THE MECHANICAL PROPERTIES

OF THE ADOLESCENT BRAIN

by

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Introduction

The mechanical properties of the brain, as imaged by magnetic resonance elastography (A. Manduca, 2001), have emerged as sensitive measures of neural tissue structure. Studies of the adult brain have revealed a high sensitivity to microstructural health in many neurodegenerative conditions and, recently, a strong structure-function relationship between hippocampal viscoelasticity and memory performance (Schwarb, 2016). However, there are currently no MRE studies that have characterized the stiffness of adolescent brains. This work seeks to address this critical gap in the literature to provide the first in vivo measurements of the adolescent human brain, and compare with previously reported values for the healthy adult brain. Ultimately, these MRE measurements can provide a novel, sensitive approach to studying how the brain matures, and potentially determine structure-function relationships in the developing brain.

Methods

A sample of N=46 healthy, adolescent children (20/26 M/F; age 12-14) completed an MRI scan session on a Siemens 3T T rio scanner, which included high-resolution MRE (2.0 mm resolution; Johnson, 2016) and T1-weighted anatomical (MPRAGE; 0.9 mm resolution) scans. Whole-brain MRE displacement data at 50 Hz was used to create maps of viscoelastic shear stiffness through the nonlinear inversion algorithm (NLI; McGarry, 2012). Regional stiffness was quantified for comparison with literature values of adult brain stiffness by creating ROIs in two ways. (1)ROIs of the cerebrum, cerebellum, and individual lobes, which are regions reported in MRE of the adult brain by Murphy (2013), were created from the WFU PickAtlas (Maldjian,

2003). Atlas masks were registered from standard space to the MRE data in FSL (Jenkinson, 2012). (2) ROIs of subcortical structures (amygdala, hippocampus, pallidum, putamen, caudate, and thalamus), as analyzed with MRE by Johnson (2016), were determined by segmentation of the MPRAGE by FIRST (Patenaude, 2011), and similarly registered to the MRE data.

Results

The stiffness values for regional brain lobes in adolescents was compared to the values for adults as reported by Murphy (2013) (Fig. 1). Both the adolescent cerebrum and cerebellum showed similar average stiffness values as in the adult brain, with adolescent brain with differences of -0.3% and 1.7%, respectively. The four main lobes of the cerebrum (frontal, temporal, parietal, and occipital) are all softer in adolescents with differences between -5% and -13%. Interestingly, the region comprising deep gray and white matter was 7.5% stiffer in adolescents.

To further examine the regions central to the cerebrum, six subcortical structures were examined and compared to the adult values reported by Johnson (2016) (Fig. 2). In this case, the caudate and the thalamus were very similar in adults and adolescents, -0.8% and 0.5% difference; the pallidum and the putamen were much stiffer in adolescents 8.4% and 6.9% respectively; and the amygdala and the hippocampus were much softer -18.3% and -10.8%.

Conclusions

This is the first report of the mechanical properties of the human adolescent brain measured in vivo with MRE. By comparing regional stiffness values with adult brain values from literature, a difference was able to be observed between adolescents and adults. Analysis of lobes suggested a gradient of stiffness from higher at the center

of the brain to lower at the periphery; while subcortical regions suggest clustering of stiffer or softer structures based on anatomical location. It is likely that these findings of stiffness in the adolescent brain relative to the adult brain reflect patterns of development as the brain matures to adulthood, similar to previous reports of age-dependent white and gray matter structure (Toga, 2006). MRE of the adolescent brain can be used to identify trends relating to the development of brain structure and potentially provide insight into behavior and social development through sensitive structure-function relationships.

Chapter 1

INTRODUCTION

1.1 Overview and Motivation

Structure-function relationships of the brain have been studied since the beginning of the 19th century; however, the complex study of mechanical properties of the brain is much more recent thanks to advances in imaging techniques in the past twenty years (L. Xu, 2007). Accurately quantifying the mechanical properties of the brain, particularly the viscoelastic shear stiffness, can provide valuable insight into the health of the brain and aid in both clinical diagnostics and assessment of treatment methods (A. Manduca, 2001).

Magnetic resonance eleastography (MRE) is a noninvasive magnetic resonance imaging (MRI) imaging technique used to quantitatively measure the mechanical properties of soft tissues in the body, specifically tissue viscoelasticity. This technique can provide sensitive and regionalized measures of the structure of neural tissue. Currently, elastography is the only non-invasive method of accurately determining the mechanical properties of soft tissues *in vivo*, and MRE is the only elastography technique capable of examining the human brain (A. Manduca, 2001).

MRE works through the use of shear wave vibrations, generated by an air pulsating plate under the subject's body part being studied. The waves are passed through a specific region of the body's soft tissue and are images are captured by the use of motion-sensitive, phase-contrast MRI (Curtis L. Johnson, 2013). The sinusoidal wave vibrations are synchronized to the MRI scanner and multiple images can be

taken to ultimately view displacement as a function of time. Analyzing how waves propagate through particular soft tissue regions over short periods of time, through the use of computer algorithms that seek to estimate the solution to the inverse problem, can give us more information about the mechanical properties of the tissue. Broadly, softer regions of tissue will exhibit shorter wavelengths than more rigid tissue, and the quantification of this displacement-time interaction can be used to create accurate stiffness maps (Lucy V Hiscox, 2016).

MRE is done in a research setting on almost every soft tissue in the body in addition to brain, including breast, muscle, and the heart. MRE is also being used clinically to help in the assessment of patients with chronic liver disease, as the liver gets progressively stiffer with disease stage; this has been found to be safe, reliable, and fast alternative to liver biopsy, and is actually a more accurate technique (Mariappan, 2010). MRE is still being studied for use in diagnosing diseases in other organs such as the brain, heart, kidneys and other muscles but has potential to be a noninvasive alternative to many other diagnostic techniques (Patrick Asbach, 2008).

The brain is a particular area of interest, as it is responsible for control of all the other functions in the body, including neurocognitive function and performance. Brain structure-function relation has been studied in depth; however, the relationship between function based on the stiffness of particular regions is less well understood (Ingolf Sack K.-J. S., 2012). The creation of brain stiffness maps can help to assess the mechanical properties of healthy humans as well as have the potential to aid in the diagnosis of many neurodegenerative diseases. Additionally, the maps created from MRE can be divided into brain regions based on their known neuroanatomical and functional parcellation, and the stiffness of these regions can be studied to determine if

specific brain region mechanical properties are related for functional output (Hillary Schwarb, 2016).

Extensive MRE studies of the adult brain viscoelasticity have been conducted, and the mechanical properties of the healthy normal adult brain have been quantified. Correlations between regional viscoelasticity and neurodegenerative diseases have also been found, include ties between Alzheimer's disease and brain stiffness (Matthew C. Murphy J. H., 2011). These studies have outlined the regional viscoelastic properties of the mature brain and have revealed a high sensitivity to microstructural health in many neurodegenerative conditions and a strong structure-function relationship between hippocampal viscoelasticity and memory performance.

Although much literature on mature brain viscoelasticity exists, there are currently no MRE studies that have characterized the stiffness of adolescent brains. Such study could provide needed insight to the structure of the typically developing adolescent brain and could eventually lead to increased understanding of pediatric brain pathophysiology and structure-function relationships underlying cognitive and social development.

1.2 Objectives

This work aims to provide the first in vivo measurements of the adolescent human brain stiffness to address the critical gap in the literature, and compare with previously reported values for the healthy adult brain to establish a baseline "normal" values for the mechanical properties of the adolescent brain. Ultimately, these MRE measurements can provide a novel, sensitive approach to studying how the brain matures, and may potentially be used to determine the relationships between stiffness of the structure and its function in the developing brain.

The study of structure-function relationships in the adolescent brain can give insight to the complex development of the brain at this stage. Quantifying the viscoelasticity of the adolescent brain can eventually provide a unique approach to diagnosing and treating patients with brain irregularities (Curtis L. Johnson, 2013). Eventually, this work could be applied to a clinical setting to diagnose neurological abnormalities that manifest in adolescence. Mental illnesses found in children, such as attention deficit disorder (ADD), severe anxiety and depression, are currently subjective to clinician's observations and judgment (John Kylan Lynch, 2002). Having a quantifiable method to diagnose these abnormalities could greatly assist in the diagnosis and treatment for these pediatric patients; finding a link between regional brain stiffness and these mental disorders will mean that MRE is an effective means of diagnosis (Hillary Schwarb, 2016).

In this experiment, the stiffness of multiple brain structures will be compared against multiple parameters: (1) bilaterally, i.e. comparison of left and right hemispheres; (2) against subject age and gender, as the properties of the adult brain change with age and differ with gender; (3) to the properties of the mature brain taken from literature values; (4) and to the functional ability to reason abstractly from a behavioral task. This investigative study is done with the hope that further identifying the characteristics of the adolescent brain, as it relates to brain stiffness, can provide insight that can help diagnose abnormal neuroanatomy later on.

1.3 Previous Work

The use of MRE to find trends in global brain viscoelasticity in adults has been studied, as well as utilized to detect neurodegeneration and more specific associated diseases. More recently, studies have been conducted to look at the viscoelasticity of

the brain regionally, as well as in the major lobes and the smaller subcortical regions. Additionally, researchers from several groups, including at Mayo Clinic and Charite in Berlin, have done work to improve the technique of MRE, to make it more efficient. These efficiency improvements include: faster acquisition speeds, higher signal to noise ratio, and more accurate mechanical property measures (Lucy V Hiscox, 2016).

These previous studies support the technique used in this thesis for data collection and processing, and provide a point of comparison for the data collected in this study.

1.3.1 *Non-invasive measurement of brain viscoelasticity using magnetic resonance elastography*

Ingolf Sack and co-authors were one of the groups to use MRE to measure brain viscoelasticity. Over a period of half a year, they studied six healthy males to establish a protocol and a margin of confidence for the technique that was used to demonstrate that his method was reliable and reproducible. They found that the brain stiffness from MRE was between 1.33–1.77 kPa on average, and that the repeated measurement variation was 1.3%. He demonstrated that it was possible to image the viscoelasticity of the brain in both two and three dimensions and set a standard for MRE studies that would follow (Ingolf Sack B. B., 2007).

1.3.2 *The Influence of Physiological Aging and Atrophy on Brain Viscoelastic Properties in Humans*

Aging of the brain is accompanied by the degeneration of neurons, generally leading to a decline in brain stiffness. In 2011, Sack et al studied 66 healthy volunteers ages 18-72 and a observed a linear decline of whole brain elasticity with age in these subjects. From these data, they estimated that the brain decreased in stiffness by

approximately 0.75% per year. This was the first paper to set a baseline for the decline of overall brain stiffness with age in the older population (Ingolf Sack K.-J. S., 2011). This work also motivates the study in this thesis, as their population started at 18 years old, and they did not provide any data on the adolescent brain.

1.3.3 *Brain Viscoelasticity Alteration in Chronic-Progressive Multiple Sclerosis*

In 2012, Streitberger et al sought to quantify the relationship between neurodegenerative diseases and the decline of brain stiffness. Through the study of patients with multiple sclerosis (MS), it was found that brain viscoelasticity is lower in patients with MS compared to healthy controls, and that the stiffness is further lower depending on MS disease severity. Patients with relapsing-remitting MS had 15% lower brain stiffness, while patients with chronic-progressive MS had 20.5% lower brain stiffness. This study showed a link between patients with neurodegenerative brain conditions and overall brain stiffness, leading to the need for further investigation into similar correlations (Kaspar-Josche Streitberger, 2012).

1.3.4 *Measuring the characteristic topography of brain stiffness with magnetic resonance elastography*

Murphy et al from Mayo Clinic reported on methods they developed for measuring the stiffness of individual brain lobes, e.g. frontal, temporal, etc.. The study proposed that a new technique was necessary to be able to look at the regional stiffness rather than just the global stiffness, and used a lobe atlas to generate regional brain stiffness measures. They found that by using a specific inversion technique for investigating lobes was necessary to overcome the effects of atrophy in aging populations. Murphy et al reported median regional stiffness for adults for the cerebellum, frontal lobe, occipital lobe, parietal lobe, temporal lobe, and the deep grey

matter and white matter (GM/WM), as well as measurement repeatability. They found that only some regions differed from the others, specifically the cerebellum and parietal lobe (Matthew C. Murphy J. H., 2013). In this thesis, we will similarly characterize the stiffness of brain lobes in children and compare with the results found by Murphy et al.

1.3.5 *Viscoelasticity of Subcortical Gray Matter Structures*

In 2016, Johnson et al studied the viscoelasticity of individual subcortical structures using a specific imaging and inversion pipeline. They proposed that MRE studies could be improved by investigating these structures possible more closely related to function and disease, as compared to global brain stiffness, which most MRE studies report. Specifically, Johnson et al looked at the amygdala, hippocampus, caudate, putamen, pallidum, and thalamus and determined the shear stiffness (kPa) and the damping ratio. He found there was significant difference ($p < 0.05$) in stiffness among the subcortical structures, as well as found the hippocampus to be significantly softer than other structures. His study further verified the need for stiffness comparisons to be made by brain regions rather than just by global brain stiffness. (Curtis L Johnson H. S., 2016)

1.4 Relevant Literature

1.4.1 Abstract Reasoning using Raven's Progressive Matrices task

Raven's Progressive Matrices are nonverbal tests used to measures general cognitive ability and abstract reasoning abilities. It is mainly used in people ages five and older. It is especially useful for educational and research purposes to compare people of specific demographics to one another. The test is a series of up to 60

multiple choice questions in order of difficulty. The individual questions are a series of square matrices and the goal is to identify the missing element in a complex pattern from 6-8 choices. The test is beneficial because it can test participants regardless of language barrier (John Raven, 2003).

The test is designed to measure two cognitive components: educative and reproductive ability. Educative ability is the ability of a test subject to think clearly and make sense of complex situations put in front of them in a timely manner. Reproductive ability is the ability of the test subject to store and reproduce information and to be able to integrate previously seen information to answer current questions (John Raven, 2003).

There are three types of matrices: standard, colored, and advanced. The standard progressive matrix, given to most subjects, is a completely black and white test and is given as described above. The colored progressive matrix is similar to the standard, however the items are presented on a colored background to make the test more visually stimulating for participants, and is usually given to patients for whom the standard matrices would be too difficult. The end parts of these matrices are the same as the standard progressive matrix, so that if a person does better than expectation, they can continue onto the standard progressive matrix. The last type of matrix is the advanced progressive matrix, used for people who score in the top 20% of the standard matrix and is similar to the standard matrices with more difficult questions (John Raven, 2003).

In this study, we used the Raven's Progressive Matrices test to investigate whether mental reasoning abilities relates to global and regional brain viscoelasticity in adolescents.

1.5 Aims

This study aims to:

1. Describe the average viscoelastic properties of the adolescent brain by region, both the major lobe regions and the subcortical gray matter regions, as well as compare how these properties vary bilaterally comparison, with age and gender, and how they compare thes to previous data about the same mechanical properties of the mature brain.
2. Investigate possible correlations between brain stiffness of certain regions and results of memory based and abstract reasoning tests.
3. Provide baseline adolescent brain viscoelastic stiffness data that can be used in future studies to examine pathophysiology of the adolescent brain.

Chapter 2

METHODS

2.1 Data Collection

2.1.1 Quantitative Data Collection

MRE data collection occurred at the University of Illinois, and all subjects and parents provided informed, written consent before beginning the study. The initial sampling was of 66 healthy, adolescent children (20 males, 26 females, ages 12-14). This sample was chosen as part of a larger study aimed at understanding the structure and function of the adolescent brain as it relates to social development and risk-taking behavior.

A Siemens 3T Trio MRI scanner and 12-channel RF receive head coil (Siemens Medical Solutions; Erlangen, Germany) was used with high-resolution MRE (2.0 mm resolution; (Curtis L Johnson J. L., 2014)).T_1-weighted anatomical (MPRAGE; 0.9 mm resolution) scans. Imaging parameters include: two in-plane spiral readouts (parallel imaging R=2); 240 x 240 mm^2 field-of-view; 150 x 150 matrix; 60, 1.6mm slices (divided into 10 slabs of 8 slices each, with 25% slab overlap); and TR/TE = 1,800/73 ms. The resulting images had 1.6 x 1.6 x 1.6mm^3 spatial resolution (Curtis L Johnson J. L., 2014). The MRE scan encodes displacement from shear vibrations generated by a pneumatic driver. The pneumatic driver is activated by pulsating airwaves traveling through a tube that is connected to a pillow the head rests on. When activated, the entire head moves and creates waves in the brain. Images are taken in time to observe how the waves propagate through the brain tissue.

A standard frequency of 50 Hertz was chosen to vibrate the head pillow, to give both high displacement amplitude with low noise. The magnitude of the vibration

can be adjusted dependent on subject's comfort level; however, in every subject a minimum signal-to-noise threshold must be obtained to get reliable data. Too large or too frequent of a wave results in phase wrapping (Huifang Wang, 2011). Noise in an image is static like pixels in the brain slices, which result from interference from other anatomical structures, such as the skull, this noise can make it difficult for the software to get an accurate stiffness reading, and thus generally tries to be minimized (Huifang Wang, 2011).

The images are output as approximately 2,300 DICOM (digital imaging and communications in medicine) files, this is the standard format for medical imaging. These files are outputted as two parts, phase files and magnitude files. The phase files are the progression of the wave propagation through the brain tissue; the magnitude files show the corresponding brain anatomy for each slice. The magnitude and phase files are paired together to generate 3D images of wave propagation and brain anatomy throughout time. Next, a nonlinear inversion was completed in order to convert displacement fields into mechanical property maps, which are the final outcomes from the MRE procedure (MDJ McGarry, 2012). This is described in a following section.

2.1.2 Qualitative Data

A Raven's Progressive Matrix test (Raven, 2000), used to analyze a subject's ability to reason, was administered to each of the 66 study subjects. Written consent was obtained from the subject's parents and each subject was asked to complete the Raven's Progressive matrix test. The test was given in a private room and all subjects were asked to answer the same 12 questions sequentially. Each of these questions were black and white multiple choice questions. Subjects were shown a series of

pictures and asked to choose the image that would come next in the sequence out of eight choices. They were given a 0 for an incorrect answer and a 1 for a correct answer and their response times were recorded. They were given a total score, representing number of questions correct, and their scores were scaled based on difficulty. Subjects were given one point for getting question one right, two points for getting question two right and so on, this was their weighted score. Lastly they were given a sample adjusted score based on how many they got correct in order to prevent an artificially inflated score based on random good guessing on the harder questions. For example, if the subject got the first ten questions incorrect and the last two they guessed correctly, their score would be decreased to fix this skewed result. Their average response time and weighted response time were calculated in the same way.

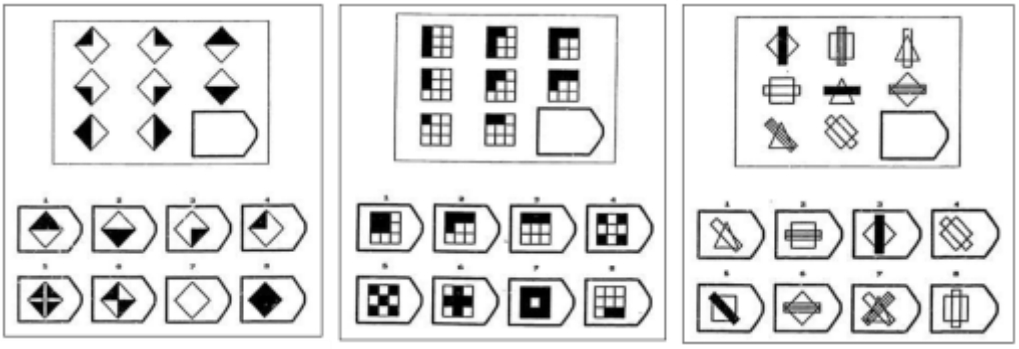

Figure 1: Three example questions Ravens Progressive Matrix test. Seen here is question with the eight multiple choice answers. Correct answers in order are 8, 3, 5.

2.2 Data Processing

Whole-brain MRE displacement data taken at 50 Hz was used to create mechanical property images, similar to topographical maps, of viscoelastic shear

stiffness through nonlinear inversion data processing (NLI) (MDJ McGarry, 2012). The property generated was the complex viscoelastic shear modulus, G,

$$G = G' + iG'', \tag{2.1}$$

where G' is the real shear modulus, or storage modulus, and describes elastic tissue behavior, and G'' is the imaginary shear modulus, or loss modulus, and describes viscous tissue behavior. Together, they are combined as the shear stiffness, μ,

$$\mu = \frac{2|G|^2}{G'+|G|}. \tag{2.2}$$

The regional stiffness was quantified for comparison internally and with literature values of adult brain stiffness.

Prior to computing μ, displacement data was pre-processed as 60 individual brain "slices" broken down with 2 mm isotropic voxels. This pre-processing is used to isolate the brain from background noise. Although much of the background noise was removed automatically with the Brain Extraction Tool (BET) in the software FSL (Mark Jenkinson, 2012), additional noise needed to be manually removed to get clean images of the displacement fields without interference. To do this, "masks" were created on each of the 60 image slices by going through the images individually in Matlab and removing areas where the software did not automatically remove the noise around the edges. These masks were created manually after the software had been run to remove additional areas of the brain that could be problematic for the nonlinear inversion.

After pre-processing, stiffness maps are created with NLI, and the next processing steps involved extracting regional stiffness measures. Different tools in FSL were used to digitally separate the individual lobes and subcortical regions of the brain (Stephen M. Smith, 2004). A standard space atlas was "warped" to fit the brain

of each individual subject and generate an affine transform that is used to convert between the “standard space” and each “subject space”. Affine transformations were created for each subject to convert between the MRE data, the anatomical MPRAGE data, and the standard space. Standard space is used to incorporate atlases created by researchers from large population studies and freely distributed with FSL.

The brain was first segmented into regions for analysis of lobe areas. This was done by creating regions-of-interest (ROIs) from a lobe atlas. The individual lobes, frontal, occipital, parietal and temporal, as well as the entire cerebrum (comprising all lobes) and the cerebellum were created from the WFU Pick Atlas (Maldjian, 2003). Atlas masks were registered from standard space to the MRE data in FSL (Jenkinson, 2012). The values stiffness values for each subject for each region were generated by averaging stiffness maps over each ROI. This is a similar procedure used by Murphy et al for adult brain viscoelasticity (Matthew C. Murphy J. H., 2013) Which were used for comparison in this study.

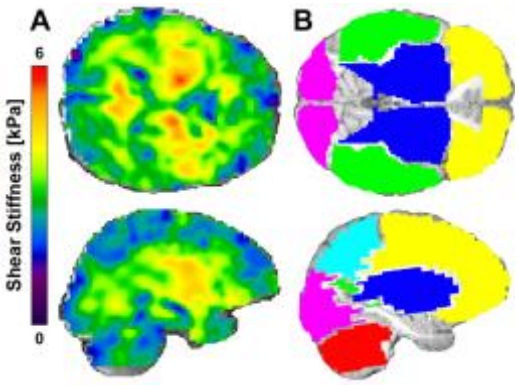

Figure 2: Regions of interest created for brain lobes. Four main brain lobes and the cerebellum (red). Frontal (yellow), Occipital (purple), Parietal (light blue), and Temporal (green).

Additionally, the subcortical structures of the white and grey matter were examined: amygdala, hippocampus, pallidum, putamen, caudate, and thalamus. These subcortical regions were determined by segmentation of the anatomical MPRAGE by FIRST analysis (Brian Patenaude, 2011), and similarly registered to the MRE data using the appropriate affine transformation. Unlike the lobe ROIs in this case, the segmented regions are subject-specific in that they come from the subject's MPRAGE. Again, each region was quantified by averaging over the appropriate ROI for each subject. These data were compared with stiffness values from Johnson et al, which included only the adult brain (Curtis L Johnson H. S., 2016).

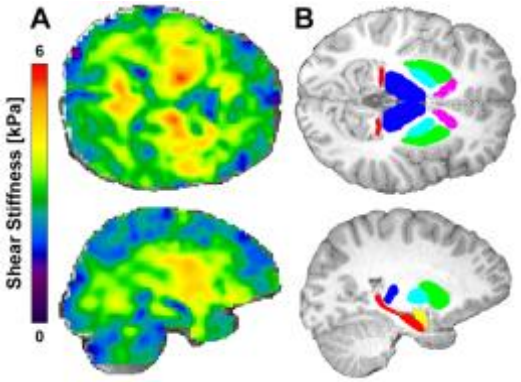

Figure 3: Regions of interest created for subcortical regions. Amygdala (yellow), Hippocampus (red), Pallidum (light blue), Putamen (green), Caudate (purple), and Thalamus (dark blue).

2.3 Data Analysis Techniques

Of the 66 subject initially examined, only 46 of the them were included in the final analysis due to failed scans or analysis procedures (e.g. low signal-to-noise ratio or failed segmentation).

Statistical tests were run for all data. First, all data more than two standard deviations away from the mean were removed. A paired *t*-test was run for each of the regions to compare properties from left and right hemispheres. Both percent differences *and* p-values from *t*-test were recorded for each brain region studied with and without the mentioned outliers. To compare age and gender, I instead used two-way ANOVA (analysis of variance) tests with age and gender as independent variables. Using individual *t*-tests or correlations in this case would increase the chance of statistical type I error; meaning that it is likely to incorrectly reject a true null hypothesis and therefore get a false positive. ANOVAs were performed for each regions and the resulting *p*-values will be reported in this thesis.

Chapter 3

RESULTS

3.1 Adolescent Brain Properties

The data collected were analyzed to present the average mechanical properties of the adolescent brain. These properties were analyzed bilaterally and by gender as well as compared to the properties of the mature brain. The data presented here are sectioned by comparison with adult values, left and right comparisons, and male and female comparison. Additionally, each of these sections are further separated into subsections of lobes and subcortical structures.

3.1.1 Adolescent and Mature Brain

The average stiffness for the adolescent brain was separated into lobes of the brain as well as subcortical regions. The global brain stiffness of the cerebrum and cerebellum was analyzed as well as the four lobes of the cerebrum – frontal, occipital, parietal, and temporal – and the region comprising deep gray matter and white matter not part of a specific "lobe" (e.g. parts of the limbic system). The subcortical regions analyzed were the amygdala, caudate, hippocampus, pallidum, putamen and thalamus. The values for adult stiffness lobes are previously reported by Murphy et al (Matthew C. Murphy J. H., 2013), and the values for adult stiffness for subcortical regions are reported by Johnson et al (Curtis L Johnson H. S., 2016). We compared these literature values with the results from our adolescent brain sample.

3.1.1.1 *Adolescent Brain Lobes compared with (Murphy, 2013)*

The adolescent brain mechanical property maps were separated into lobar regions and analyzed. Average global stiffness of the cerebrum and cerebellum, the four main cerebral lobes, and the deep GM/WM were calculated and compared to values reported by Murphy et al (Matthew C. Murphy J. H., 2013). In this case, the standard deviation values for adult brain stiffness was not reported by Murphy, and thus we do not include these values with the adult lobe data (Matthew C. Murphy J. H., 2013).

Table 1: Stiffness difference between adolescents and adults major brain lobes

	Adolescent Average	Adult Average	Difference
Cerebellum	2.422	2.38	1.77%
Cerebrum	3.009	2.99	0.65%
Frontal	2.768	3.15	-12.11%
Occipital	2.804	3.21	-12.63%
Parietal	2.722	2.87	-5.14%
Temporal	2.924	3.17	-7.75%
Deep GM/WM	3.664	3.41	7.47%

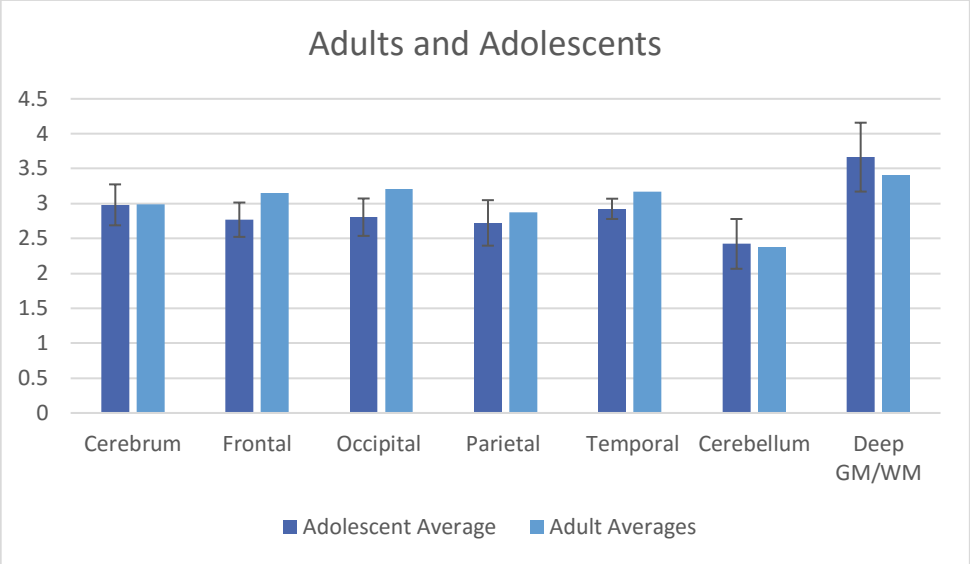

Figure 4: Average adult and adolescent brain stiffness by lobe; values for standard deviation of adult stiffness was not present in the literature.

As seen in Figure 4 and Table 1 the average stiffness for the cerebrum in adolescents is 3.009 kPa, while in adults the average stiffness is 2.99 kPa (Murphy). This small difference of 0.65% suggests that there is no difference between adult and adolescent global brain stiffness. The frontal lobe was an average stiffness of 2.768 kPa in adolescents and 3.150 kPa in adults, and the occipital lobe was 2.804 kPa in adolescents and 3.21 kPa in adults. These lobes exhibited relatively differences of 12.11% and 12.63%, respectively, with the child's brain being softer in those regions. The temporal and parietal lobes were also stiffer in adults but not as large of a difference, for temporal 2.924 kPa in adolescent as compared to 3.17 kPa in adults, and for parietal 2.722 kPa in children and 2.87 kPa in adults. These were differences of 7.75% and 5.14%, respectively. Overall, all four brain lobes were stiffer in adults,

however the deep gray matter and white matter region was stiffer in adolescents: 3.664 kPa in adolescents and 3.41 kPa in adults, representing a 7.47% difference.

3.1.1.2 *Adolescent Subcortical Structures compared with (Johnson 2016)*

The subcortical regions analyzed in this paper were the amygdala, caudate, hippocampus, pallidum, putamen, and thalamus. These regions were chosen as Johnson et al reported values for adult stiffness in these regions, which we will use for comparison (Curtis L Johnson H. S., 2016).

Table 2: Stiffness difference between adolescents and adults subcortical structures

	Adolescent Average	Adult Average	Difference
Amygdala	3.129	3.83	-18.30%
Caudate	3.719	3.75	-0.82%
Hippocampus	2.988	3.35	-10.79%
Pallidum	4.163	3.84	8.41%
Putamen	4.138	3.87	6.92%
Thalamus	3.838	3.82	0.48%

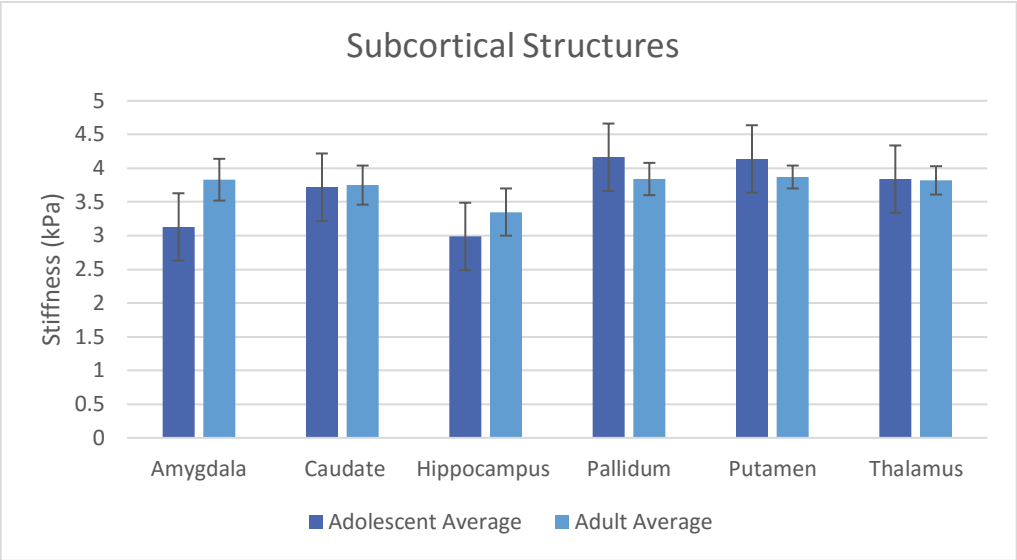

Figure 5: Average adult and adolescent brain stiffness by subcortical structure.

The amygdala and the hippocampus are both much softer in adolescents than adults. The amygdala has a stiffness of 3.128 kPa in adolescents as compared to 3.83 kPa in adults, which is an 18.30% difference. The hippocampus has a stiffness of 2.988 kPa in adolescents and 3.35 kPa in adults, a percent difference of 10.79%. The caudate and thalamus show almost no stiffness difference between adolescents and adults. The caudate has a stiffness of 3.719 kPa in children and 3.75 in adults, only a 0.82% difference. The thalamus has a stiffness of 3.823 kPa in adolescents and 3.82 kPa in adults which is only a 0.68% difference. The pallidum and putamen are more rigid in adolescents than adults. The pallidum is an average of 4.163 kPa in adolescents and 3.84 kPa in adults, a 8.41% difference. The putamen has a stiffness of 4.138 kPa in children and 3.87 kPa in adults, which is a 6.92% difference.

3.1.1.3 *Difference Values between average stiffness of the Adolescent and Adult Brain*

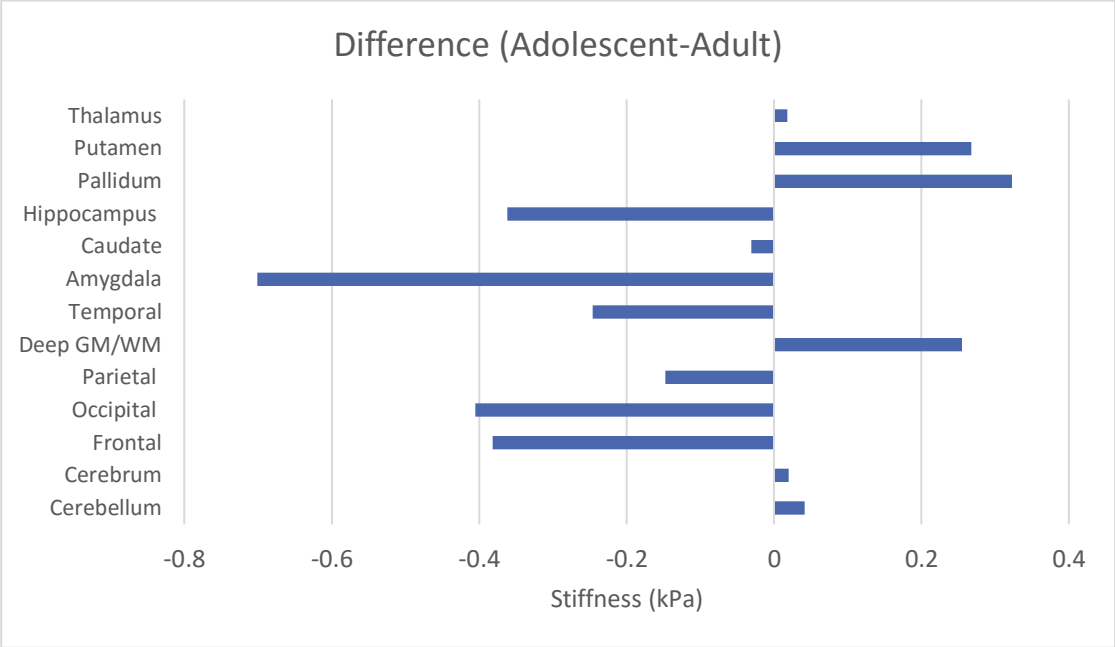

Figure 6: Difference (adolescent-adult) brain stiffness, negative values represent stiffer regions in adults; positive values are regions stiffer in adolescents.

Figure 6, shows the average stiffness for adults subtracted from adolescents to give a representation of the amount of stiffness difference. Positive values above the axis represent regions stiffer in adolescents: the pallidum, the putamen, and the deep GM/WM. The values below the axis are stiffer in adults: the frontal lobe, the occipital lobe, the parietal lobe and the temporal lobe, as well as the amygdala and hippocampus. The most notable stiffness difference being the amygdala, which is 0.701 kPa stiffer in adults than adolescents, on average. The cerebellum, cerebrum, caudate, and thalamus are of nearly identical stiffness in adolescents and adults.

3.1.2 Left and Right Side of Brain

The brain was digitally segmented into the left and right hemispheres and stiffness values were calculated for each lobe and subcortical structure, and the difference between hemispheres was found. The entire brain stiffness, the cerebrum, was analyzed as well as the four lobes: frontal, occipital, parietal and temporal. The cerebellum was also considered. The subcortical regions were the amygdala, caudate, hippocampus, pallidum, putamen and thalamus. The left and right sides of the brain were compared in each subject and then averaged.

3.1.2.1 *Left and Right Hemisphere Compared Bilaterally by Lobes*

The brain was digitally separated into brain regions and analyzed. Average global brain stiffness and the four main brain lobes and cerebellum were calculated and compared bilaterally to each other.

Table 3: Left and right side of brain stiffness measurement separated by lobe

	Left Stiffness (kPa)	Right Stiffness (kPa)	Difference (Left-Right) (kPa)
Cerebrum	3.038	2.981	0.056
Frontal	2.801	2.736	0.064
Limbic	3.610	3.486	0.123
Occipital	2.788	2.808	-0.020
Parietal	2.754	2.695	0.059
Temporal	2.942	2.924	0.017
Deep GM/WM	3.784	3.694	0.089

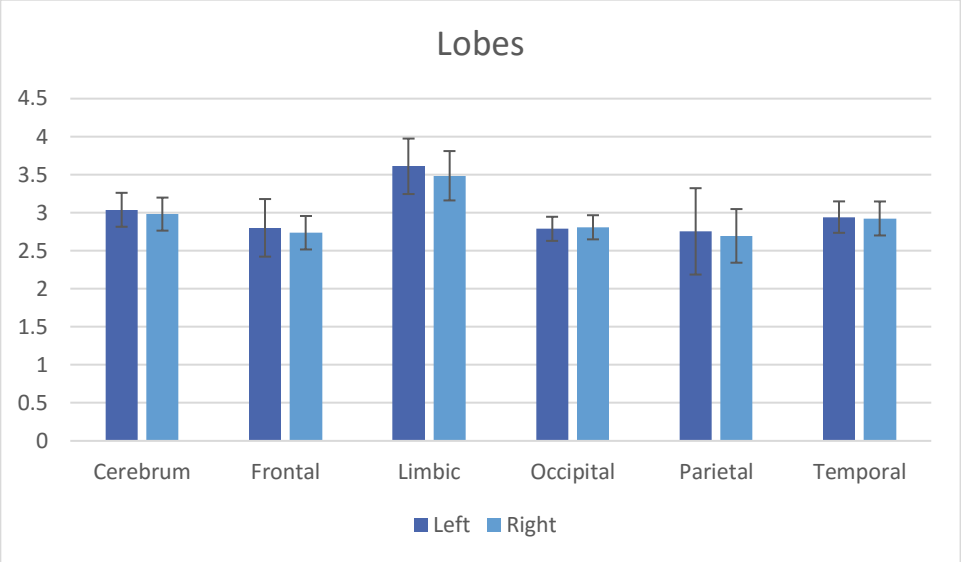

Figure 7: Stiffness of right and left side of the brain compared bilaterally by lobes in (kPa). Error bars representing the variability among subjects.

As seen in Table 3 and Figure 7 the left side of the adolescent brain has an average stiffness of 3.038 kPa and the right side has an average stiffness of 2.982 kPa. Of the four main brain lobes, the frontal, limbic and parietal lobes were stiffer on the left side with the largest difference being 0.123 kPa, the occipital lobe was slightly stiffer on the right side by 0.02 kPa.

3.1.2.2 *Left and Right Hemisphere Compared Bilaterally by Subcortical Regions*

The left-right analysis was also performed for each of the six subcortical structures: amygdala, caudate, hippocampus, pallidum, putamen, and thalamus.

Table 4: Left and right side of brain stiffness measurement by subcortical region

	Left Stiffness (kPa)	Right Stiffness (kPa)	Difference (Left-Right)
Amygdala	3.244	3.019	0.224
Caudate	3.778	3.719	0.059
Hippocampus	3.057	2.921	0.136
Pallidum	4.217	4.110	0.107
Putamen	4.200	4.137	0.062
Thalamus	3.879	3.794	0.084

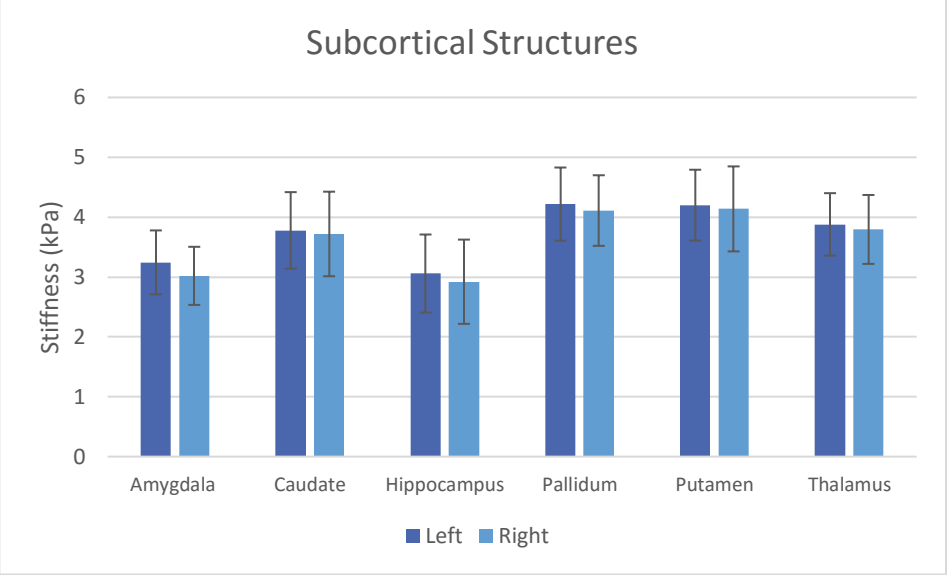

Figure 8: Stiffness of right and left side of the brain compared bilaterally.

As seen in Figure 8 and Table 4, all of the subcortical regions are stiffer on average on the left side than on the right side with the range of 0.059 kPa to 0.224 kPa. The greatest difference was the amygdala and the smallest difference was the caudate. The standard deviation bars represent a difference among different children, meaning

that the left and right hemisphere stiffness may be different between the subjects, but when internally comparing the left and right side of a subjects, it is almost always the case that the left side is stiffer than the right side.

3.1.2.3 *Left vs Right Hemisphere Stiffness Differences*

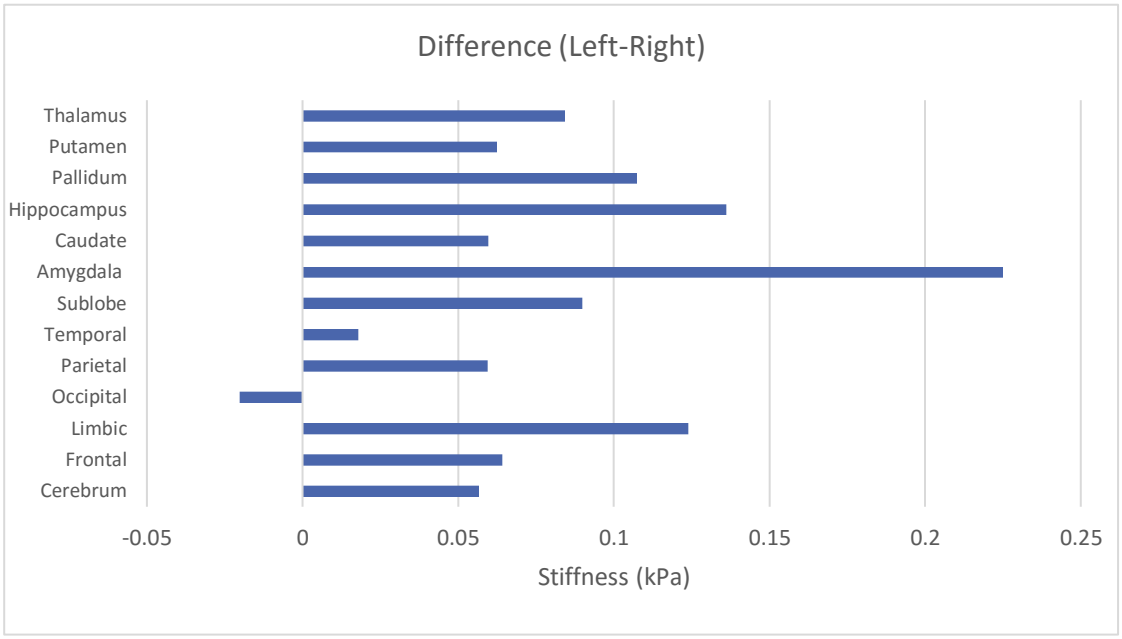

Figure 9: Stiffness difference between the left and right side of the brain for each subcortical region. Positive indicated stiffer in the left side, negative indicated stiffer in the right side.

The bilateral differences between the left and right side of the adolescent brain can be seen in figure 3.1.1.2 where values above the x-axis indicate the brain region is stiffer on the left side, and regions below the x-axis indicate the brain is stiffer on the right side. It can be seen that all brain regions are stiffer on the left side except the occipital lobe, and the amygdala has the largest bilateral difference.

3.1.3 Male and Female Brain

Similarly, each brain region was analyzed to determine if there was any difference in stiffness between the male and female brains.

3.1.3.1 *Male vs Female Adolescent Brain by Lobes*

Table 5: Male and female bilateral brain stiffness measurement by lobe

	Males Stiffness (kPa)	Female Stiffness (kPa)	Difference (Male-Female)
Cerebrum	3.010	2.975	0.0347
Frontal	2.812	2.681	0.1311
Occipital	2.816	2.792	0.0234
Parietal	2.725	2.718	0.0067
Temporal	2.925	2.922	0.0028
Cerebellum	2.391	2.454	-0.0629
Deep GM/WM	3.741	3.735	0.0063

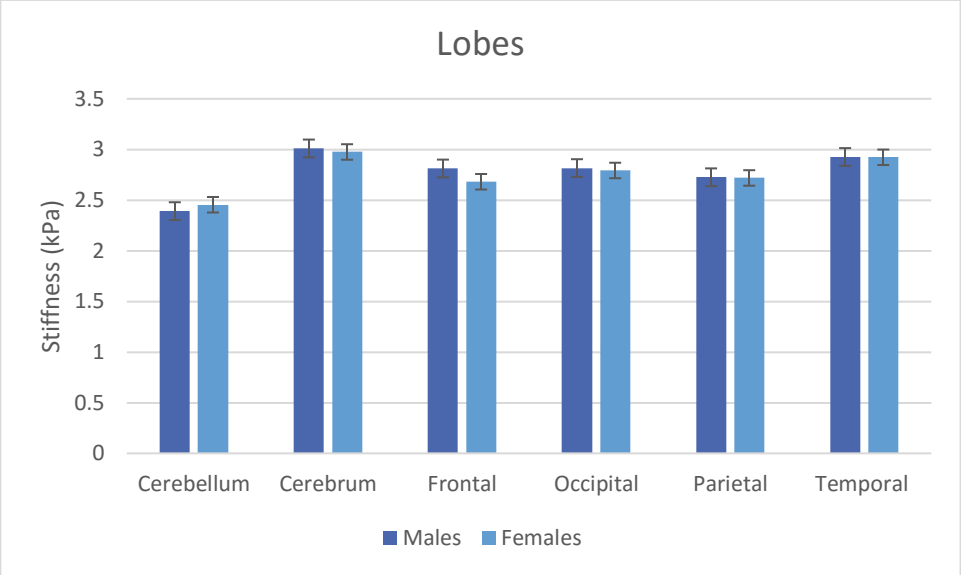

Figure 10: Stiffness values for males and females by lobe

In Figure10 and Table 5 the male brain and female brains are of very similar stiffness for almost every region of the brain. With the largest difference being in the frontal lobe with males on average being 0.131 kPa stiffer than females. The overall cerebrum is nearly identical with less than a 0.04 kPa stiffness difference between males and females. None of the regions showed a significant difference.

3.1.3.2 *Male vs Female Adolescent Brain by Subcortical Structures*

Table 6: Male and female bilateral brain stiffness measurement by subcortical structure

	Males Stiffness (kPa)	Female Stiffness (kPa)	Difference (Male-Female)

Amygdala	3.018	3.239	-0.221
Caudate	3.685	3.753	-0.067
Hippocampus	2.911	3.068	-0.157
Pallidum	4.176	4.149	0.026
Putamen	4.171	4.104	0.066
Thalamus	3.722	3.960	-0.238

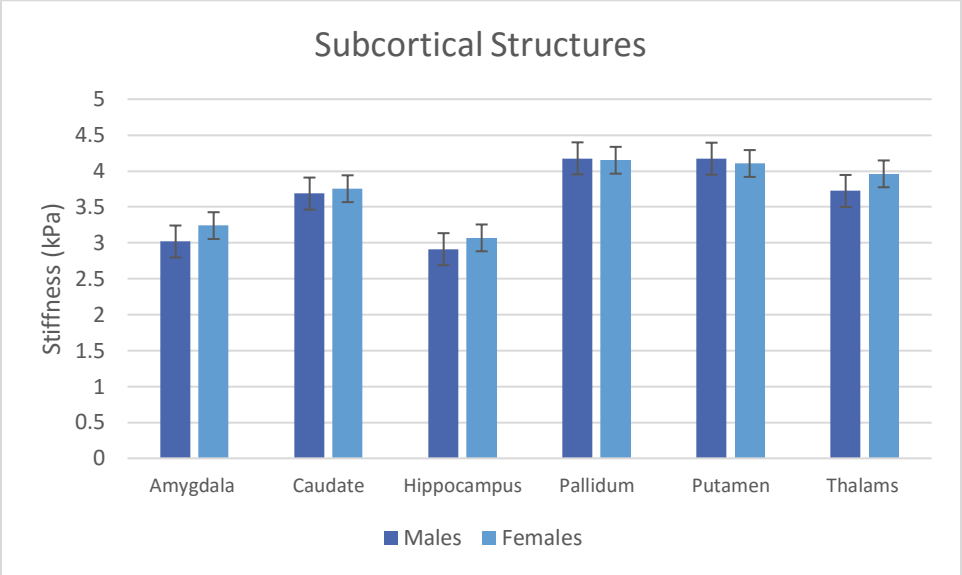

Figure 11: Male and female brain stiffness for each subcortical region of the brain.

As seen in Table 6 and Figure 11 above, the male and female brain show very similar stiffness in all of the subcortical regions. The pallidum and putamen are slightly stiffer in males, and the rest of the regions are slightly stiffer in females; however, none of the differences is significant.

3.1.3.3 *Male and Female Difference*

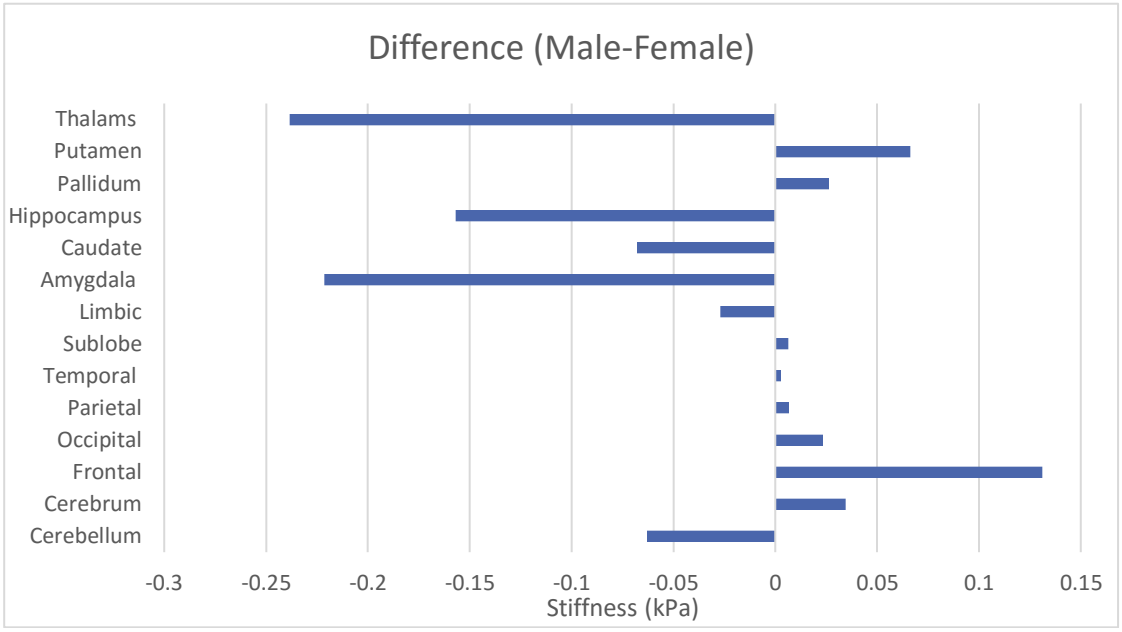

Figure 12: Stiffness difference between male and female subjects by subcortical region. Positive indicated males are stiffer, negative indicates females are stiffer.

3.2 Tasks performed (Ravens progressive matrix)

The subjects who had an MRE study done were also asked to complete a Ravens Progressive Matrix test. This test was meant to determine mental acuity and analytical reasoning skills on a level that is easy enough for children ages 12-14. The raw data was then processed and the scores were weighted by which questions they got correct, because the test goes in order of difficulty. The results of this study are as follows.

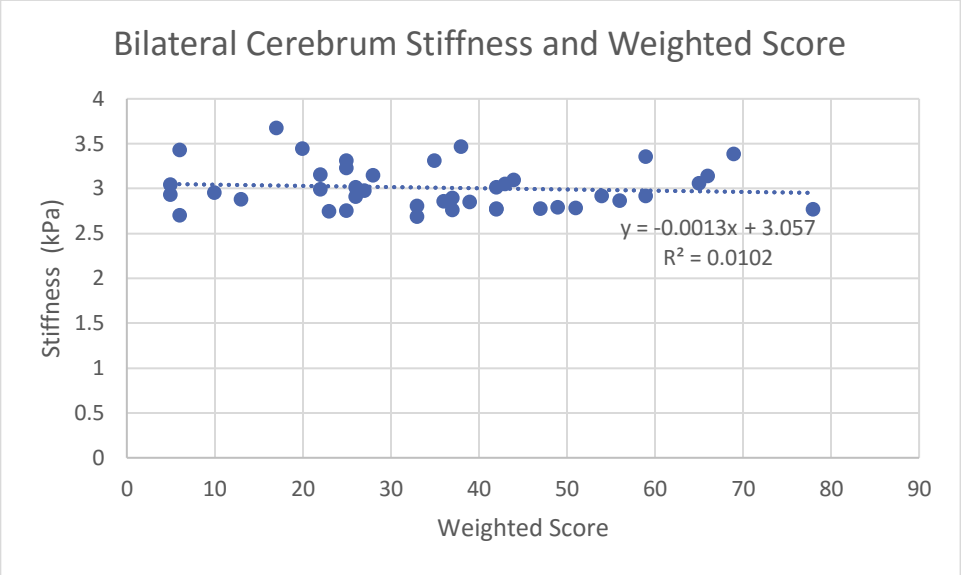

Figure 13: Stiffness of brain and weighted score from Ravens Progressive Matrix

Figure 13 shows the difference between stiffness of the bilateral cerebrum (kPa) and weighted score on the Raven's Progressive Matrix. The average stiffness was approximately 3.0 kPa with task scores ranging from a 4 to a 78. No correlation was seen between average stiffness and score received ($p>0.05$). The other individual lobes of the brain showed similar findings with no correlation between score received and rigidity of any brain region ($p>0.05$).

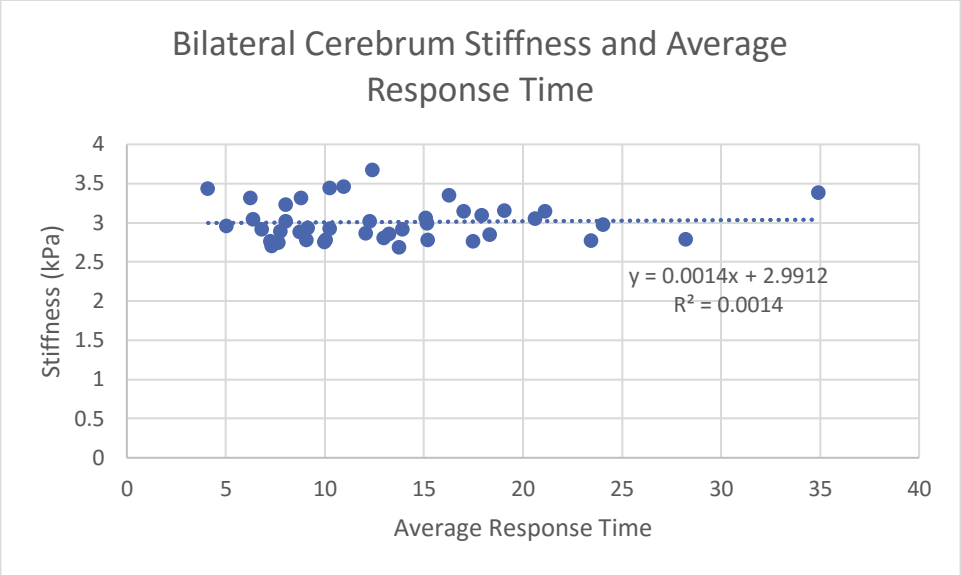

Figure 14: Stiffness of the Cerebrum and Average Response Time of Ravens Progressive Matrix

As seen in Figure 14 the average stiffness of the adolescent cerebrum shows no correlation with the average response time of the questions on the Raven's Progressive Matrix task. The average stiffness was approximately 3.0 kPa with response times ranging from 3 to 35 seconds. No correlation was seen with a slope of 0.0014 ($p>0.05$).

Chapter 4

DISCUSSION

4.1 Adolescent and Adult Brains

4.1.1 Overall Brain Stiffness

The purpose of this study was to quantify the mechanical properties of the adolescent brain (ages 12-14) and it was found to be very similar to the properties of the adult brain at the global level. The average stiffness for the cerebrum in adolescents is 3.009 kPa in adults the average stiffness is 2.99 kPa (Matthew C. Murphy J. H., 2013), this difference of 0.65% shows no statically significant difference between adult and adolescent global brain stiffness. In studies done on very young children, less than five years old, the adult brain appears to be three to four times stiffer. This indicates that brain starts out very soft and will get rapidly more rigid until around age 9 or 10. From here the global stiffness remains the same until older adulthood and remain constant for the majority of the person adult life (Daniel S. Marcus, 2007). This does not necessarily mean however that the individual regions of the brain will remain of constant stiffness over the course of a person's brain's maximal rigidity time period (Daniel S. Marcus, 2007).

As the brain matures fibers connecting nerve cells are wrapped in a myelin sheath, this increases the speed in which information is transmitted between cells (J. Weickenmeier, 2016). The number of connections has been well studied in that it proportionally is related to a person's intellectual capacities such as memory and reading ability (Alan Peters, 2000). Neurons covered with myelin sheaths are more rigid than unmyelinated neurons. This means that brains with more myelination will be stiffer overall. The body will reallocate the distribution of myelinated neurons

throughout a person's life time to the region where they can be the most beneficial (Alan Peters, 2000). Additionally, the patterns of myelination in the developing brain, through adolescence, and into adulthood vary in space, and different regions experience myelination at different times and rates (C. Lebel, 2012).

In adolescents, a person's ability to explore, learn, and retain information is the most necessary function, where in adulthood a person's ability to recall and utilize information becomes much more necessary (Harry T. Chugani, 1986). While the actual number of myelin sheaths in the brain might remain consistent, the allocation of these sheaths is likely changing throughout development into adulthood and beyond (Alan Peters, 2000).

Gray matter in the brain has steadied in volume around age 11 or 12 years old, however white matter will continue to grow and develop until the early twenties. Although the structure of grey matter has matured, the volume distribution continues to change (S Groeschel, 2010). White matter is approximately 39% more stiff than gray matter , meaning that redistribution of gray matter will mean a redistribution of stiffness in the brain (S Groeschel, 2010).

4.1.2 Lobes

The lobes of the brain were segmented by functional region. The brain lobes compared were the frontal lobe, occipital lobe, temporal lobe, and parietal lobe.

The frontal lobe was an average stiffness of 2.768 kPa in children and 3.150 kPa in adults and the occipital lobe was 2.804kPa in children and 3.21kPa in adults, this is a difference of 12.11% and 12.63% respectively. Many studies have found that the frontal lobe is typically the last part of the brain to finish developing neural connections with the occipital at a close second (Goldberg, 2001). This is not

surprising as the frontal lobe controls many cognitive skills such as emotional expression, problem solving, memory, language, judgement and sexual behavior. These traits are not fully developed until early adulthood, meaning that the majority of the neurons will be unmyelinated in this brain region until later in life. With later development of these regions it would be expected that these brain regions are less stiff in the pubescent years (Goldberg, 2001).

The temporal and parietal lobes were also stiffer in adults, but with less of a difference, for temporal 2.924 kPa in adolescent as compared to 3.17 kPa in adults and for parietal 2.722 kPa in children and 2.873 kPa in adults. The temporal and parietal lobes finish development much earlier than the other brain lobes. The parietal lobe is responsible for proprioception, the ability to understand space, touch and volume (Goldberg, 2001). The temporal lobe controls hearing, smell and language. The functions controlled by the temporal and parietal lobe develop and therefore have more myelin sheats much sooner, with 90% of these brain regions fully developed by age five (Goldberg, 2001).

4.1.3 Subcortical Regions

The subcortical regions examined in this study to be compared to adult structures are the amygdala, the caudate, the hippocampus, the pallidum, the putamen and the thalamus. These have a much larger difference between children and adults than the lobes do. While the amygdala and hippocampus are stiffer in adults, the pallidum and putamen and are softer in adults, and the thalamus and caudate show nearly identical stiffness in adolescents and adults.

The amygdala has a stiffness of 3.128 kPa in adolescents as compared to 3.83 kPa in adults, this is an 18.303% difference. The amygdala is primarily responsible for memory, decision making and emotional reaction, traits that are developed much more toward adulthood (Bernard W. Balleine, 2006).

The hippocampus has a stiffness of 2.988 in adolescents and 3.35 in adults, a difference of 10.79%. The hippocampus is important for transferring short term memories to long term memories. This function gets better in adulthood. In childhood, information is absorbed as just the raw information rather than the exact memory of how that information was obtained, as humans grow older the brain becomes more equipped to store exact memories including time and space information. We get better at this due to more myelin sheaths in that region of the brain, leading to a stiffer hippocampus in adults. In patients with Alzheimer's disease you would expect to see a much less stiff hippocampal region due to degradation of myelin sheaths (John O'Keefe, 1978).

Interestingly, both the amygdala and the hippocampus are located in the medial temporal lobe. Our findings suggest that this region may develop mechanically later than others, hence the similar stiffness differences in the amygdala and the hippocampus. Both structures are also part of what is called the "limbic" system, and their properties could tell us about the function of that system.

The pallidum is responsible for voluntary movement and can regulate movements that occur on the subconscious level. The pallidum is an average of 4.153 kPa in adolescents and 3.84 kPa in adults. Especially in very young children, movement is a critical part of development, the ability to explore surroundings is crucial for children which is why one would expect to see more myelin sheaths in that

area of the brain, as the children get older the need for constant movement and exploration is replaced by other necessary brain functions and the brain will remove some of the myelin sheaths in that area to more efficiently use them elsewhere (Mikail Rubinov, 2010).

The Putamen has a stiffness of 4.137 kPa in children and 3.87 kPa in adults, this is a 6.92% difference. The putamen has many functions and it has been concluded that it has no specific specialization, it is a regulatory mechanism between many other structures and so broadly it controls motor skills. It has also been shown to be of use in reinforcement and implicit learning, these involve repeated exposure to information in the environment. This is a crucial learning technique for young children and is a style of learning that is heavily used up through the late teenage years (Chad H. Moritz, 2017).

The caudate has a stiffness of 3.7191 kPa in children and 3.75 in adults a 0.82% difference, which is extremely small. The caudate is responsible for associative learning and inhibitory control. These functions are developed at an early age and are retained and very necessary through adulthood (Mikail Rubinov, 2010).

The last subcortical region looked at was the thalamus, which has a stiffness of 3.823 kPa in adolescents and 3.82 kPa in adults which is only a 0.68% difference. The thalamus, while technically a subcortical region plays a huge roll in overall brain function. It acts as central information relay for various subcortical regions and the cerebral cortex. Such a complex structure as this would be expected to show similar amounts of myelin sheath over the course of a person's lifetime (Chad H. Moritz, 2017).

4.2 Left and Right Hemispheres of the Brain

The right hemisphere of the brain is responsible for control of the left side of the body. The right side of the brain is also the creative side, and it is responsible for face recognition, music processing, understanding spatial areas, and comprehending visual imagery – all things necessary for the developing brain. The left hemisphere of the brain controls the right side of the body and it is primarily responsible for more analytical skills performed, such as logical reasoning and exact math computations. It is also plays a dominant role in language processing and speaking.

The left side of the brain is stiffer in all of the lobes except the occipital and all of the subcortical regions. Many people are right hand dominant, which is controlled by the left side of the brain. In our study, the adolescents studied were entirely right handed. In young children, the dominant side of the body is responsible for more than in adults and young children are prone to do more with their dominant side (Lisa Aziz-Zadeh, 2002). For example, almost every young child will ascend and descend a flight of stairs with their dominant foot on every step. Additionally, many children process information through recall and replication, and creativity is not as prevalent until later. Language, speaking, and basic reasoning skills are all extremely important for developing children. Because many functions performed in young children take place in the left hemisphere of the brain, it would be expected for this side to have more myelinated axons, thus being stiffer (Sandra Weintraub, 1987). Pubescent children, studied in this work, are in the transition stage from children to adults, therefore their brains still may retain many of the features of childhood. It is likely that if even younger children were studied, their brains would show an even greater difference between the left and right side of the brain in favor of the former.

4.3 Male and Female Brain

Males and Females showed nearly identical brain stiffness's on average for all lobes and all subcortical regions. This is not surprising as the male and female brain have similar makeups and develop in similar ways. According to (Ingolf Sack B. B., 2009) significant difference in the viscoelasticity of the brain by gender were found. The female brain was on average 9% more stiff than the average male brains of the same age. Furthermore (Arvin Arani, 2015) concluded that as the male and female brains mature the gap of difference in viscoelasticity increases. This can indicate that although the male and female brain are of similar stiffness in adolescence, the male brain average viscoelasticity will decline more rapidly with age. Further exploration on the prepubescent gender stiffness differences will have to be conducted to get a further understanding of whole lifetime male and female brain viscoelastic properties with age.

Chapter 5

CONCLUSION

Axons are wrapped in a myelin sheath to increase the speed of electrical impulses in the brain. While these myelin sheaths are very effective, they also consume a lot more energy than unmyelinated neurons. To increase overall efficiency, the brain only uses these myelinated sheaths where they are the most needed and effective. Over the course of a person lifetime, the distribution of the myelin sheaths will change location to where they are the most useful.

In children of an adolescent age (12-14) the myelin sheath, and thus the more stiff regions, are mainly found in the putamen, pallidum. These regions are responsible for voluntary motion, as well as regulation of subconscious movement and control of fine motor skills. The amygdala and hippocampus, responsible for memory, decision making, emotional reaction and transferring short term memory to long term memory are more stiff in adults (Chad H. Moritz, 2017).

Additionally, in adolescents, the left side of the brain is more stiff than the right side of the brain, something that is not usually seen in adulthood. The left side of the brain is primarily responsible for analytic thought, reasoning and mathematical skills, additionally it is responsible for controlling the right side of the body, many children's dominant side. This increased stiffness on the left side could indicate that in adolescent years, these skills are the more important ones, thus requiring more myelinated axons. (Jonathan Bishop, 1998)

It appears that the brain region responsible for relevant functions to specific age groups, have a higher viscoelasticity in that region. This could indicate that in addition to a structure-function relationship for regions of the brain; there is a structure-stiffness-function relationship.

Determining the relationship between healthy adolescents and the stiffness of specific brain regions can provide baseline data for identifying a relationship between neurological diseases in children and the stiffness of their brain regions. Correlations such as these could help in the diagnosis and treatment of neurological conditions that are presently difficult to identify.

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