Segmentation and Analysis of MRIs of Infants with Dysphagia

A thesis submitted in partial fulfillment of the requirements for the degree of Master of Science in Engineering

by

Irfaan A. Dar
B.S., Ohio State University, 2011

2014
Wright State University
Wright State University
SCHOOL OF GRADUATE STUDIES

January 23, 2015

I HEREBY RECOMMEND THAT THE THESIS PREPARED UNDER MY SUPERVISION BY Irfaan A. Dar ENTITLED Segmentation and Analysis of MRIs of Infants with Dysphagia BE ACCEPTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF Master of Science in Engineering.

Nasser H. Kashou, Ph.D.
Thesis Director

Thomas N. Hangartner, Ph.D.
Chair, Department of Biomedical, Industrial and Human Factors Engineering

Committee on Final Examination

Nasser H. Kashou, Ph.D.

Subhashini Ganapathy, Ph.D.


Robert E.W. Fyffe, Ph.D., Vice President for Research
Dean, School of Graduate Studies
ABSTRACT

Dar, Irfaan. M.S.Egr., Department of Biomedical, Industrial, and Human Factors Engineering, Wright State University, 2014. Segmentation and Analysis of MRIs of Infants with Dysphagia.

Neonates are at a rapid stage of development from birth throughout childhood. Impairments to certain cortical areas can result in long lasting neuro-cognitive dysfunctions. Disorders to the swallowing neural pathways can have detrimental effects throughout life course since methods to provide nutrition can be comprised. Dysphagia, or the inability to swallow, can be caused by a multitude of reasons, chiefly neurological, but the underlying disruptions to the neural pathways are not defined. In this study we investigated the growth of multiple cortical areas involved in the swallowing pathway and categorized feeding outcomes with neural growth. Results showed that infants that were discharged on oral feeds had higher growth rates compared to those that had a feeding tube implanted. This is the first study to look at volumetric analysis for neonates with feeding issues.
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Acknowledgment

I would like to take this opportunity to extend my thanks to my advisors: Dr. Nasser Kashou, Dr. Sudarshan Jadcherla, and Dr. Subhashini Ganapathy. Your help has been tremendous in this project.
Introduction

A major function that every human learns is swallowing. Without the ability to feed, we would not be able to grow and partake in complicated tasks. Understanding the musculature and cortical areas that are involved in swallowing helps diagnose problems that can arise. A crucial time where feeding can affect growth is during infancy and early childhood. Having a poor swallowing mechanism lowers the possibility of acquiring nutrients. Extensive research has been done in trying to characterize how infants feed, and what can be done to improve their chances to live a healthy life after discharge[1, 2, 3, 4, 5, 6, 7]. While the physiological aspect of swallowing has been documented[6, 7, 8, 9, 10], the cortical influence on the development of swallowing is not fully understood. Studies have looked at the activation of the brain during swallowing[7] and non nutritive sucking[3], but correlating brain growth with feeding outcomes is not discernible as of yet. In this study, we investigate at the background of neurodevelopment in infants, the process of swallowing, cortical structures involved in swallowing, and the background of magnetic resonance imaging.
Background

2.1 Neurodevelopment

The neurodevelopment of the brain is key in the early years of childhood as characterized by a 14 cm increase in head diameter in the first two years of life compared to only a 7 cm increase until adulthood[11]. There is a rapid change in brain structures in the first postnatal month, however structures grow at varying rates. For instance, sensory structures grow quicker than associative structures[11]. The volume of the infant brain is around 72% of the adult volume and reaches to 92% at around nine years of age[12]. Since post-mortem studies of infants add little to the physiology, non-invasive imaging is key to understanding the physiology and pathophysiology of these areas. Studies have shown correlations between newborn brain structure sizes and later neural disabilities[13, 14, 15], and others have shown that improved head growth and weight gain can reduce cerebral palsy and cultivate high cognitive function[16].

The timeline of a normal brain growth and development is known. Approximately 22 days after conception the neural tube, which later forms the brain and spinal cord is formed[17]. In the fourth week of gestation, the neural tube divides into four parts: the prosencephalon, mesencephalon, rhombencephalon, and the spinal cord. The prosencephalon becomes the forebrain, the mesencephalon becomes the midbrain, and the rhombencephalon becomes the hindbrain. Figure 2.1 displays the end cortical regions these
three structures form. The mesencephalon and rhombencephalon together help form the brain stem. The cerebral hemispheres, telencephalon, form at around the sixth week. The cranial nerves emerge at the sixth week. Seven weeks after conception, neurons and glial cells start to form and divide thus starting the neural connections of the brain and spinal cord[17]. At fourteen weeks gestation, the insula can be seen and is a point of reference for the expansion and formation of the cerebral hemispheres. By 40 weeks, the surface topology of the neonatal brain mimics that of an adult. Myelination of the nerves occurs over a long period of time, but rapidly occurs during the first 6 months of postnatal life[18].

![Diagram of brain regions](image)

Figure 2.1: Formation of certain cerebral regions from the neuro plate. Areas in red are those that are significant to the neural swallowing pathway. The Prosencephalon and Rhombencephalon development are key to the neural swallowing pathway. (Adapted from Estomih [19])

In terms of swallowing, development starts at around 11 weeks gestation, while sucking develops at 18-24 weeks of gestation[18]. Full coordination of the suck-swallow pattern does not occur until 33-34 weeks of age. Difficulties with these feeding reflexes can be indicative of an abnormal neurological growth[18].
2.2 Swallowing

Swallowing is a vital task in the maturation of infants. The transportation of nutrients is important for the growth of infants to adults, and providing energy for humans to function throughout the day or night. The process of swallowing is a complex task and involves coordination between both the digestive and respiratory tract\[^8\]. The sequence for chewing food is broken down to four parts\[^20\]. First the food is inserted into the mouth, followed by the chewing of the food, the preparation of swallowing by moving the bolus to the oropharynx, and the final step; swallowing\[^20\]. In regards to swallowing there are three phases of swallowing\[^10, 20\]. These phases are oral, pharyngeal and esophageal\[^10, 20\]. The oral phase involves the conversion of the food to a substance of consistent texture that is able to travel down the esophagus. The tongue and soft palate move the bolus from the oral cavity to the opening of the pharynx for the start of the pharyngeal phase. Since there are a multitude of processes involved in the oral phase, it is very complex and requires coordination between the senses and the neural pathway\[^10, 20\]. The pharyngeal phase onset is when the mylohoid muscle is activated by the bolus\[^21\]. This leads to a cascade of contractions of other muscles that push the bolus down the pharynx towards to the esophagus\[^10, 21\]. This process follows a pattern of excitation and inhibition of the muscles involved\[^10, 21\]. Since the pharynx also houses the opening of the trachea, interactions between the respiratory pathway and swallowing pathway happen, where the trachea is closed and the bolus is moved down towards the esophagus\[^10\]. Once the bolus enters the upper esophageal sphincter the pharyngeal phase ends and the esophageal phase begins\[^21\]. This is characterized by deglutition apnea, a stop in the respiratory cycle\[^8\]. The esophageal phase of swallowing involves a peristaltic, or a contraction and relaxation, wave that travels down the esophagus along with the bolus\[^21\]. This constricts and relaxes the esophageal muscle to help push the bolus down the esophagus towards the lower esophageal sphincter, which is doorway to the stomach\[^21\]. During rest, the lower esophageal sphincter is a high-pressure zone to prevent reflux from the stomach\[^21\]. The esophagus is composed of
two different types of muscle, smooth and striated. Striated muscles comprise the upper one-third portion of the esophagus, while smooth muscle comprises the lower two-thirds of the esophagus. These different types of muscles are innervated by either the motor neurons in the brain stem and receive communication from neurons located in the basal ganglia[10]. Figure 1.2 displays the musculature of the face and neck and the locations of the hyoid bone and cricopharyngeus muscle.

Figure 2.2: Musculature of the face and neck. The labeled areas denote the transition areas between the phases of swallowing. The pharyngeal phase starts at the mylohyoid muscle and the esophageal phase starts at the cricopharyngous muscle. (Adapted from Shaker[10])

There are two types of peristalsis that can occur. The first type of peristalsis is primary peristalsis, which is what happens during normal swallowing. This is due to the closure of the respiratory pathway to protect the trachea and the lungs[8]. Secondary peristalsis occurs when the sensory receptors in the esophagus are activated by a mechanical or liquid stimulation the esophagus[8]. The type of peristalsis seen during a study can be controlled by where the infusion of liquid is done.
There are many different ways to view the physiological aspect of deglutition. Manometry involves inserting an infusion catheter and another catheter with pressure sensors. The sensors detect the pressure changed in the oropharynx and the esophagus during the stages of deglutition, and the infusion port allows for a precise placement of the stimulus. Videofluoroscopy uses barium covered food and an xray machine to look at oropharyngeal phase of swallowing. Electromyography (EMG) uses electrodes to detect the electric potential of skeletal muscles. Many animal studies have used intramuscular electrodes to map most of the neural connections and areas involved in swallowing[22, 23]. Figures 2.3 to 2.5 display an example of the output for these modalities.

Figure 2.3: Example of a manometry study. After the infusion there is an cascading wave down the esophagus that shows the movement of the bolus. (Adapted from Jadcherla[8])
The organization and activation of the loci involved in deglutition is very complex and requires the coordination between both cortical and subcortical areas[8]. The process and how locations of the brain are involved in swallowing are not fully understood[8]. Some of the cortical and subcortical areas involved are the cranial nerves (CN), the brain stem, cerebellum, and cerebrum.

In regards to cranial nerves, a multitude are involved in the process of feeding, and
these cranial nerves range from conveying the sensation of taste to the control of facial muscles[20]. The cranial nerves involved are CN V, VII, IX, X, and XII[20]. Figure 2.6 shows the locations of the different cranial nerves from an inferior view. The cranial nerves of interest are located near the brain stem, making this location very important to the neural control of swallowing.

Figure 2.6: Cranial nerves and locations exiting the brainstem.

Cranial nerve V (trigeminal) conveys sensory information except taste from the anterior part of the mouth, tongue, and mandible; and innervates the muscles in mastication, propelling the bolus backward through the mouth[20]. Cranial nerve VII (facial) sends taste information from the tongue and soft palate, stimulates saliva secretion, and controls the muscles in the lips[20]. Cranial nerve IX (glossopharyngeal) stimulates the saliva secretion from the parotid gland and helps innervate the stylopharyngeus muscle, which helps with the cricopharyngeal muscles relaxation[20]. Cranial nerve X (vagus) is one of the most important cranial nerves involved in swallowing because of the su-
perior laryngeal nerve (SLN). The SLN is a branch of the vagus nerve and its primary role is the activation of swallowing[25]. Stimulation to the SLN activates the process of swallowing[20, 21]. The SLN also innervates the esophagus, but its effects on esophageal function are not clearly understood[25]. Innervation of the ipsilateral SLN stimulates only the oropharyngeal phase, while stimulation of the contralateral nerve initiates the whole deglutition process[10]. The vagus nerve also innervates muscles that are part of the respiration process[20]. The last cranial nerve involved in feeding is XII (hypoglossal), which innervates all of the muscles in the tongue that are not innervated by cranial nerve XI.

These cranial nerves and motor neurons are involved in different stages of the deglutition process. The striated muscles in the oropharyngeal phase are driven by the motor neurons and cranial nerves located in the brain stem[10]. The esophageal phase is governed by cranial nerves, if the esophagus of the species is composed of striated muscle[10]. Otherwise if the lower esophagus is composed of smooth muscle, as such in primates, it is controlled by the central preganglionic neurons and peripheral neurons of the enteric nervous system[10]. The process of swallowing is controlled and generated by a central pattern generator (CPG) located in the brain stem[10, 21]. This CPG is composed of an afferent, efferent, and organizing module located in the medulla oblongata[10, 21]. Nerves that innervate the oropharyngeal phase of deglutition are composed of the V, VII, XII, and a portion of the vagus cranial nerves. The majority of the preganglionic nerves are located within the vagus cranial nerve, while the rest are localized to the V, VII, and XII cranial nerves. These swallowing nerves are localized to two regions in the brain stem. The dorsal swallowing group (DSG) located within the nucleus tractus solitarii (NTS) in the medulla and the ventral swallowing group (VSG) in the ventral medulla just above the nucleus ambiguus[10, 21]. The NTS and DSG innervate the muscles of the esophageal phase and most of the muscles of the oropharyngeal phase during deglutition, while the VSG houses a majority of the interneurons involved in the oropharyngeal phase of deglutition[10, 21].
Detailed analysis of the connections in the CPG have found that the DSG activates the VSG based on the latency between synaptic firings, which was also confirmed by lesions located at the DSG removing the VSG response[10, 21]. Cortical inputs from supramedullary areas are connected with the DSG and not the VSG[10]. The neurons located in the VSG are likely switching neurons that distribute and coordinate innervations from the DSG[10]. Since swallowing is not a continuous task, the neurons involved in the CPG are also activated during other tasks. Studies have shown that some of these motor neurons are involved in respiration, mastication, or vocalization[10, 21]. These motorneurons and interneurons are part of at least two different functions[10]. Not only is the CPG located dorsally and ventrally, it is split between two bilateral locations in the brain stem. The synchronization between these two areas is key to the process, and as stated before, innervation of the SLN on opposite side activates different portions of the swallowing process[10]. Also some dysphagic issues that are localized to either the ipsilateral or contralateral portion of the CPG can be explained with the split of the SLN[10]. While most of the coordination and activation of swallowing is handled by the CPG, sensory inputs also activate or inhibit the neurons in this region[10].

Cortical areas also have been shown to have a role in swallowing[20]. These areas range from the basal ganglia to the insular cortex, and have shown activation during both reflexive and volitional swallowing. How these areas are connected in the swallowing pathway is not fully understood as of yet[10]. Since deglutition is a very complex task that involves mastication, licking, and lapping, whether these cortical areas are involved in those tasks or the specific actions of swallowing is unclear[10]. Multiple imaging modalities such as positron emission tomography (PET), transcranial magnetic stimulation (TMS), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI) have been used to study the activation of regions of interests (ROIs) that control the swallowing musculature. Multiple cortical regions such as the frontal operculum, prefrontal cortex, basal
ganglia, thalamus, and insula have been shown to be involved in swallowing because of damage to these regions has an adverse effect on deglutition[26]. There are other cortical areas are involved in swallowing[26], but are not mentioned in this thesis.

The sensorimotor cortex has been shown to be involved in the control of the tongue and face[26], and is important for the initiation of volitional swallowing[26]. The insular cortex is an important cortical area for visceral stimulation[26, 27], and direct stimulation of the insula will initiate swallowing[26]. The face, tongue, and pharynx of the homunculus lie directly on the insular cortex, which explains its involvement in the process. The frontal operculum has been shown to initiate mastication when stimulated, but at higher stimulation levels it will start the swallowing sequence[26]. Damage to either of these areas can result in dysphagia[26]. The prefrontal cortex is involved in the preparation and coordination of cognitive tasks and may play a cursory role in the higher networking of swallowing[26]. The thalamus houses the upper motor neurons descending from the cortical areas to the pattern generator in the brain stem[28]. These motor neurons pass to the basal ganglia, which modulates the final response before sending it to the brain stem[29].

Sensory information from the tongue and the pharynx helps stimulate the insular cortex, while the operculum, and cingulate cortex are involved in the control of the tongue[10]. Except the insular cortex, cortical areas are influenced by sensory information such as taste and smell giving credence to the connection between sensory input and cortical activity[10]. In regards to the pharyngeal and esophageal portions of deglutition, since these are more reflexive tasks, cortical activation is smaller compared to the oral phase. A study by Hamdy et al. viewed the activation of the primary motor cortex during the pharyngeal portion of a swallow, which means it has some role during that phase[10].

Lateralization has also appeared in multiple functional studies on volitional swallow-
ing, which leads towards the theory that certain hemispheric areas are more involved in deglutition compared to others. Studies have shown that the right insula has an increased activation versus left during volitional swallowing[26]. This centralized activation is not consistent across all people and can vary even between twins[30]. If only one hemisphere is impaired by a lesion, the unaffected side will assume greater control as the brain adapts to the lesion[30].

Figure 2.7: Flow chart of the deglutition neural pathway. (Adapted from Mistry and Hamdy[20])

All together these cortical and subcortical areas make up the neural pathway for deglutition. As shown in Figure 2.7, this pathway is very complex and issues at any of these areas can cause feeding problems. For example, in adults, there are over 600 different neurological disorders that result in dysphagia[10]. Some of these disorders include Parkinson’s, Multiple Sclerosis, Ataxia, Dystonia, Chorea, Wilson’s Disease, and Guillain-Barre Syndrome. Similar info in infants is not well characterized. Diagnosing the issue will pave way for developing proper treatment so that fully and speedy recovery can ensue. In order to diagnose these neurological issues, imaging of the brain is important in the rapidly developing infant.
2.3 MRI

Dr. Carr first developed Magnetic Resonance Imaging (MRI) in the 1950s[31]. Since its inception, MR imaging has resulted in many different imaging sequences such as Diffusion Tensor Imaging (DTI) and functional MRI (fMRI). MRI is used to acquire anatomical images in most parts body because of its high resolution and contrast. DTI is used to analyze the connectivity of a patient's brain by calculating the diffusion of water throughout the brain while fMRI is used to determine the activation of certain brain regions by monitoring hemoglobin concentration changes to better understand neural pathways and the inner workings of the brain. Figure 2.8 shows a typical MRI machine used in the clinical setting.

![A typical MRI scanner. (Courtesy of DR. Kashou)](image)

MRI relies on one magnet, a radio frequency (RF) coil, and multiple gradient coils to produce an image of the region of interest. A main magnet produces a homogeneous field and for clinical use is around the range of 1.5-3 tesla. Three called gradient coils are in place to adjust certain parameters of the image. By adjusting the strength of the gradient
and main magnetic coil, researchers can adjust the field of view (FOV), resolution, and number of slices obtained. The FOV is the resolution in centimeters or millimeters instead of pixels. The main trade off to these alterations is time of the scan. MRI appointments can take to upwards of an hour depending on the region imaged, parameters, and number of scans done.

Figure 2.9: A diagram that displays the orientation of the body and hydrogen atoms while a MRI scan is not in process. (Courtesy of Dr. Kashou)

The patient is laid down in the MRI scanner in the same way as shown in Figure 2.9. By assigning each coordinate axes to a different plane in the body, different images are taken. The main magnet is homogenous and is used to align all the hydrogen atoms in one direction, typically the z-plane. Hydrogen is the atom of choice because of its prevalence in the human body. Using a RF pulse signal, the hydrogen atoms are tipped a certain degree, called the flip angle, into the x-y plane, and slowly return to their original orientation in the z-plane as shown in Figure 2.10. The protons rotate around the x-y plane at a specific frequency called the Larmor frequency. This frequency is calculated using the formula

$$\omega = \gamma (B_0 + B_f)$$  \hspace{1cm} (2.1)

where $\gamma$ is the gyromagnetic ratio, and is an intrinsic property of the particle being imaged. For Hydrogen, $\gamma$ is 42.66 MHz/T. $B_0$ is the strength of the magnetic field, and
Figure 2.10: An example of the process during a MRI scan. (A) and (B) displays the orientation of the hydrogen ions during the scan. The hydrogen atoms are oriented in the z-axis, then the x-y plane during the RF pulse then oriented back to the z-axis. (C) displays the longitudinal and transverse energy after the RF pulse. (Courtesy of Dr. Kashou)

$B_f$ is the strength of gradient coil aligned along the frequency encode axis. The addition of 3 gradients in the x,y, and z direction to the main magnet allows for different (x,y,z) coordinates to be chosen. By altering the gradients slightly, which different locations of the tissues are imaged. These gradients are called the slice selection, frequency encoding, and phase encoding gradient. The direction of the slice select gradient determines if a coronal, sagittal, or axial scan is produced. A coronal scan looks from anterior to posterior of the head, axial looks from inferior to superior of the head, and sagittal looks from the lateral side of the head. Depending on the protocol, these gradients can be assigned to any of the three coordinates. These gradients also help reduce artifacts and are tailored to the protocol to get the best image. Two intrinsic constants, T1 and T2, are different for each tissue in the body and are used to determine how the output image will look. T1 is the time it takes for the z-component of the protons magnetic field to reach its equilibrium value. T1 is also called the spin-lattice interaction. T2, called the spin-spin interaction, is the time taken for the xy-component of the protons magnetic field to return to its equilibrium value. These two times are intrinsic to the tissue that is being imaged, and used to determine the repetition time and echo time. The repetition time (TR) is the time between one RF pulse and the next one, and is based on T1. Echo time (TE) is the time between the RF pulse and
the maximum value of the output signal, and is dependent on $T_2$. Depending on the time after the RF pulse, the location of the hydrogen atoms in the $x$-$y$ or $z$ plane is changing, and this correlates to the power of the signal obtained. The number of hydrogen atoms in the imaged region, $N(h)$ also determines the strength of the echo. Equations 2.2 and 2.3 show that the intensity of these signals are dependent on $T_1$, $T_2$, $TE$, and $TR$.

$$M_z = N(H)M_0(1 - e^{-\frac{TR}{T_1}})$$  \hspace{1cm} (2.2)$$

$$M_{xy} = N(H)M_0(e^{-\frac{TE}{T_2}})$$  \hspace{1cm} (2.3)$$

$M_0$ is the initial energy of the atoms right before the RF pulse. The equations show that as $TR$ gets longer, $M_z = M_0$ and a very short $TE$ means $M_{xy} = M_0$. The return from the $x$-$y$ plane releases energy that is picked up by the RF coil around the patient. By adjusting $TE$ and $TR$, the intensity of different tissues are enhanced, thus affecting the contrast. By setting $TR <= T_1$ and $TE << T_2$ of the desired tissues, $T_1$ weighted images are obtained. $T_1$ weighted images have their contrast dominated by the $T_1$ characteristics of the tissues imaged. By setting $TR >> T_1$ and $TE >= T_2$ of the desired tissues, $T_2$ weighted images are obtained. $T_2$ weighted images have their contrast dominated by the $T_2$ characteristics of the tissues imaged. An example would be that for $T_1$ weighted images, the cerebrospinal fluid (CSF) would appear dark, but for a $T_2$ weighted image would appear bright due to the different values set for $TR$ and $TE$. By adjusting the $TE$ and $TR$ of the MRI sequence, different contrasts can be obtained, which highlight different focal areas in the region of interest.

Figure 2.11 displays a simple pulse sequence. A $90^\circ$ pulse is used, and so is a $180^\circ$ pulse. The $180^\circ$ pulse rephases the hydrogen atoms to improve the image quality. $G_z$ is
set as the slice selection gradient and is turned on during the RF pulse. $G_y$ is the phase encoding gradient and the multiple lines represents that different strengths of the gradient field are used to get different phase encodes. $G_x$ is the frequency encode gradient and is turned on when the output signal is obtained. An opposite gradient value is activated during the phase encode gradient so that the majority of hydrogen atoms will be in phase at the center of the acquisition period, giving the highest signal intensity. By altering the pulse sequence, when the gradient fields are turned on/off and TE/TR, new MRI sequences can be used that can allow for better resolution or faster scanning. One such scan, the Fast SPoiled Gradient Recalled echo (FSPGR), allows for 3D imaging by utilizing small flip angles and a specific pulse sequence for each gradient that would not be possible with a conventional pulse sequence. By adjusting the pulse sequence used, one can analyze different regions and inspect regions of interests in different ways. Figure 2.12 shows what a FSPGR pulse sequence looks like.

The image contrast is very important for segmenting different regions of interest, but there are some limitations. Even though different pulse sequences are used, imaging infants has some drawbacks. As the brain is developing, myelination of cortical regions occur at different periods. With the incomplete myelination, image contrast in the brain is lowered.
Figure 2.12: Revised pulse sequence for a FSPGR 3D scan.

Since the myelination is not complete in the white matter portion of the brain, discerning gray matter and white matter is difficult due to similar tissue characteristics. Also due to the small head size of infants, image resolution is reduced and so are scan times. Scan times affect the TE and TR used, which in turn affect the image contrast. To improve contrast on a T2 weighted image, TE needs to be increased due to the lack of myelination and the same for TR for a T1 image weighted image.

### 2.4 Significance

As stated earlier, feeding is an integral part of development. Impairment to the neural pathway can cause issues to develop and cause hardships on the child and the family. Much research has been done on characterizing the swallowing pathway\cite{3, 7, 30}, and manifestations of dysphagia in infants\cite{7, 8, 9}. Regardless, little has been done to characterize the anatomical regions of the brain that are involved with swallowing in infants. By characterizing certain regions of interests utilizing anatomical MR images in neurologically vulnerable infants, differences can be ascertained between them and healthy infants.
Methods

3.1 Recruitment

For this study, 45 neonates with swallowing disorders were investigated. Every infant was consulted by a neonatologist and was recommended to have a head MRI scan done to confirm if there was any anatomical problems. Multiple MRI sequences were done to help the radiologist determine if there was any anatomical deficiency. IRB protocol was obtained for the study. Along with volumetrics, feeding outcomes at discharge and neural abnormalities were obtained. Patients were either discharged on oral feeds or on a gastrostomy tube (G-tube). Some patients at discharge were on both based on if they could not finish all their feeds orally and needed a G-tube. Preterm infants were designated as those who were born at less than 38 weeks of gestation. Lesions were identified and characterized for patients that had them as well. Some patients had multiple MRI scans, which allowed for longitudinal segmentation.

3.2 MRI Acquisition

All patients were transported to the MRI machine at Nationwide Children’s Hospital by a trained nurse and were observed throughout the study to ensure there was no complications. Vital signs were monitored as well throughout the imaging. No sedation was given,
but if excessive motion was present, sedation was given by the anesthesia staff. Scans administered on a 1.5 or 3 Tesla General Electric (GE) Scanner. Total scanning time was around 30 minutes for each patient. Axial scans were acquired for all patients and were used for the segmentation. Sagittal scans were available, but varied between 2D and 3D scans, while coronal scans were consistent, they were not as simple to segment compared to the axial scans. The axial scans were T1 FLuid Attenuated Inverse Recovery (FLAIR) with a TE/TR of 8.5ms/2000ms, slice thickness of 4mm, FOV of 180mm, matrix size of 256x256, and a 3:00 minute acquisition time. Other axial scans were T2 Fast Spin Echo (FSE) with a TE/TR of 102ms/4000ms, slice thickness of 4mm, FOV of 180mm, matrix size of 256x256, and a 2:32 minute acquisition time.

3.3 MRI Segmentation

MRI sequences were anonymized to protect patient identity and were uploaded into AnalyzeDirect (www.analyzedirect.com, MayoClinic). These scans were checked for motion artifacts that would impair the segmentation process and if so were discarded. Next, the scans were segmented manually using the region of interest (ROI) tool. The ROIs included the basal ganglia, brainstem, cerebellum, and thalamus. After the segmentation was completed, volumetrics were calculated for each area. A flow chart of the segmentation process is shown in Figure 3.1.

To verify the locations of each segmented areas, their locations were cross-referenced with an online atlas[32] and a neonatal MRI atlas[33]. The basal ganglia region of interest was defined as the area encompassing the striatum, globus pallidus, substantia nigra, and subthalamic nucleus. These areas were distinguishable by their intensity compared to the surrounding white matter and being superior to the thalamus in the axial plane. The thala-
mus includes the hypothalamus, prethalamus, and epithalamus. It is located inferior to the basal ganglia and has a lower intensity compared to its surrounding. The brainstem was segmented based on its darker intensity compared to the CSF surrounding it and is located anterior to the cerebellum. The cerebellum was distinct in its location and was located posterior to the brain stem and inferior to the cerebrum. The cerebrum was defined as the region of the brain that did not include the brain stem or cerebellum. Axial scans were segmented starting at the most inferior slice and moving upwards. Final segmentations were crosschecked with a neonatal neuroradiologist to ensure accuracy and location. Figures 3.2 and 3.3 show an example of how segmentation of these areas look for a single slice. The brain stem is colored red, cerebellum is green, cerebrum is yellow, basal ganglia is blue, and the thalamus is purple.

3.4 Statistics

All values are reported as Mean±SE. MATLAB (Mathworks Inc) and R (www.r-project.org) were used for statistics, and p-values < .05 were considered significant. Regions of interest were plotted against time due to patients having scans taken at different ages. $R^2$ were calculated for these regions of interest based on linear regression. Students t-test was used
to determine if there any significance between the regions of interest for infants that were discharged on oral feeds versus those discharged on G-tubes.

Figure 3.2: An inferior slice showing the cerebrum (yellow), cerebellum (green), and brain stem (red).
Figure 3.3: A middle slice showing the cerebrum (yellow), basal ganglia (blue), and thalamus (purple).
Results

Table 4.1 lists the demographic data for the analyzed patients. Analysis and segmentation were divided up between feeding outcomes (G-Tube, Oral, Both), preterm vs. full-term, Lesions versus non lesions, and time 1 versus time 2. 8 out of the 12 infants with lesions were preterm.

<table>
<thead>
<tr>
<th>Feeding Outcome</th>
<th>Total</th>
<th>Number with Lesions</th>
<th>Preterm</th>
<th>GA (wks)</th>
<th>PMA (wks)</th>
<th>Number of Time 2 MRI</th>
<th>Time 2 PMA (wks)</th>
</tr>
</thead>
<tbody>
<tr>
<td>G-Tube</td>
<td>13</td>
<td>5</td>
<td>10</td>
<td>31.5±1.7</td>
<td>46.9±3.1</td>
<td>3</td>
<td>70.7±25.1</td>
</tr>
<tr>
<td>Oral</td>
<td>22</td>
<td>5</td>
<td>19</td>
<td>31.5±1.1</td>
<td>42.8±1.1</td>
<td>3</td>
<td>52.4±10.4</td>
</tr>
<tr>
<td>Both</td>
<td>10</td>
<td>2</td>
<td>10</td>
<td>30.2±1.1</td>
<td>42.7±1.2</td>
<td>0</td>
<td>NA</td>
</tr>
</tbody>
</table>

Average and range of volume of the four regions of interest based on feeding outcomes are displayed in Figure A1 in Appendix A. Statistical analysis was not done on these since dates of MRI scans were different for each patient so the data is biased to when the infant had the MRI. Figure 4.1 displays graphs for the volumetrics of the brain stem, cerebellum, basal ganglia, and thalamus for the three different feeding outcomes. Post Menstrual Age (PMA) is used instead of Gestational Age (GA) since studies were done at different times for each patient and a linear fit was calculated to determine the trend of growth of these regions. Those on oral feeds at discharge had the fastest growth in these ROIs compared to those on G-tube or both. Patients on both G-tube and oral feeds had a mix of slopes compared to the other two demographics. Figures A2 and A3 display the brain stem/cerebellum...
and basal ganglia/thalamus ratios. The brain stem/cerebellum ratio graph shows a downward slope for all three categories, while the basal ganglia/thalamus ratio shows different slopes for each category. Tables A1, A2, and A3 in Appendix A display the p-values for correlation between each ROI for all three subgroups. Significant values are bolded, and show there is correlation between the two groups for that ROI pairing.

![Brain Stem](image1.png) ![Cerebellum](image2.png) ![Basal Ganglia](image3.png) ![Thalamus](image4.png)

Figure 4.1: Volume analysis versus PMA for brain stem (top left), cerebellum (top right), basal ganglia (bottom left), thalamus (bottom right) of feeding outcomes.

Growth of the ROIs compared between infants with lesions and those without are shown in Figure 4.2. Trendlines show similar growth between all ROIs except for the brain stem and thalamus. Brain stem growth was greater for those with lesions compared to the infants without, and the opposite trend for the thalamus volumetric analysis. Table A4 in Appendix A displays the p-values for correlation between each ROI for the two subgroups.
Significant values are bolded, and show there is correlation between the two groups for that ROI pairing.

Figure 4.2: Volume analysis versus PMA for brain stem (top left), cerebellum (top right), basal ganglia (bottom left), thalamus (bottom right) of lesion characteristics.

Six patients had a second MRI segmented as shown in Figure 3.3. Only five patients are shown in the figure since the sixth patient was an outlier as their second MRI was done at 120 weeks PMA compared to the significantly lower PMA of the other five. This figure shows an increase in the volume of all ROIs with patient 3 not having any growth in the basal ganglia and a smaller volume in the thalamus at the second scan compared to the first. Figure A8 in Appendix A displays the change in volume of the ROIs for all six patients versus the time between the first and second scan. A linear fit was also included.

Since segmentation was done for every slice, volume renderings were possible for
each infant. Figures A4 and A5 display the brain stem/cerebellum and basal ganglia/thalamus ratio between preterm and full term infants with different feeding outcomes. The plots show very similar slopes for all categories except the brain stem/cerebellum ratio for full terms on oral feeds and the basal ganglia/thalamus ratio for preterm infants on G-tubes. Figures A6 displays the plots of each ROI divided by the patient’s head circumference. This accounts for the variation between MRI dates of each patient. Oral feeds had a higher $R^2$ value and steeper linear regression compared to G-tube for each ROI. Table 4.2 displays the Mean±SE, $R^2$, and p-values of the comparisons of the ROIs between infants discharged on oral feeds and G-tubes. The 4th and 7th column also display the p-value of the linear regression analysis done on each group.

Table 4.2: Statistical Analysis of ROIs

<table>
<thead>
<tr>
<th>Region of Interest</th>
<th>Oral Feeds</th>
<th>G-Tube</th>
<th>Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean±SE ($mm^3/cm$)</td>
<td>$R^2$ (ROI $mm^3/cm$ vs PMA)</td>
<td>P-value</td>
</tr>
<tr>
<td>Brainstem</td>
<td>190.9±7.8</td>
<td>0.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>658.8±35.4</td>
<td>0.49</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cerebrum</td>
<td>9453.3±336.4</td>
<td>0.46</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>274.0±12.1</td>
<td>0.3</td>
<td>0.02</td>
</tr>
<tr>
<td>Thalamus</td>
<td>212.6±10.4</td>
<td>0.14</td>
<td>0.1</td>
</tr>
</tbody>
</table>
Figure 4.3: Volume analysis versus PMA for brain stem (top left), cerebellum (top right), basal ganglia (bottom left), thalamus (bottom right) of time 1 versus time 2 scans.
Discussion

Neurologically vulnerable infants have a risk of developing feeding difficulties due to key structures being damaged early on in life\[29, 34, 35, 36, 37, 38\]. Lesions in the brain stem or basal ganglia area cause feeding and other impairments later in life\[29\]. By employing techniques to help reduce the impact of hypoischemia\[39\] and stimulating the areas involved in sucking and swallowing\[1, 5\], these infants can start the process of developing a normal sucking and swallowing pattern. As stated in the background, other neurological impairments can lead to dysphagia\[29, 40, 41\]. The variability in neural outcomes and diseases associated with dysphagia is an area of interest and future work needs to be done to better characterize these neural and feeding outcomes\[29, 38\]. Other studies have looked at structural analysis to determine any long lasting neurological outcomes\[13, 14, 15, 42, 43\]. By using the same techniques that these other studies use and applying them to regions pertinent to feeding, we can start to correlate growth in these regions with swallowing impairment.

The regions analyzed were based on existing studies that have outlined how these areas are integral to the swallowing pathways. The neonatal brain is not fully developed thus certain regions have a more predominant role in the pathway such as the basal ganglia, cerebellum, thalamus, and brain stem. Demographic data for each infant shows that even though they all had some issue feeding, some infants show no neurological defects, which means that a functional problem may be the issue. What this can mean is that there is a
functional or connectivity issue related to the impairment that the structural MRI can not detect. Other imaging modalities will need to be included in the imaging protocol to help clinicians look at the entire picture before diagnosis.

For infants that were discharged on oral feeds, their rate of growth in the cerebral ROIs was greater than those that discharged on G-tubes or both. Reasons could be that the infants were able to ingest more compared to those on G-tubes thus accelerating their growth. Other factors could be therapeutic treatments that were administered to the infant, which have shown to improve motor and oral functions in these vulnerable neonates[5, 44, 45]. When factoring in head circumference of each infant, we see that the volumes/cm is more closely related to PMA for infants discharged on oral feeds compared to G-tube. The p-values shown in table 4.2 show that there isn’t any correlation between most of the ROIs except the cerebellum. The average mean volume is higher for those discharged on G-tube, which could be due to the higher PMA of those infants. Improving the neural growth and plasticity of these neonates can help improve their feeding outcomes at discharge allowing them to feed normally. The patients that were both orally feeding and using a G-tube at discharge had neural growth that was higher than those discharged on oral feeds only in the thalamus, and lower than those discharged on G-tubes in the cerebellum. This can be due to the lower number of infants that were discharged on both as the $R^2$ values for these linear fits were low. The p-values shown in tables A1-A3, show that there is correlation between the two ROIs for the two subgroups. Significant p-values mean there is a correlation in the values the two ROIs. If there is no difference between feeding regiments then the same ROIs of each group will have significant p-values. There are very few significant values between same regions, which can mean that the growth between these regions is different per feeding outcome. Significant p-value for correlations between two different regions can mean similar growth as well, but asymmetrical development of the brain should mean there should not be any correlation between different ROIs. The significant values between
different ROIs can also be due to the low number of data points for the feeding groups.

The comparison between neural growth of neonates with lesions versus those without, show that both had similar neural growth. The only difference was the volumetric data of the thalamus. Since the $R^2$ value was very small for the linear fit of the patients with lesions, a conclusive difference could not be ascertained. A larger sample size can help alleviate this problem. Statistical analysis showed correlation between basal ganglia and cerebellum and basal ganglia between both the subgroups. In the linear fit, basal ganglia for both subgroups were growing at the same rate, which confirmed the p-value. As stated before, the significant value between the cerebellum and basal ganglia could be the different sample size between the subgroups. The time 1 versus time 2 scans shows that most infants had an increase in the specified regions between scans. Patient 3 was an outlier in this, which could be due to the segmentation done or the protocol used. The same issue applies for patient 6, shown in Figure A7. Since the number of slices in the axial plane was fairly small, portions of these regions could be missed during the scanning process. A thinner slice gap and other parameters can be changed to help alleviate this issue in future studies. The differences between preterm and full term was not apparent due to the low sample size of full-term infants. More patients need to be analyzed, but preliminary data showed that the rate of growth is similar for both of preterm and full term. Oral versus G-tube feeds showed that the rate of growth is faster for the infants discharged on oral feeds.

While MRI looks at the structural components and health of the brain, not all feeding issues are structurally based. These other issues may be due to functional irregularities such as incorrect pathways. Analyzing MRIs cannot determine if functional issues are the source of feeding problems, so other techniques need to be employed. Looking at feeding problem from a multitude of angles will help diagnose problems faster and will lead to better treatments of the fundamental issue.
One way to look at the structural connectivity of the infants brain is to use diffusion tensor imaging. DTI looks at the diffusion of water in the brain to determine the connectivity of the brain. The pathway of the water is called a tract. By looking at the pathway and number of tracts in a certain region, researchers and clinicians are able to diagnose any issues at that region. Changes in the pathway can correlate to tumors or other issues[46, 47]. By using DTI, we can look at the functional connectivity of the infants brain and develop treatments based on their growth[48]. Researchers have looked at swallowing using DTI, but in adults[49]. By combining DTI and structural MRIs, we can spot discrepancies between them and can determine the underlying issues of the patients. Figure 5.1 displays an example of a DTI.

Functional Magnetic Resonance Imaging (fMRI) uses specific sequences to calculate the oxygenation in the brain. By performing tasks, certain portions of the brain are activated and this shows if these areas are involved in the specific task. In regards to swallowing, multiple studies have been performed on adults to look at which areas are involved in swallowing[26, 50]. Functional connectivity between regions activated during volitional swallowing has been shown[50], confirming that there is a neural pathway between these regions and a disruption of these connections can cause issues. fMRI is very useful in adults but not infants since adults are able to respond to instructions and have the ability to keep still during resting periods of the study. While fMRI is not viable in infants, other technologies have come forth to fill the void of functional imaging at young ages. Figure 5.2 displays an example of a fMRI data.

Near-infrared spectroscopy (NIRS) is a new technology that correlates functional tasks with brain activation[51]. NIRS uses light sources and photodetectors to measure light ab-
sorption and converts it to oxyhemoglobin and deoxyhemoglobin concentration changes in the regions of interest. Due to the limitations of NIRS, the areas that can be analyzed is limited to cortical areas. Structures located deeper in the brain such as the brain stem, basal ganglia, and thalamus are not capturable by NIRS. Since these areas are very important to swallowing at a young age, using NIRS to determine if there is any issue with these structures is difficult and cannot be used to verify any issues with these areas. Multiple studies utilizing different tasks have been done on infants[52, 53, 54] and recently a study has been published using NIRS to determine cortical activation during swallows in neonates[7]. This article is one of the first to look at swallowing with NIRS and shows promise in combining functional imaging with physiological imaging on neonates. Figure

Figure 5.1: Example of a DTI scan. The different colors of the lines denote which way the water is diffusing through the brain. (Courtesy of Dr. Kashou)
Figure 5.2: An example of a fMRI scan during a volitional swallowing study. Different slices of the brain are used to show the activation throughout the brain. Bright colors are meant to show increase in oxyHemoglobin, while cool colors show an increase in deoxy-Hemoglobin. (From Babei et al. [50])

5.3 displays an example of a NIRS signal during concurrent manometry.

Figure 5.3: NIRS used during concurrent manometry on infants. As shown, there is an increase in oxyHemoglobin and a decrease in deoxyHemoglobin concentration during a stimulus to the pharynx. (From Jadcherla et al.[7])
5.1 Strengths

MRI has many strengths that were used in this study. MRI scans give in-depth analysis of the brain, which allow for diagnosis of any neurological problems. The resolution of MRI scans also allow for accurate measurements of ROIs and other information such as head circumference and brain development. The flexibility of the different MRI sequences also allowed for multiple views of the brain and a definitive picture of the brain and ROIs.

5.2 Limitations

Some difficulties that arose in the study were mainly in the segmentation section. Since myelination in the brain does not finish at birth, the contrast on some of the images was lower compared to others and adults. This meant that segmentation of certain areas such as the basal ganglia was more difficult since it was harder to discern the difference between white matter and the region of interest. Also since neonates are in a time of development, the head size differed from patient to patient since they were not scanned at the same age. This led to some bias, so age matched patients is a necessity for future works. Reliability of segmentation is an important facet of this and other studies and would need to be improved upon to solidify the analysis. Cross verification and multiple segmentations would be a way to ensure this[55]. A standard protocol was not used for the study, which meant that some infants had certain scans done while others did not. By producing a standard protocol we could help remove this problem from other studies.

Improvements to this study and others like it, would be the use of automatic segmentation. With manual segmentation, the area and volume of the objects registered are varied between each operator and these variations can give different results. Automatic segmentation takes this variability out of the equation and gives the same result based on
input. There are some papers using watershed filter to segment regions of interest[56, 57]. Certain algorithms are able to discern multiple areas in the neonates brain, allowing for volumetrics to be determined[57]. The main issue that arises for both techniques is that cross checking is a requirement to make sure that there are no false identifications added to the data. Automatic segmentation can also be tuned to detect lesions in the brain[58], which can complement the neuroradiologist findings. Another challenge for automatic segmentation is, in order for the parameters to be set correctly, a wide variety of MRIs need to be obtained to initialize the code, but this is a one time step if the patient population does not change. Automatic segmentation allows for faster analysis of each patient, and is an integral tool when comparing large population.

5.3 Future Works

For the future, there are many things that need to be addressed and optimized to improve clarity. A standard protocol needs to be set to ensure that there are no issues with segmentation and that all regions are clearly visible. A larger sample population can also help improve statistical analysis done giving a stronger foundation for further studies. As mentioned before, other imaging modalities will need to be included to get a clearer picture on what the neurological issue is. As the data shows, structural issues are not the only cause of dysphagia, thus including functional modalities such as NIRS and structural connectivity modalities such as DTI can help paint a clearer picture on the underlying issues. For longitudinal studies, age, gender, neurological diagnosis, and feeding outcome will need to be matched to solidify the data since all of these factors can have an effect on the volumetric data of the study.
Conclusion

This is the first study to look at the segmentation of certain ROIs involved in the swallowing pathway in neonates. We analyzed head MRIs of 45 infants and manually segmented each of them. By comparing feeding outcomes with brain growth, we found that infants that were discharged on oral feeds had a more rapid growth in these ROIs compared to those that were discharged on G-tubes. Lesions did not seem to affect neural growth rate, but more data is needed before a conclusion is reached, and for those patients that had a secondary scan we confirm that there is an increase in all the regions with the exception of one patient. Using MRI scans to look at the neurological state of the neonate can help determine what the root cause of their swallowing issue is. By combining MRIs with the other modalities discussed such as NIRS, DTI, and fMRI, both structural and functional information can be ascertained and used to provide a detailed diagnosis of the underlying issue the patient may have. A predictive method such as this can assist the primary caretakers of what the best treatment for the patient is.
Bibliography


[29] M. Martinez-Biarge, J. Diez-Sebastian, C. J. Wusthoff, S. Lawrence, A. Aloysius, M. A. Rutherford, and F. M. Cowan, “Feeding and communication impairments in
infants with central grey matter lesions following perinatal hypoxic-ischaemic injury,” 


Appendix A

Additional Results

Figure A.1: Box plot of volume for each feeding outcome. Brainstem (upper left), cerebellum (upper right), basal ganglia (bottom left), and thalamus (bottom right).
Figure A.2: Brainstem to cerebellum ratio per feeding outcome.

Figure A.3: Basal ganglia to thalamus ratio per feeding outcome.
Figure A.4: Brain stem to cerebellum ratio categorized by preterm versus full term and feeding outcomes.

Figure A.5: Basal ganglia to thalamus ratio categorized by preterm versus full term and feeding outcomes.
Figure A.6: Volume/Head circumference for each ROI per feeding outcome.

Figure A.7: Difference in Volume of ROIs versus Difference in PMA for Time 1 and Time 2. Brainstem (upper left), cerebellum (upper right), basal ganglia (bottom left), and thalamus (bottom right)
Table A.1: P-Values for G-Tube-Oral Correlation between ROIs

<table>
<thead>
<tr>
<th>G-Tube</th>
<th>Brainstem</th>
<th>Cerebellum</th>
<th>Basal Ganglia</th>
<th>Thalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>0.3927</td>
<td>0.9421</td>
<td>0.5766</td>
<td>0.9179</td>
</tr>
<tr>
<td>Cerebellum</td>
<td>0.3632</td>
<td>0.9286</td>
<td>0.8247</td>
<td>0.8929</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>0.7832</td>
<td>0.837</td>
<td>0.8498</td>
<td>0.968</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.8092</td>
<td>0.9977</td>
<td>0.7159</td>
<td>0.9312</td>
</tr>
</tbody>
</table>

Table A.2: P-Values for G-Tube-Both Correlation between ROIs

<table>
<thead>
<tr>
<th>G-Tube</th>
<th>Brainstem</th>
<th>Cerebellum</th>
<th>Basal Ganglia</th>
<th>Thalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>\textbf{0.0473}</td>
<td>0.3344</td>
<td>\textbf{0.0581}</td>
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</tr>
<tr>
<td>Cerebellum</td>
<td>\textbf{0.0422}</td>
<td>0.2034</td>
<td>0.1059</td>
<td>0.3498</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>0.0658</td>
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<td>0.5898</td>
<td>0.5037</td>
</tr>
<tr>
<td>Thalamus</td>
<td>0.2812</td>
<td>0.7377</td>
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<td>0.7025</td>
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</table>

Table A.3: P-Values for Oral-Both Correlation between ROIs

<table>
<thead>
<tr>
<th>Oral</th>
<th>Brainstem</th>
<th>Cerebellum</th>
<th>Basal Ganglia</th>
<th>Thalamus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brainstem</td>
<td>0.2635</td>
<td>\textbf{0.0161}</td>
<td>\textbf{0.0336}</td>
<td>0.0787</td>
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<tr>
<td>Cerebellum</td>
<td>0.6287</td>
<td>0.0827</td>
<td>0.1641</td>
<td>0.2797</td>
</tr>
<tr>
<td>Basal Ganglia</td>
<td>0.8268</td>
<td>0.2266</td>
<td>0.1355</td>
<td>0.1671</td>
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<tr>
<td>Thalamus</td>
<td>0.8341</td>
<td>0.3839</td>
<td>0.297</td>
<td>0.6778</td>
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</table>

Table A.4: P-Values for No Lesions versus Lesions Correlation between ROIs

<table>
<thead>
<tr>
<th>No Lesions</th>
<th>Brainstem</th>
<th>Cerebellum</th>
<th>Basal Ganglia</th>
<th>Thalamus</th>
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<tr>
<td>Brainstem</td>
<td>0.6272</td>
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<td>Cerebellum</td>
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<td>0.1335</td>
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<tr>
<td>Basal Ganglia</td>
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<td>Thalamus</td>
<td>0.4673</td>
<td>0.4481</td>
<td>0.1479</td>
<td>0.8369</td>
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