 1-2 sessions at the NBCSL, which took approximately 2 hours. Those participants enrolled in the NIRs portion of the study also spent 1-2 sessions at the NBCSL after the consent process was completed. The NIRS sessions took approximately 3-4 hours.

Recording Procedures

After the consent process was complete, the devices were placed (Figures 3, 6). A microphone was also clipped to the clothing of either the caregiver/parent or the infant. If the infant was participating in the NIRS portion of the study, the NIRS probes headband was placed on the head. All experimental sessions digitally video recorded. Digital video recordings were stored on a secure NBCSL server with no names to protect the anonymity of each participant.

Figure 6. Infant participant wearing NIRS probe headband and "suck" accelerometer (circled in white). "Swallow" accelerometer not visible in picture.

Following an experimental session, each parent/caregiver was asked to confirm that the infant did not experience any adverse events before departing the session. A follow-up phone call or email was made to determine if any subsequent adverse had occurred due to participation in the study.

Risks/Discomforts

Both the pacifier and vibrotactile device were non-invasive forms of stimulation with no known risks. The vibrotactile device was secured on the throat region using medical or double-sided tape, which could cause redness when removed. Baby lotion was offered to reduce redness per parent/caregiver request. The accelerometer(s) were secured on the throat and in the facial region using medical or double-sided tape, which could cause redness of the skin when removed. The two elastic Inductotrace bands stretched, producing no discernable discomfort, other than light pressure when wrapped around the rib cage and abdomen. The bands were not restrictive and easily stretched to measure chest wall and abdominal movement.

Markers were used on the scalp to indicate the International 10-20 system locations before probe placement. Laser light emitted from the NIRS optodes could potentially cause eye damage if the light makes contact with the eyes. The lasers were only turned on once they were securely positioned on the infant's head. The infants may have felt light pressure from the sensor probes being held in place by a headband. Every effort was made to apply the probes slowly to allow the infant to adapt to them.

Outcome Measure

This study involved two outcome measures, the mean frequency of swallows per minute over a period of five minutes. The mean frequency of swallowing was measured for each condition: no stimulation, pacifier stimulation, and vibrotactile stimulation.

Data Analysis Procedures

Following data collection from the first six participants enrolled in the current study (three in each age group), a second power analysis was performed using the current study's data. The second power analysis used the swallowing frequency data collected from the first six participants of the current study (three infants in each age group). Mean differences and standard deviations of the differences in swallowing frequency per condition were calculated and the *N* required per group at a power of .8 and an alpha of .05 per repeated analysis using Systat13 software (see Table 2 below).

Table 2

Second Power Analysis

Stimulation type by group	Expected difference	Standard deviation of difference	Effect size	Alpha	Power	No. of subjects
Young group with pacifier	-5.833	4.215	1.384	0.05	0.80	7 per group
Old group with pacifier	4.467	2.715	1.645	0.05	0.80	6 per group
Young group with vibrotactile	-2.800	1.735	1.614	0.05	0.80	6 per group
Old group with vibrotactile	-2.900	1.735	1.672	0.05	0.80	4 per group

Results estimated that six participants in each age group, yielding a total sample size of twelve participants, would be sufficient to answer the research questions.

The mean frequency of swallowing between conditions was compared using a repeated-measures ANOVA while testing for age group between subjects and the interaction of age group by stimulation effects. The significance level was set at $\alpha = .05$, as no ANOVA was planned for the NIRS results. A Bonferroni correction is not necessary at this time, as we only have one outcome variable.

Video Recording Observation and Marking Swallows Procedures

The investigator conducted the analysis using de-identified data files. For each participant, the video recordings were first reviewed and detailed notes made, noting all times when the infant moved or produced a vocalization. If motion artifact in the LabChart data accompanied a movement, this was also noted. The audio channel from the LabChart data was converted into a WAV audio file. The WAV audio files were compared to the video files in order to match timing between the LabChart files and videos. For the first seven participants, the video files for the pacifier condition were also carefully reviewed and all sucking interval times were noted. Sucking activity was clearly visible in watching the videos. For the remainder of the participants, sucking activity was carefully

marked using a pulse generator, which yielded marked sucking intervals in a channel in the

LabChart data. All notes from the videos were then added as comments in the LabChart

data files. Sucking intervals and vibrotactile epochs were also added as comments (see
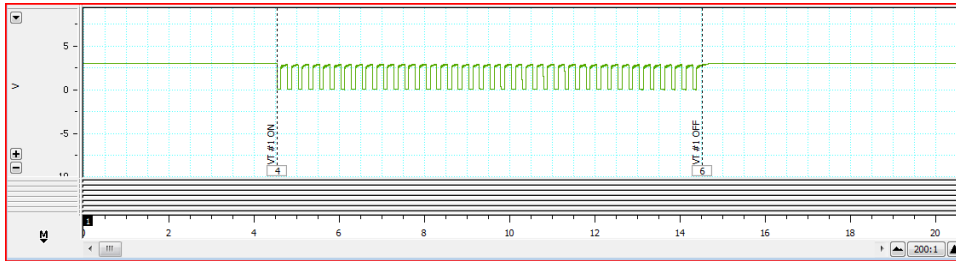
Figures 7-9 below).

Figure 7. Comments identifying a vibrotactile stimulation epoch as displayed in LabChart.
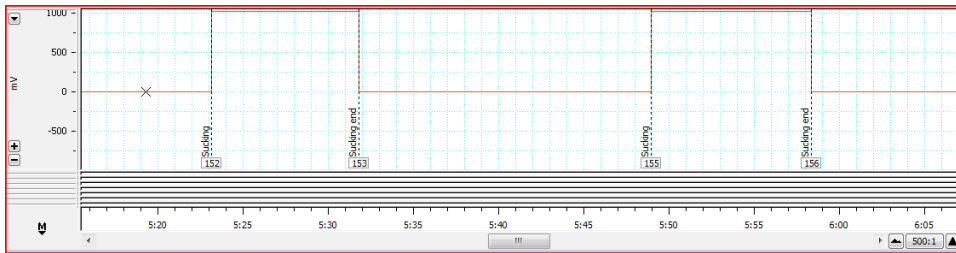
Figure 8. Comments identifying sucking intervals marked via pulse generator as displayed in LabChart.
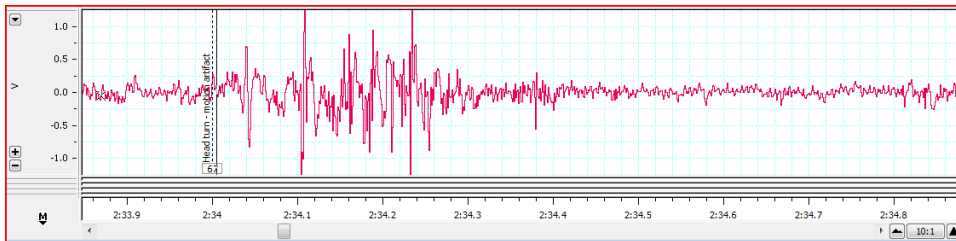
Figure 9. Comment identifying movement and motion artifact as observed in video recording as displayed in LabChart.

Next, all swallows were marked in the de-identified LabChart data files for each

condition (see Figure 10 below). Files were blinded by a staff co-investigator so that the

investigator was not aware of which condition file was being reviewed. The infant swallow

pattern was identified through extensive review of LabChart files recorded during bottle

feedings, as well as data files which included reliable "marking" of swallows using a pulse

generator. Swallows were identified by the above determined typical swallowing pattern

with a corresponding apneic moment in the "Sum" Inductotrace signal of at least 350 ms

(Lau 2006). The phase of respiration in which a swallow occurred was determined using a

channel in LabChart that displayed the first derivative of the "Sum" Inductotrace signal

(999 point window width). In the "Sum 1st Derivative" channel, a line was drawn at zero.

A swallow occurring when the "Sum 1st Derivative" signal was below zero was considered

to occur during exhalation and was considered to occur during inhalation when this signal

was above zero.
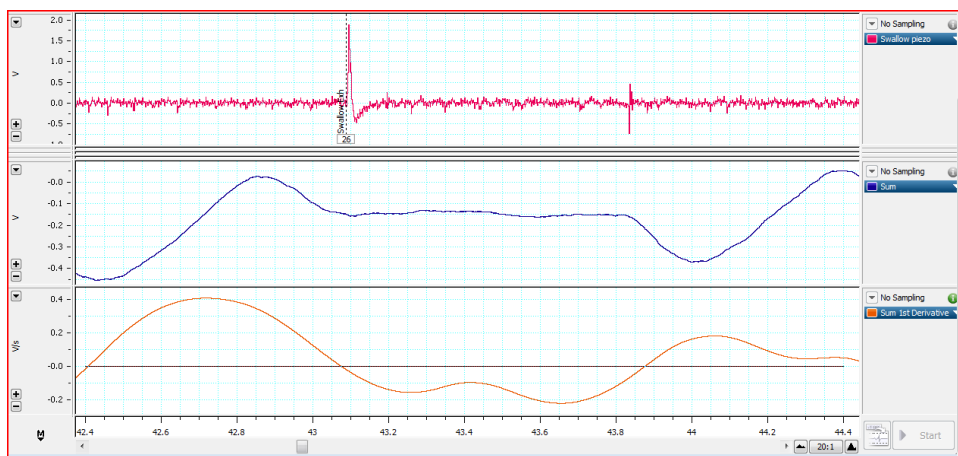
Figure 10. Swallow on exhalation and corresponding apneic moment as marked in LabChart.

Swallowing Frequency Procedures

All raw data comments from each LabChart data file were then exported to an

Excel spreadsheet that captured the timing of all events from each condition for each

participant. The Excel spreadsheets were then utilized to determine all "calm time" that

could be pulled for each condition to reach the accrued five minutes of time for data

analysis of swallowing frequency. Target "calm time" included time when the infant was

not moving or crying. Given that the present study's sample included infants, motion

artifact was unavoidable, as infants tend to move spontaneously. This represents a

limitation of the current study, particularly in analysis of the near-infrared spectroscopy

data. Therefore, after all completely "calm time" was identified and if additional time

periods were needed to reach the accrued five minutes, additional "calm times" were included. However, if swallows occurred within three seconds following motion artifact or crying, or within one second following a crying event detected in the accelerometer recording, data were omitted from analysis. For all usable time periods, the longest durations of uninterrupted time were included in the analysis. Swallows were then counted within the accrued five minutes of usable time and the swallowing frequency per minute was calculated. For each swallow, it was also noted whether or not respiration was interrupted on inspiration or exhalation.

Intra-rater Reliability

Following data collection and analysis of the ninth participant, intra-rater reliability in identifying and marking swallows was assessed. Data from the first nine participants yielded 25 files that could be used for assessing intra-rater reliability; 20% were randomly chosen and blinded, re-labeled as files "A-E." Swallows and the phase of respiration were then re-marked for each blinded file and then compared to the originally marked files for consistency and accuracy.

NIRS Analysis Procedures

Near-infrared spectroscopy data files were opened and analyzed in HomER data analysis software (Huppert & Boas, 2005). After a file was opened in HomER, all channels were assessed in an unfiltered view for a cardiac signal and appropriate signal intensity. Channels which did not contain a cardiac signal, were too noisy, or were not of appropriate intensity in raw data form ($.5\text{-}2 \times 10^6$) were not included for processing. A low pass filter (.5 Hz) high pass filter (.016 Hz) and were then applied in order to reduce respiration and cardiac components of the signals, since the hemodynamic response of interest is relatively slow in comparison to the other physiological signals. The "Cov. Reduced dConc" filtering

was then applied (a third principle component analysis performed on the concentration

data), for data processing.

The periods that represented the least motion artifact after filtering were identified

and epochs during this time were chosen for event-related averaging (see Figure 11 below).

Between six and 16 stimulation or control (no stimulation) epochs were included in the

event-related averages, depending on the individual's data. A minimum of six epochs proved

sufficient in seeing the hemodynamic response. The epoch times were identified through

identifying vibrotactile stimulation time, pacifier time, or non-stimulation times and manually

entered into HomER. The vibrotactile epochs, as controlled via E-Prime, were included as

an auxiliary channel in the NIRS machine and were recorded in HomER. The sucking

interval epochs were either noted from observation of the video recordings and converted to

HomER time or pulled directly from the NIRS auxiliary channel that received the "sucking"

marking via a pulse generator. The no stimulation epochs were identified in the LabChart

data files and manually entered in HomER. Non-stimulation epochs did not include any

swallow events. The time intervals between each epoch for each condition were set as closely

to uniform and identical as the raw data allowed. The average was then performed over 25

seconds for epochs in each condition (no stimulation, vibrotactile, or pacifier), from five

seconds before the start of an epoch to 20 seconds following the initiation time of each

epoch. Averaged data were then exported to an Excel spreadsheet. A hemodynamic

response was characterized by a peak value equal to or greater than a 2% increase in

oxygenation.
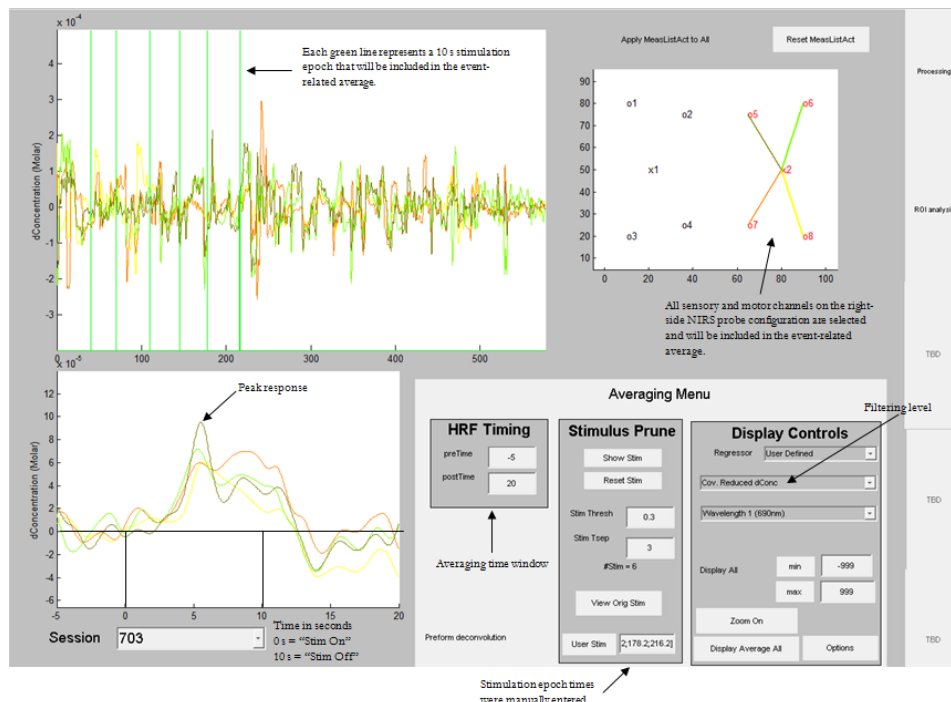
Figure 11. Screenshot of event-related averaging in HomER for a stimulation condition.

As a point of reference, see Figure 12 and Figure 13 below to view the typical hemodynamic response (or cerebral blood blow response) as a result of neural activation in a region of interest in the brain.

Figure 3: Schematic of a typical CBF response to brief neural activation.
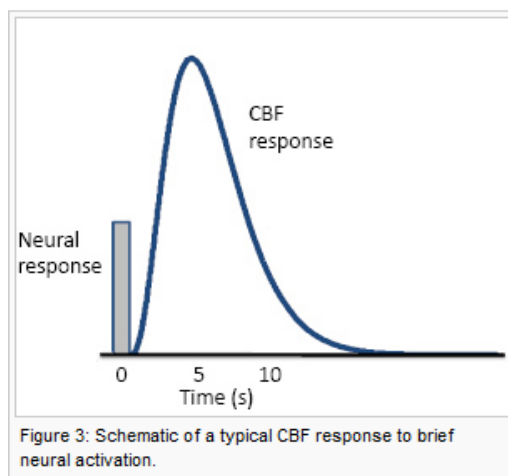
Figure 12. Typical hemodynamic response from Pasley & Freeman (2008).

Figure 13. Averaged NIRS oxygenation data from a region of interest from Bunce, Izzetoglu, Izzetoglu, Onaral, & Pourrezaei (2006).

Results

Participants

Recruitment contacts were with 21 parents/caregivers willing to volunteer their infants. Of those, nine infants did not qualify (seven infants were not using a pacifier, one infant was being treated for a diagnosed reflux, and one was born before 37 weeks gestation). The study included 12 healthy infant volunteers with parent-reported normal swallowing, forming two different age groups (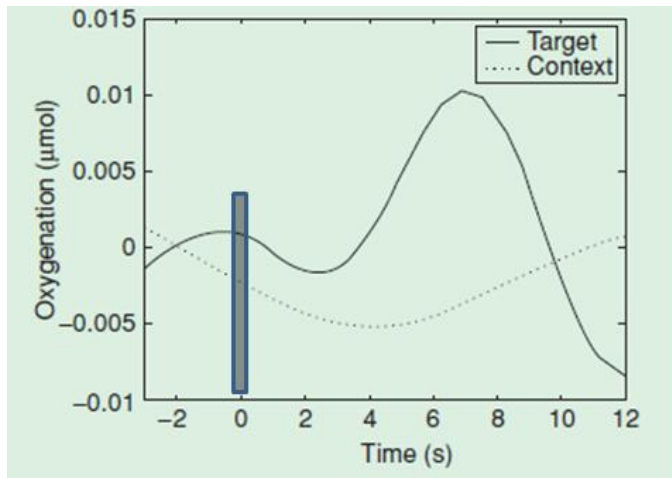six 2-4 month old infants and six 7-9 month old infants). A total of 13 experimental sessions were completed, with 12 unique participants (8 females, 4 males) completing the study. Longitudinal data was collected from one infant who participated in the study as a younger infant in the 2-4 month range and returned to participate again as an infant in the older 7-9 month range. The average age of the younger infants was 3:16 (range 2:16 to 4:19) months and the average age of the older infants was 8:6 (range 7:4 to 9:19) months. All participants scored within in normal limits on the Ages & Stages-3 developmental questionnaire, meeting age-appropriate developmental milestones in communication, gross motor, fine motor, problem solving, and personal-social categories. Wassenaar and Van den Brand (2005) found that the higher levels of melanin interfered with the reflected wavelength transmission in near-infrared spectroscopy measurements for those with "black, very black, and incredibly black skin" color. (p. 196) No participants from the current study who participated in the near-infrared spectroscopy portion of the study had black skin color; all infants who participated in the NIRS portion of the study were Caucasian with very light skin color. Therefore, all near-infrared spectroscopy data collected during the current study is believed to be accurate and reliable in regard to the skin pigmentation issue. There are no adverse events to report following data collection from the first 13 participants. Per parent report, the redness

caused by removal of medical tape typically disappeared within eight hours after removing the tape.

As many infants, particularly in the older age range, use a pacifier for a short period of time in early infancy and then prefer to use their own fingers for oral stimulation, infants who no longer used a pacifier or refused the pacifier during the experimental session only received vibrotactile stimulation. From the group of 12 unique participants, two infants (one from each age group) refused the pacifier during the experimental session. For the purpose of the repeated-measures ANOVA concerning swallowing frequency, datasets that included data collected from all three conditions (no stimulation, vibrotactile, and pacifier) were used for the statistical analysis, which included 5 participants in each group.

Vibrotactile Device Amplitude

The first three participants from the younger age group and the first four participants from the older age group were considered to receive low vibrotactile amplitude, as the battery was at around 67% full capacity. All other participants were considered to receive normal vibrotactile amplitude (see Figures 14, 15 below illustrating swallowing frequency during the vibrotactile condition, comparing low amplitude and normal amplitude for each age group). For the younger group, the mean swallowing frequencies between the two vibrotactile amplitude groups were nearly identical (4.67 $\pm$ .31 for the low amplitude group and 4.67 $\pm$ .68). For the older group, the mean swallowing frequency for the low amplitude was slightly higher than the mean swallowing frequency for the normal amplitude group (5.30 $\pm$ .81 and 4.93 $\pm$ .31), respectively). Independent samples *t*-tests comparing the mean swallowing frequencies between the two vibrotactile amplitude groups for each age group indicated no significant difference in mean

swallowing frequencies for the two different vibrotactile amplitude groups within the

younger infant group and the older infant group, $t(4) = 0.00$, $p > .05$ and $t(5) = 0.73$, $p > .05$, respectively.
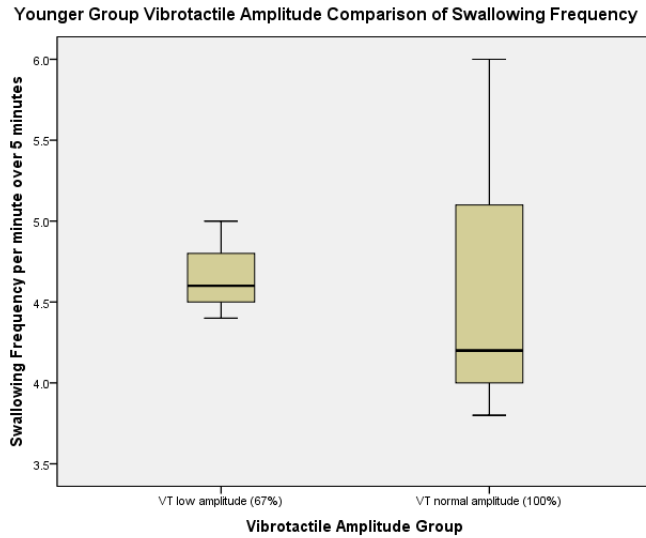
Figure 14. Comparison of mean swallowing frequency between vibrotactile amplitude groups for the younger infants.
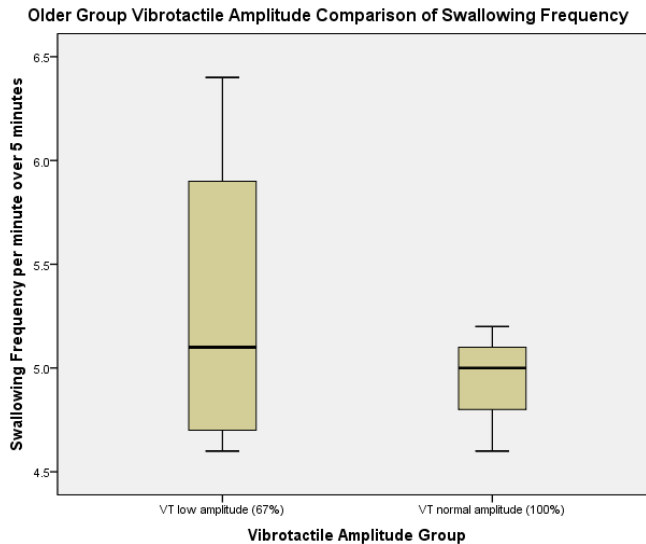

Figure 15. Comparison of mean swallowing frequency between vibrotactile amplitude groups for the older infants.

Marking Swallows and Intra-rater Reliability

During data collection, a staff investigator attempted to visually observe the

hyolaryngeal movement indicating the beginning of pharyngeal swallowing, and pressed

the button on a pulse generator to "mark" swallows as a supplemental confirmation for

swallowing activity. This method proved unreliable, as visual observation of the infant

neck area was often impossible due to posturing, and was discontinued early on in the

participant enrollment phase. Re-identification and marking of swallows was identical to

the initial swallows marked in 98% of the swallows identified, demonstrating adequate

intra-rater reliability.

Individual variation in the accelerometer placement for the suck differed, given that

the type and size pacifier that each infant uses varied. The "suck" accelerometer proved

unreliable in detecting sucking activity and yielded unusable data signals. Due to pacifier

construction, the investigators were unable to find a reliable placement to detect sucking

activity. Furthermore, many infants would not tolerate the "suck" accelerometer. Therefore

the investigators decided to discontinue use of the "suck" accelerometer after the seventh

participant. Instead, sucking activity was "marked" manually via visual observation and the

use of a pulse generator, the button of which was pressed and held down during all times

that an infant sucked.

Swallowing Frequency

Table 3 below outlines the mean swallowing frequencies and standard deviations

for each condition within each of the two age groups, as well as the combined swallowing

frequencies for all participants in which data was collected (see Figures 16, 17 below

illustrating swallowing frequency by condition for only the data used for the ANOVA

analysis ($n = 10$, 5 in each age group)):

Table 3

Mean Swallowing Frequency by Condition and Group

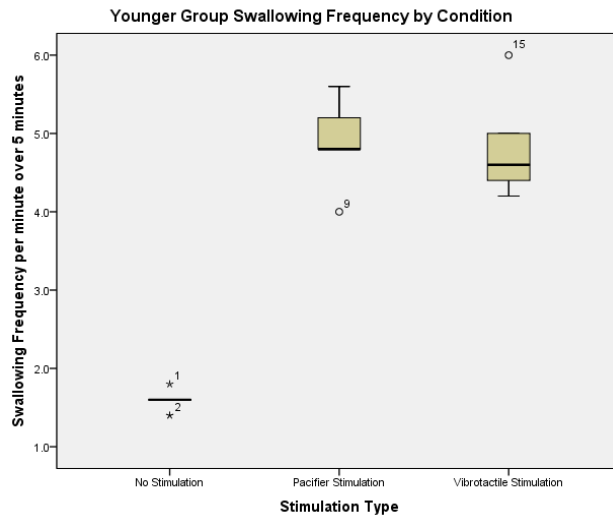| Mean swallowing frequency (*M* + *SD)* (swallows per minute over 5 minutes)	No stim	Pacifier	Vibrotactile
2-4 month olds	1.60 +.14	4.88 + .59	4.84 + .71
7-9 month olds	1.77 +.61	4.87 + .68	5.13 + .69
Combined	1.69 +.45	4.87 + .61	5.00 + .68

Figure 16. Mean swallowing frequency by stimulation condition in younger group of five infants with complete datasets.
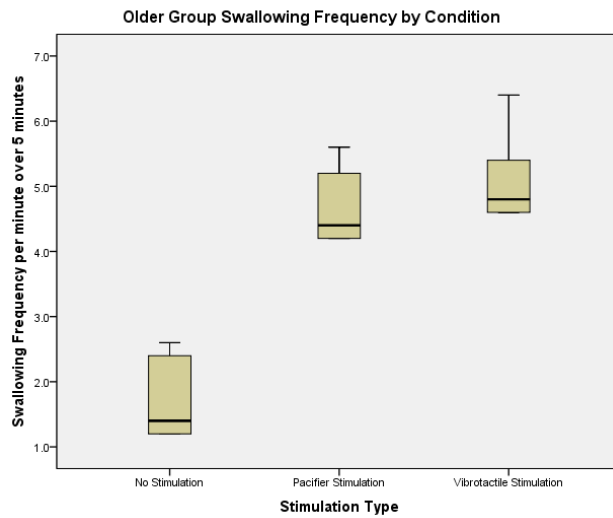

Figure 17. Mean swallowing frequency by stimulation condition in older group of five infants with complete datasets.

The Kolmogorov-Smirnov and Shapiro-Wilk tests of normality indicated normal distributions (test statistics $p > .05$) for swallowing frequencies within each condition (no stimulation, pacifier, and vibrotactile) for both age groups, indicating that normal distributions can be assumed. The Levene test of homogeneity of variance indicated that we can assume roughly equal variance for the pacifier and vibrotactile swallowing frequencies, as they were non-significant ($p > .05$). The Levene test statistic based on the mean for the no stimulation swallowing frequencies was significant ($p < .05$), as some outlier higher swallowing frequencies occurred in the older group. The Levene test statistic for the no stimulation condition based on the median, which is a better measurement when outliers are involved, was non-significant ($p > .05$) and homogeneity of variance could be assumed.

The repeated-measures ANOVA Mauchly's test statistic was non-significant ($p > .05$), demonstrating sphericity and equal variances. There was a significant main effect of stimulation type, $F(2, 16) = 192.21, p < .001$ and no significant interaction effect between the type of stimulation and the age group, $F(1, 8) = .105, p > .05$. Cohen's d effect size was 0.94. Pairwise comparisons using a Bonferroni correction indicated a significant difference ($p < .001$) between the mean swallowing frequency for the no stimulation condition and the mean swallowing frequencies for the pacifier stimulation and vibrotactile stimulation conditions. Pairwise comparisons indicated no significant difference ($p > .05$) in mean swallowing frequency between the pacifier and vibrotactile stimulation types.

Near-infrared spectroscopy

The cortical activation data that was collected represents pilot data for future studies involving infant swallowing and near-infrared spectroscopy. NIRS event-related changes in O_2 concentration data was collected from five participants, two in the younger

2-4 month old group and three in the older 7-9 month group. For some participants, only

partial NIRS data was collected, as some channels, and in some instances the entire

condition or condition for a particular side of the head, were too noisy to yield useful

results. As only 5 experimental sessions included NIRS data collection (from four unique

participants, as longitudinal NIRS data was collected twice from the same participant),

there was not enough NIRS data to run a repeated-measures ANOVA involving age group

by change in percent blood oxygenation change between conditions and the interaction of

group and mean change in blood oxygenation. The presence of a hemodynamic response

was defined as $\geq 2\%$ increase in oxygenation. Table 4 below includes the all available raw

data for the peak value of percent blood oxygenation change and time the peak value

occurred for each stimulation condition, according to the type of NIRS channel (area of

interest in the brain) and separated by age group.

Table 4

NIRS Percent Change in Oxygenation and Latency by Condition, Brain Region, and Group

Age group	No Stim	Vibrotactile	Pacifier
Type of NIRS Channel (% change from zero for peak value)	Peak Value (Peak Time in s)	Peak Value (Peak Time in s)	Peak Value (Peak Time in s)
Younger Group (2-4 months)			
Motor	NS	8 (5)	NS
	NS	7 (8)	NR
	NS	9 (7)	NS
	NS	NR	NS
Sensory	NR	7 (4)	NR
	NR	9 (8)	NR
	NS	7 (9)	NR
	NS	12 (8)	NS
	NS	2 (1.9)	NS
	NS	NR	NS
Older Group (7-9 months)			
Motor	NS	|-4| (8)	5 (7.5)
	NS	7 (6)	NR
	NS	9.9 (6)	2 (7)
	NS	3 (5)	NS
	NS	NR	NS
	NR	2.1 (2)	NR
	NS	2.1 (2)	NS
Sensory	NS	|-8| (8)	15 (7)
	NS	NS	4 (6.5)
	NS	6 (6)	NS
	NS	7 (8)	NR
	NS	NR	NS
	NS	NS	NR
	NR	NS	NS

NS = No Sensor Signal
NR = No Hemodynamic Response (<2% change)

Table 5 below includes mean peak values of percent blood oxygenation changes for
hemodynamic responses and mean peak times for each stimulation condition, according to
the type of NIRS channel (area of interest in the brain), and separated by age group.

Table 5

NIRS Hemodynamic Responses – Mean Peak Values and Latencies

Age group	No Stim	Vibrotactile	Pacifier
Type of NIRS Channel (% change from zero for peak value)	Peak Value (Peak Time in s)	Peak Value (Peak Time in s)	Peak Value (Peak Time in s)
Younger Group (2-4 months)			
Motor	NS	8 (6.7)	NR
Sensory	NR	7.4 (6.2)	NR
Older Group (7-9 months)			
Motor	NR	4.7 (4.8)	3.5 (7.3)
Sensory	NR	7 (7.3)	9.5 (6.8)

NS = No Sensor Signal
NR = No Hemodynamic Response (<2% change)

Two-sample t-tests were used to compare mean peak amplitudes of a hemodynamic
response and mean latencies for the peak response amplitudes between the vibrotactile
and pacifier conditions. The non-stimulation condition was not included, as this condition
yielded no hemodynamic responses. The mean peak amplitude during the pacifier
stimulation condition was 6.50 ± 5.80 and 4.81 ± 5.05 during the vibrotactile stimulation
condition. Results comparing the mean peak response amplitudes between the two
stimulation conditions indicated no significant difference in the amplitude of the mean
peak response between the pacifier condition and the vibrotactile condition, $t(17) = 0.58$, p
$>.05$. The mean latency in seconds for the peak response during the pacifier stimulation
condition was 7 ± 0.41 and 6 ± 2.33 during the vibrotactile stimulation condition. Results
comparing the mean peak latency between the two stimulation conditions indicated no
significant difference in latency of the mean peak response between the pacifier condition
and the vibrotactile condition, $t(17) = 0.84$, $p >.05$.

Table 6 below includes proportions of the number of total data points collected (total number of "No Response" and hemodynamic responses) to the total number of hemodynamic responses for each stimulation condition, according to the type of NIRS channel (area of interest in the brain) and separated by age group.

Table 6

NIRS Proportions of Total Data Points to Hemodynamic Responses by Condition, Brain Region, and Group

Age group Type of NIRS Channel	No Stim Total # of NR+R (Total # R)	Vibrotactile Total # of NR+R (Total # R)	Pacifier Total # of NR+R (Total # R)
Younger Group (2-4 months)			
Motor	NS	4 (3)	3 (0)
Sensory	2 (0)	6 (5)	NR
Older Group (7-9 months)			
Motor	1 (0)	7 (6)	4 (2)
Sensory	1 (0)	4 (3)	4 (2)

NR = No Hemodynamic Response (<2% change)
R = Hemodynamic Response ($\geq$2% change)

Using information from Table 6 above, a chi-square test comparing the number of responses in the no stimulation condition against each of the stimulation conditions indicated a significant association between the type of stimulation condition (non stimulation versus stimulation) and the presence of a hemodynamic response, χ^2 (2) = 15.17, p < .05. The "Likelihood Ratio" chi-square test statistic value was used, as this is preferred for a small sample. Based on the odds ratio, the odds of a hemodynamic response during the no stimulation condition were zero times higher than with both the vibrotactile condition and the pacifier condition.

A second chi-square test comparing the number of responses between the vibrotactile condition and the pacifier condition indicated a significant association between the type of stimulation condition and the presence of a hemodynamic response, χ^2 (1) = 7.93, p < .05. As with the first chi-square test above, the "Likelihood Ratio" chi-square test

statistic value was used. Based on the odds ratio, the odds of a hemodynamic response was

10 times higher with the vibrotactile condition than with the pacifier condition.

Finally, a third chi-square test comparing the number of responses between the

two age groups indicated a non-significant association between the age of the infant

(younger versus older age groups) and the presence of a hemodynamic response, χ^2 (1) =

0.81, p > .05.

Figure 18 below illustrates an example of no hemodynamic response during the

non-stimulation condition, while Figure 19 below illustrates and example of a

hemodynamic response during a stimulation condition.

0 s = "Control epoch On"
10 s = "Control epoch Off"
Response = > 2% dConcentration change

—— Lower sensory channel
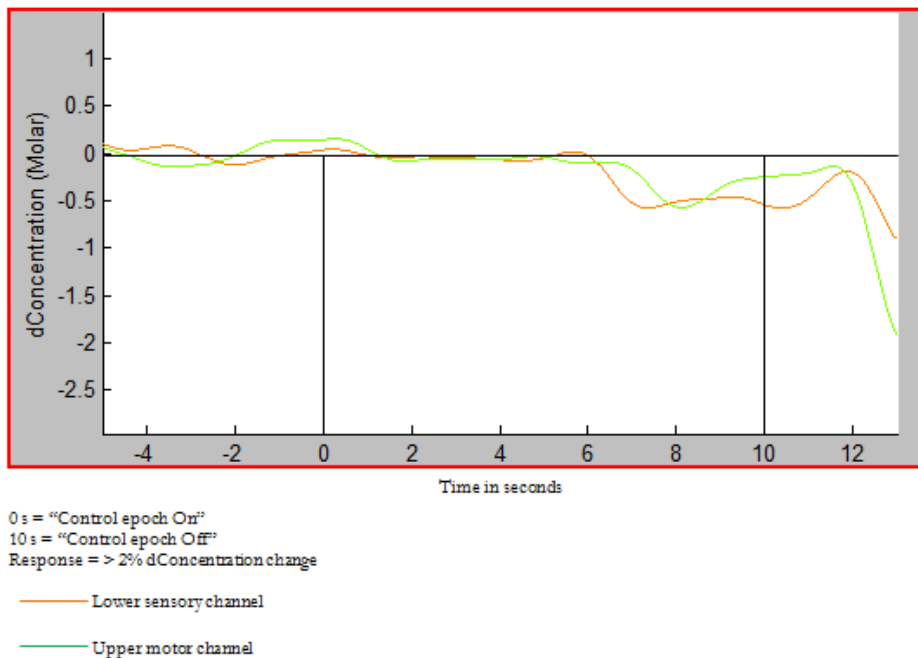
—— Upper motor channel

Figure 18. Event-related average of control epochs during non-stimulation condition illustrating no hemodynamic response.
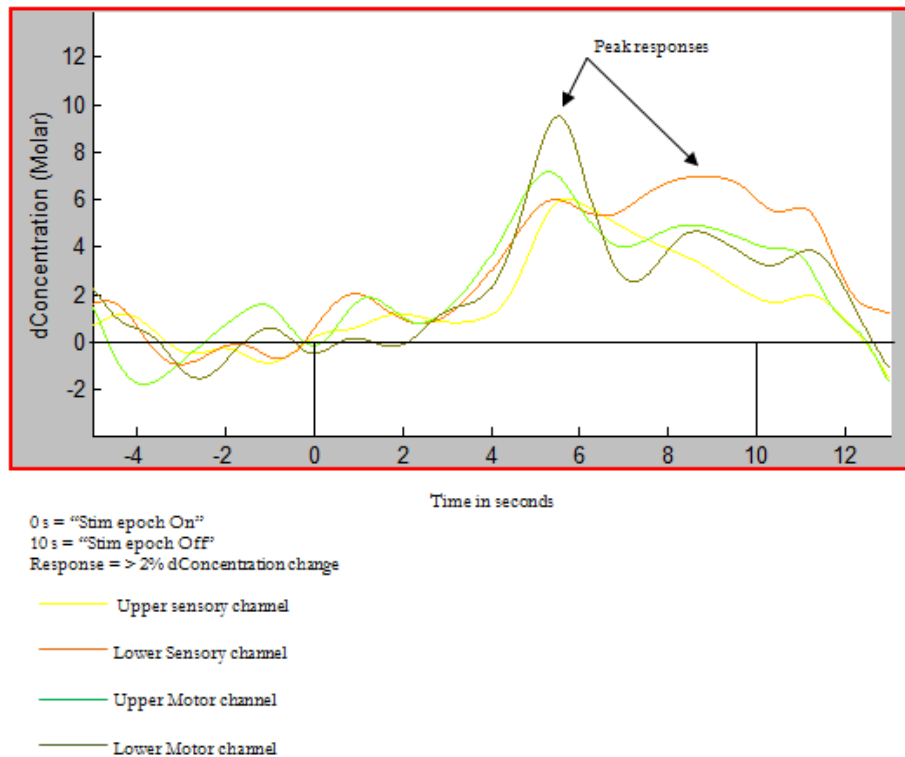
Figure 19. Event-related average of stimulation epochs during a stimulation condition illustrating a hemodynamic response.

The phase of respiration in which a swallow occurred was also recorded (see Table 7 below). A majority of the time, swallows occurred on exhalation. Only four participants (three in the younger group and 1 in the older group) demonstrated a larger percentage of swallows occurring during inhalation for only one out of the three study conditions. Swallows occurred during the inhalation phase of respiration on average 42% of the time during the non-stimulation condition, 36% of the time for the pacifier condition, and 35% of the time for the vibrotactile condition. Overall, current findings indicate a split in the vicinity of 60/40% between swallowing on exhalation and swallowing on inhalation.

Table 7

Phase of Respiration during Swallow Events for each Participant by Stimulation Condition

Participant No. (excludes participants with incomplete datasets)

% of swallows occurring within each phase of respiration	No Stim Exhalation / Inhalation	Pacifier Exhalation / Inhalation	Vibrotactile Exhalation / Inhalation
200	56/44	46/54	64/36
201	29/71	65/35	68/32
202	37/63	64/36	57/43
204	75/25	80/20	71/29
205	75/25	71/29	53/47
700	50/50	65/35	75/25
701	50/50	50/50	48/52
702	83/17	71/29	71/29
703	69/31	68/32	70/30
706	57/43	57/43	70/30

200s = Participants in the younger group
700s = Participants in the older group

Discussion

Swallowing Frequency

The current study sought to gain a better understanding of normal infant swallowing patterns without stimulation and in response to peripheral stimulation to better understand mechanisms of swallowing control in healthy infants. Findings from the current study indicate an average, combined spontaneous non-nutritive swallowing frequency of 1.68 $\pm$ .47 per minute at during the no stimulation condition. The older group of infants in the 7-9 month age range seemed to have a slightly higher mean swallowing frequency and a greater range of non-stimulated swallowing frequency (1.76 $\pm$ .68 per minute) than in the younger group of infants in the 2-4 month age range (1.60 $\pm$ .14 per minute), which has less variation in their swallowing frequency. These were not significantly different. This was likely due to increased activity in the older infants as compared with the younger infants who did not move around as much. Wilson et al. (1981) reported a relationship between behavioral state and swallowing events, that is swallowing occurred more frequently during active behavior states, when other motor movements were happening, and observed a decrease in swallowing activity during less active, quieter behavior states. The literature concerning infant swallowing frequencies is quite variable and inconsistent. The current study most closely parallels findings by Jeffery and colleagues (2000), who reported that term infants swallowed spontaneously around 1.6 times per minute. Literature also reveals that the frequency of swallowing decreases in sleep, although the frequency during sleep is still higher than the adult frequency of swallowing during sleep (Pickens, 1988, Don, 2003, Jeffery, 2000, Nixon, 2008, Reix, 2003, Thach, 1985). The current study also found a decreased frequency of swallowing during sleep, as observed in two infants (one from each age group) who happened to fall asleep

during the experimental session during the non-stimulation condition. We observed a swallowing frequency 0.6 swallows per minute in the two participants during sleep.

The results of a repeated-measures ANOVA performed on the participants' swallowing frequency data indicate a significant ($p <.001$) difference in mean swallowing frequencies for each condition (no stimulation, pacifier, and vibrotactile). The pairwise comparison findings indicated that both pacifier stimulation and vibrotactile stimulation significantly increased swallowing frequency in normal infants when compared to swallowing frequency without stimulation. Furthermore, the pairwise comparisons indicated that there was no significant difference between the pacifier and vibrotactile conditions, that is, both served to up-regulate swallowing frequency in the normal infant to a similar degree. Additionally, there was not a significant interaction with the age group of the infants, suggesting that the effect was similar across the two age groups. Therefore, the higher frequency of swallowing found using the pacifier and vibrotactile stimulation continued through early infancy (2-4 months) into later infancy (7-9 months).

Findings from the current study have several important implications. First, a discussion regarding non-nutritive sucking intervention and the close relationship between sucking and swallowing is warranted. The benefits of non-nutritive sucking practice in the development of sucking and feeding skills has been demonstrated and enhanced with Barlow and colleagues' NTrainer device (Barlow, Finan, Chu, et al., 2008; Poore, Zimmerman, et al., 2008). Extensive reviews of non-nutritive sucking and oral stimulation intervention studies however do not specifically address how such intervention techniques affect the pharyngeal swallow component of the overall motor act of feeding and swallowing (J. Arvedson, et al., 2010; Delaney & Arvedson, 2008; W. F. Liu, et al., 2007). Rather, outcome variables such as weight gain, total oral intake percentage, and decreased

hospitalization are used to measure feeding and swallowing performance. As discussed

earlier, it has been suggested that stimulation of afferent fibers of the trigeminal

(specifically, of the maxillary branch) may play a role in stimulating the pharyngeal

component of the swallow, but this has been underexplored (Barlow, 2009a, 2009c;

German, et al., 2004; Jean, 1990, 2001; A. J. Miller, 1999; Mistry & Hamdy, 2008). The

results of the current study confirm that non-nutritive sucking using a pacifier does serve

to elicit and up-regulate swallowing frequency in the normal infant.

Additionally, since both pacifier and vibrotactile stimulation serve to up-regulate

swallowing frequency in normal infants, it is possible that such mechanisms could serve to

up-regulate the swallowing frequency of infants with disordered swallowing, such as

premature infants in the neonatal intensive care unit. This warrants expanded

investigation into the effect of such peripheral stimulation within the disordered

population. Both pacifier and vibrotactile stimulation could provide crucial swallowing

practice and aid in the encouragement of proper feeding development at a point in life

when the neocortex and central pattern generators important to deglutition are actively

growing and developing (Barlow, 2009a, 2009c; Barlow, Finan, Chu, et al., 2008; Bingham,

2009; Hensch, 2004; Illingworth & Lister, 1964; Kelly, et al., 2007a; McFarland &

Tremblay, 2006; Penn & Shatz, 1999; Poore, Zimmerman, et al., 2008; Stevenson &

Allaire, 1991). The results indicate that the pacifier, which is typically offered to premature

infants in the NICU before oral feedings are introduced, may effectively stimulate both

swallowing and sucking practice. The affect of combining the pacifier and vibrotactile

stimulation as a potential complementary intervention technique on swallowing frequency

is needed. Once infants begin to transition to oral feeding trials, results indicate the

vibrotactile device may serve as a robust intervention technique that could be used during feeding trials to up-regulate swallowing frequency and aid in pattern formation.

Near-infrared Spectroscopy

The second aim of the current study was to explore cortical activation in response to swallowing stimulation over a period during infancy, between 2-4 months of age and between 7-9 months of age. At this time, NIRS data collection continues; however, preliminary pilot data suggest some interesting patterns. Literature suggests the absence of volitional swallowing during the neonatal period and transition, with transition from a reflexive swallowing primarily controlled by the reflexive brainstem central pattern generator to more volitionally controlled swallowing as pathway formation evolves in the cortex through feeding experience and suprabulbar control expands (Bosma, 1986; Gibson, 1991; Huttenlocher & Dabholkar, 1997; Jadcherla, et al., 2007; Jadcherla, et al., 2009; Kelly, et al., 2008; Loughlin & Lefton-Greif, 1994; Sarnat, 1989; Stevenson & Allaire, 1991). This transition period from primarily reflexive to growing suprabulbar control may occur around six months, as primitive reflexes for feeding begin to diminish around this time (J. C. Arvedson & Brodsky, 2002). Furthermore, Kelly et al. (2008; 2007b) have suggested that the brainstem may control non-nutritive breathing-swallowing coordination during the first year following birth. A chi-square test indicated that the type of stimulation used (non stimulation versus either type of swallowing stimulation) resulted in a significant association regarding whether or not a hemodynamic response occurred. During the condition when no swallowing stimulation was present, event-related averaging of control periods produced no hemodynamic response. Findings from the NIRS pilot data collected thus far suggest that for swallowing stimulation, which we know increased the frequency of swallowing in the infants, the cortex is active in motor and somatosensory areas of

interest related to swallowing activity. This is demonstrated in the presence of a hemodynamic response even in the younger infant group during vibrotactile and pacifier stimulation conditions. Furthermore, chi-square results indicated no significant difference between age group and the number of hemodynamic responses.

Results indicated that there appears to be no difference between vibrotactile and pacifier stimulation in terms of peak amplitude of the hemodynamic response or the time at which the peak response occurs. That is, both vibrotactile and pacifier stimulation produce the same type of hemodynamic response in infants. Even though both types of stimulation (vibrotactile and pacifier) produced a hemodynamic response in motor and somatosensory areas of the brain important to swallowing, findings from a statistical analysis comparing responses between the two stimulation conditions indicated a significant association between the type of stimulation and the number of hemodynamic responses. Based on the odds ratio, the odds of a hemodynamic response was higher with vibrotactile stimulation as compared to the pacifier condition. Findings may suggest that when comparing the two types of peripheral sensory stimulation, vibrotactile stimulation may better enhance cortical activation (and reflect the possibility that non-nutritive sucking on a pacifier is more brainstem-mediated), which could be important when considering the encouragement of pathway formation and network mapping during critical periods for deglutition development. Therefore, even though it appears that pacifier and vibrotactile stimulation both serve to equally up-regulate swallowing frequency in normal infants, pacifier sensory input may not be as useful in encouraging cortical sensory responses important for cortical pathway formation for swallowing as vibrotactile sensory input. Perhaps vibrotactile stimulation could provide an intervention technique with infants for up-regulating swallowing as well as activating cortical networks for swallowing, one that

will not interfere with the process of nutritional intake, as the vibrotactile device is situated on the exterior neck area. The NIRS pilot data from the current study presented above do suggest notable patterns for which exploration will continue in normal infants and warrant expansion to exploration in infants with disordered swallowing. It would also be beneficial for future investigation to explore the effects of combining pacifier and vibrotactile stimulation.

Phase of Respiration Interrupted during Swallow Events

A secondary, rudimentary analysis of the phase of respiration during swallowing in healthy infants was performed. As discussed earlier, infants and adults both experience an apneic moment, a temporary interruption of respiration, as a swallow is performed. In adults, the duration of the apneic moment during a swallow appears to last between 1 and 1.5 seconds (Clark, 1920; Curtis, et al., 1984; B. Martin, et al., 1994; Nishino, et al., 1985). The period of time in which respiration is interrupted during a swallow event appears to be shorter in infants, lasting around 0.35 and 0.7 seconds (Lau, 2006).

Unlike that typical pattern of the apneic moment occurring during the expiratory phase of respiration in adults, this patterning appears to be more variable and irregular in the infant population (Clark, 1920; Martin-Harris, 2008; B. Martin, et al., 1994; Nishino, et al., 1985; Selley, et al., 1989a; Smith, et al., 1989). Lau (2006) observed that the phase in respiration interrupted during a swallow event happened at safer time-points in respiration as infants developed and matured. Safer time-points for a swallow apneic moment were defined as at the beginning of inspiration or at the end of expiration. During feeding, the respiration-swallow patterning was marked by change and variability (Bamford, et al., 1992; Gewolb & Vice, 2006).

In summary, patterns of respiratory cessation during swallowing events appear to develop and change as an infant matures, and safe patterning of respiration during a swallow may be the final piece to be incorporated into safe infant feeding (Barlow, 2009c; Gewolb & Vice, 2006; Hanlon, Tripp, Ellis, & al., 1997). An equal interruption of respiration by swallowing during both expiratory and inspiratory phases of respiration has been suggested in infancy (Martin-Harris, 2008; Wilson, et al., 1981). Results of the current study indicate that the majority of swallows occurred during the expiratory phase of respiration. However, the current findings demonstrate that infants in both age groups did swallow during inspiration and that the pattern varied among infants. Perhaps the patterning of respiration-swallow coordination more closely mimics the typical adult patterning when infants sleep (Nixon, et al., 2008). Kelly et al. (2007b) observed an interesting sequence of respiration-swallow coordination over the first year of life in healthy full-term infants. During the first 48 hours following birth, the apneic moment due to swallowing during feeding was observed to occur in the typical adult-like pattern, during the expiratory phase of respiration. In older infants 9 to 12 months of age, a change towards a trend for apneic moments interrupting inspiration was observed, followed by the return to a more adult-like coordination of respiration and swallowing by the first year mark. Such data indicate the changes in respiration-swallow coordination during infant development is not uncommon (Martin-Harris, 2008). Clearly, the developmental timeline for respiration during swallowing events in healthy and disordered infant populations warrants further investigation.

Limitations and Future Directions

The main limitation encountered throughout the experimental sessions was that the infant population is active – it was not possible to request that the infants remain still

during the session. The older infants seemed to move more than the younger infants, though even infants in the younger age group exhibited spontaneous movement. Therefore, it would be beneficial to find a technique to uniformly control attention and reduce movement, keeping the infants awake but less active. Perhaps an engaging video could be played to maintain attention during the experimental conditions. Similarly to the current study, Wilson, Thach, Brouillette, & Abu-Osba (1981) concluded that visual observation of the hyolaryngeal elevation was unreliable as a method to identify non-nutritive swallows in infants. It would be beneficial to find a reliable method for "marking" swallows, i.e. using a pulse generator during visual observation of swallowing activity, as is possible during observation of adult swallowing but complicated while observing infant swallowing due to anatomical differences. An effective method may involve alteration in positioning of the infants during the study.

As discussed earlier, the investigators will continue to collect swallowing frequency and NIRS data from the normal infant population. The promising preliminary results and observations warrant an expanded exploration within disordered swallowing populations, such as with premature infants in the neonatal intensive care unit. Though not an aim or form of data collected for the current study, the use of the vibrotactile device in stimulating vocalizations may also warrant future investigation, as it was observed that the vibrotactile device appeared to be associated with a potentially increased frequency of vocalizations among infants in both age groups, as compared to the amount of vocalizations informally observed in the non-stimulation and pacifier conditions. The vibrotactile device may prove beneficial as an intervention technique possibility in more than the realm of disordered swallowing.

Appendix A

Figure 20. Recruitment pamphlet.

Appendix B

Infant's Name _____

Parent/Guardian Name _____

Infant's Age _____

Phone Number _____

<div style="border:1px solid black; padding:10px;">
Qualifies for study
□ Yes
□ No
If yes, appointment is scheduled for:
_____
</div>

Infant Swallowing Phone Screening Interview Questions

Hi, my name is _____ and I am calling from James Madison University's Neural Bases of Communication and Swallowing Laboratory about your interest in participating in our research study. How are you today? Is this a convenient time for us to be calling? Ok, great! Thank you so much for your interest. First, I need to ask you some questions to make sure your infant qualifies for the study. You can answer with a simple yes or no. If I need more information I will ask you to elaborate. Are you ready?

Has your infant ever had feeding or swallowing problems? **(Inclusion = NO)**

Is your infant currently being treated for a diagnosed reflux? **(Inclusion = NO)**

Has your infant ever been exposed to either a bottle or a pacifier? **(Inclusion = YES)**

Was your infant born prematurely (before 37 weeks gestation)? **(Inclusion = NO)**

Is your infant able to maintain a quiet, calm behavior state for at least 5 minutes at a time? **(Inclusion = YES)**

Does your infant have a history of any of the following medical conditions? **(Inclusion = NO TO ALL)**

- Seizures
- Neurological disorders
- Congenital anomalies (abnormalities present at birth) or facial abnormalities

This study also involves the use of near-infrared spectroscopy (NIRS) during the rest and stimulation periods. NIRS is a system used to measure your infant's brain responses to swallowing. NIRS is a safe, non-invasive system that measures blood flow changes in the brain. The changes in blood flow signal a brain response. We will be looking for brain responses at the same time your infant's swallowing is stimulated using the pacifier and vibrotactile stimulation. We are specifically looking for brain responses in two areas of the infant brain – a motor area and a sensory area. The brain response will be measured by placing NIRS probes on your infant's head around the motor and sensory areas. The probes contain laser light that will travel through your infant's head and determine the brain responses. NIRS is a safe technique to use with infants, as it does not involve radiation, and has been used with even premature, medically-fragile infants. You may choose to decline your infant's participation in using NIRS and choose to allow your infant to participate in the swallow stimulation study without NIRS.

If **NO** to NIRS and infant qualifies for the study, proceed to schedule an appointment. The session should take approximately 3 hours.

If **YES** to NIRS and infant qualifies according to first set of questions, ask the additional questions:

We need to know if your infant has highly-pigmented (dark) skin color? This is because dark skin interferes with light transmission for measuring the brain function using NIRS. **(Inclusion = NO)**

Does your infant have any known cardiovascular disorders, including cerebrovascular disease (stroke) or peripheral neuropathies? **(Inclusion = NO)**

Is your infant able to maintain a quiet, calm behavior state for at least 5 minutes at a time? **(Inclusion = YES)**

Does your infant have any broken areas of skin on the scalp? **(Inclusion = NO)**

*If qualified, proceed to schedule an appointment. If they enroll in the optional NIRS portion of the study, the session should take approximately 4 hours.

Appendix C

Parent/Guardian Informed Consent

Identification of Investigators & Purpose of Study

Your infant is being asked to participate in a research study conducted by Dr. Christy Ludlow (Primary Investigator), Dr. Cynthia O'Donoghue, Sarah Hegyi, Katie White, and Lara Karpinski (co-investigators) from James Madison University, Department of Communication Sciences and Disorders. The purpose of this study is to better understand two different stimuli on the frequency of infant swallowing, as well as brain activation patterns for swallowing during stimulation. This study will contribute to Sarah Hegyi's completion of her doctoral dissertation. The findings of the study will also contribute to our overall understanding of infant swallowing and could potentially help infants with swallowing disorders in the future.

Study Population

25 healthy infant volunteers (6 2-4 month old infants and 6 7-9 month old infants) may participate in this study.

Exclusion Criteria

Exclusion criteria by parent/guardian report:

- History of feeding or swallowing problems
- Currently being treated for a diagnosed reflux
- Never been exposed to either a bottle or a pacifier
- Born prematurely (before 37 weeks gestation)
- Fails the Ages & Stages-3 developmental screening
- Unable to maintain a quiet, calm behavior state for less than 5 minutes at a time
- History of seizures
- History of neurological or neurodevelopmental abnormalities
- Congenital anomalies or craniofacial malformation

Additional exclusionary criteria for participants enrolling in the near-infrared spectroscopy (NIRS) portion of the study:

- Highly-pigmented (dark) skin color, which interferes with the measurement of light transmission through the scalp.
- Known cardiovascular disorders, including cerebrovascular disease or peripheral neuropathies.
- Unable to maintain a quiet, calm behavior state for less than 5 minutes at a time.
- Broken skin in the area of the head that NIRS probes will be placed on the scalp.

All subjects in this study will potentially receive both the pacifier and vibrotactile stimuli. The parent/guardian may decline the use of NIRS and have their infant participate in the pacifier and vibrotactile stimulation portion of the study without NIRS. NIRS will be used to determine brain response patterns for swallowing in the somatosensory and motor regions of the brain.

Research Procedures

Should you decide to allow your infant to participate in this research study, you will be asked to sign this consent form once all of your questions have been answered to your satisfaction. If your infant participates in this study, you may decline from using NIRS or discontinue the use of NIRS during the study if your infant becomes fussy or uncomfortable.

All study sessions will be videotaped. Your infant's name and personal information will be confidential. Videotape footage will be stored on a secure computer server and all names will be coded to protect the anonymity of each participant. We also ask that you remain with your infant throughout the study session. Your infant will be allowed to feed during the session should they become hungry.

Stimulation + near infrared spectroscopy (NIRS)

Your infant will participate in a study designed to understand two different stimuli (pacifier stimulation and vibrotactile stimulation) on the frequency of infant swallowing. Both the pacifier and vibrotactile stimulation will potentially be administered at different times during the study. If your infant refuses or no longer uses a pacifier, we may stop that portion of the study and move to the vibrotactile portion of the study. Both stimulation types are safe and non-invasive. To determine how the pacifier affects the frequency of swallowing, your infant may be given a pacifier to suck on for a period of time. You will be asked to bring pacifier from home that your infant is comfortable using. To determine how the vibrotactile stimulation affects the frequency of swallowing, a small motor device (about the size of a dime) will be taped to the outside of your infant's throat using double-sided or medical tape. Your infant will feel a series of vibrations to the throat when the motor device is activated. There will be periods in which the motor device is on and vibrating, and periods when the device is still taped to the outside of the throat, but the device is turned off and not vibrating.

Each stimulation type will be administered separately. As your infant receives each form of stimulation, we will be measuring the sucking and swallowing responses in several ways. First, a small instrument may be taped to a region near your infant's mouth using double-sided or medical tape. This instrument will allow us to see your infant's sucking motions on a computer. Secondly, another small instrument will be taped to the outside of your infant's throat. This instrument will allow us to see when your infant swallows on a computer. Lastly, two elastic bands will be placed on your infant – one band will be placed around your infant's stomach and one a little higher around your infant's rib cage. These bands will be used to measure your infants breathing patterns and help confirm when your infant swallows.

During the periods of rest and stimulation, NIRS may be used to understand brain activation patterns for swallowing. NIRS is a safe, non-invasive system that measures blood flow changes in the brain. It is the same technology as a pulse oximeter, which is placed on your finger to measure blood oxygen levels. The changes in blood flow signal a brain response. We will be looking for brain responses at the same time your infant's swallowing is stimulated using the pacifier and vibrotactile stimulation, as well as during the periods of rest. We are specifically looking for brain responses in two areas of the infant brain – a motor area and a sensory area. The brain response will be measured by placing NIRS probes on your infant's head over the motor and sensory areas. The probes contain laser light that will travel through your infant's skull and determine the blood oxygenation levels. NIRS is a safe technique to use with infants, as it does not involve radiation, and has been used with even premature, medically-fragile infants. You may choose to decline the use NIRS or discontinue the use of NIRS if your infant becomes fussy or uncomfortable, while still allowing your infant to participate in the pacifier and vibrotactile stimulation parts of the study.

Time Required

The consent process and study participation can be completed in one session, or can be divided into two sessions depending on your schedule of availability. Participation in this study will require approximately 3-4 hours of you and your infant's time.

Risks, Inconveniences, and Discomforts
The investigators do not perceive more than minimal risks from your involvement in this study.

Both the pacifier and vibrotactile device are non-invasive forms of stimulation and involve no known risks. The vibrotactile device and small instruments used to measure sucking and swallowing will be secured on the area around your infant's mouth and throat region using double sided or medical tape, which may cause redness of the skin when removed, much like when a Band-Aid is removed from the skin. Baby lotion to soothe the redness will be administered at your request. In our experience so far, any redness on the skin from the tape is usually gone within 8 hours. The two elastic bands used to measure breathing patterns and confirm swallows stretch and should produce no discomfort, other than potential light pressure felt from the bands being wrapped around your infant's stomach and rib cage.

There is potential risk to people in the room from the NIRS lasers, which use light in the near infrared region, and could potentially injure the eyes if they were shone into your eyes. Therefore, the lasers will not be turned on until they are positioned on the scalp. Looking directly at the lasers may cause eye damage. However, the lasers are similar to a laser pointer used in the classroom and the risk is minimal. The infants may feel light, uncomfortable pressure from the sensor probes being held in place by a wrapping around the head. Markers will be used on the scalp during probe placement of the sensors. These marks will wash away and no hair will be removed. Lastly, the infants may need to make limited body movements for short periods of time.

Benefits

The healthy infant volunteers will receive no direct benefit for participation in this study. However, it is anticipated that the results of this swallowing stimulation study will produce applicable and generalizable knowledge, potentially benefiting intervention techniques for infants with swallowing disorders in the future. If you would like to receive a copy of the published research, please fill out the attached card with your name and address and we will send it to you when it becomes available.

Compensation

You will be paid for your infant's participation in this study. You will receive $20 for the first hour of you and your infant's time and $10 for each additional hour.

Confidentiality

Your participation in this study is entirely confidential. All data will be stored in the secure and locked Neural Bases of Communication and Swallowing Laboratory at James Madison University, which can only be accessed by authorized investigators. The results of this research study will be coded in such a way that your infant's identity will not be attached to the final form of this study. Your identity will be disassociated from your infant's personal data and your infant will be assigned a participant number. The researchers retain the right to use and publish non-identifiable data.

The overall findings from this research may be reported in two forms. In written form, the data will appear in a doctoral dissertation and/or journal articles. In oral form, findings from this research project may also be reported at conference presentations. Upon request, you will be allowed view group results of the study. You may sign a release form to obtain your results from this study and to allow use of your non-identifiable data for educational purposes here at JMU.

Disclaimer

Dr. Ludlow is an inventor on three patent applications concerning the use of devices and methods for vibrotactile stimulation for the treatment of dysphagia (swallowing problems). These patents are owned by the National Institutes of Health (NIH) and if they were awarded, licensed and commercialized in the future both Dr. Ludlow and the NIH could benefit financially.

Participation, Right of Withdrawal, and Conditions for Early Withdrawal

Your infant's participation is entirely voluntary. You are free to choose not to participate on your infant's behalf. Should you choose for your infant to participate, you and your infant can withdraw at any time without consequences of any kind. If you withdraw, you will be reimbursed based on the time that you have contributed to the study. However, failure to complete all required sessions will be your data unusable to the investigators. Additionally, the investigators can remove your infant from the study at any time if continuation is not in your infant's best medical interest or if your infant is unable to fully meet study requirements.

Questions about the Study

If you have questions or concerns during the time of your infant's participation in this study, or after its completion or you would like to receive a copy of the final aggregate results of this study, please complete the attached card providing your name and address.

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Questions about Your Rights as a Research Subject

Dr. David Cockley

Chair, Institutional Review Board

James Madison University

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Giving of Consent

I have read this consent form and I understand what is being requested of my infant as a participant in this study. I freely consent for my infant to participate. I have been given satisfactory answers to my questions. The investigator provided me with a copy of this form.

☐ I give consent for my infant to participate in the stimulation with NIRS study and consent to videotape my infant _____ (parent/guardian's initials)

☐ I decline consent for using NIRS, but give consent for my infant to participate in the stimulation part of the study without NIRS and consent to videotape my infant _____ (parent/guardian's initials)

_____

Name of Infant (Printed)

_____

Name of Parent/Guardian (Printed)

_____ _____

Name of Parent/Guardian (Signed)   Date

_____ _____

Name of Researcher (Signed)   Date

_____ _____

Name of Witness (Signed)   Date

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