THE CORPUS CALLOSUM OF INDIVIDUALS WITH MICROCEPHALY

AN MRI STUDY

by

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This thesis was prepared under the direction of the candidate's thesis advisor, Dr. Meredith Ellis, Department of Anthropology, and has been approved by all members of the supervisory committee. It was submitted to the faculty of the Dorothy F. Schmidt College of Arts & Letters and was accepted in partial fulfillment of the requirements for the degree of Master of Arts.

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ABSTRACT

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Microcephaly is neurological condition within which the brain fails to develop to a normal size resulting in the appearance of a smaller head. Microcephaly often accompanies various neurodevelopmental disorders. The corpus callosum is the largest white matter structure in the brain, comprised primarily of heavily myelinated axons. The corpus callosum connects the left and right hemisphere and allows for communication to occur between hemispheres. Using MRI measurements from a sample of 18 microcephalic patients, I analyzed whether the corpus callosum was impacted as a result of microcephaly. When compared to normocephalic controls, the corpus callosum was generally smaller in relation to overall cerebral hemispheric volume, suggesting that white matter brain tissues may be affected by microcephaly. A deeper understanding of the brain through research on the underlying mechanisms responsible for brain evolution and development is critical to our ability to detect, treat and prevent neurodevelopmental, neurodegenerative and psychiatric disorders.

THE CORPUS CALLOSUM IN INDIVIDUALS WITH MICROCEPHALY: AN MRI STUDY

LIST OF TABLES

LIST OF FIGURES

1 INTRODUCTION

1.1 BACKGROUND

With the rise of modern technology, biological anthropologists have been able to assess human phenotypic variation beyond our own limited modes of perception. The integration of Magnetic Resonance Imaging (MRI) into the study of human phenotypic variation has allowed researchers to come to deeper and more precise understandings of differences that are invisible to the naked eye. This remarkable invention has allowed researchers to peer into the brain to assess neuroanatomical variation, which has led to advancements in medical research.

The study of human variation has also benefitted from the study of human biological evolution. Insights from the overarching field of evolutionary biology have also assisted in broadening our understanding of how Homo sapiens sapiens became separate and distinct species from other members of the Homo genus, the various ancestral hominids, primates and other mammalian species. The variation of the human skull has largely profited through the integration of the emerging field of studying brain evolution. This branch of biological anthropology holds within it much promise for the study of various disorders, for in order to understand abnormal functioning and development, it is essential to understand how normal functioning and development of the brain came to be in the first place. In the context of this research, the use of the word ‘normal’ is meant to denote a healthy developmental pattern with no or minimal dysfunction.

This research focused on the assessment of the corpus callosum, the largest white

matter structure in the mammalian brain, in a medical condition called microcephaly. MRI images were used to obtain linear measurements of the corpus callosum, as well as cerebral hemispheric area and volume. These measurements were compared to a dataset of normocephalic brain measurements. I expected to observe a reduction in the overall size of the corpus callosum within the brains of individuals with microcephaly when compared to age-matched and sex-matched normocephalic controls. Functional inferences were then assessed in the microcephalic patients that displayed evidence of developmental delay and other comorbidities.

1.2 DEFINITION OF MICROCEPHALY

Microcephaly is a neurodevelopmental anomaly that is associated with over 900 disorders (Von Der Hagen, 2014). Due to this association, microcephaly is described as a sign or clinical observation, rather than as a disorder in itself (Abdel-Salam et al., 2000, Mochida, 2009). The diagnostic criterion for this the condition is dependent upon the occipital-frontal head circumference (OFC) and ranges from mild to severe (Abuelo, 2007, Von Der Hagen et al., 2014, Vannucci et al., 2011). There are two types of microcephaly which are denoted as “primary” and “secondary” (see below). While microcephaly is generally characterized by a OFC that is 2 standard deviations below the mean for characteristics like age and sex at birth (Von Der Hagen et al., 2014, Abuelo, 2004, Passemard et al., 2016, Vannucci et al., 2011), an OFC of 3 standard deviations below the mean is categorized as severe (Abuelo, 2004, Mochida, 2009, Woods, 2004, Vannucci et al., 2011). Individuals who exhibit cases of severe microcephaly are often extremely handicapped and many do not live past 5-6 months of age (Abuelo, 2007).

2 OBJECTIVES OF STUDY

The purpose of this study was to assess the size and configuration of the corpus callosum of individuals with microcephaly. The first hypothesis tested whether the size of the corpus callosum in microcephalic patients is smaller in relation to the designated control group. The second hypothesis tested for regional differences in the corpus callosum when comparing the microcephalic cohort with the designated control group. The final objective of the study was to test whether functional inferences could be made with the data.

Previously designated age groups based upon developmental stages from infancy through adolescence were utilized to compare the two populations within the study (Vannucci et al, 2017, Vannucci et al., 2011). Initially, regional differences within the corpus callosum of each individual were assessed. Since the causes of microcephaly were highly variable, each individual was assessed separately and compared to the designated control group. Then, measurements were scaled to overall cerebral hemispheric volume and each individual microcephalic was once again compared designated control groups to determine whether corpus callosum size was smaller in relation to overall cerebral hemispheric volume.

This study is the first to use quantitative methods to compare the corpus callosum of individuals with the microcephalic brains to individuals with the normocephalic brains. Statistically significant differences were expected to be seen in the overall size of the corpus callosum of individuals with microcephaly relative to their brain size. The results

indicate that the methods used will be useful for doctors when assessing individuals with microcephaly and associated comorbidities, since the corpus callosum plays a fundamental role in overall development, while also broadening our understanding of the corpus callosum and the roles of white matter tissues in neurodevelopmental disorders, neurodegenerative disorders, psychiatric disorders and hominid brain evolution.

3 HISTORICAL CONTEXT OF MICROCEPHALY

Individuals with microcephaly were often exploited within circus side shows. Within these exhibitions, microcephalics were often labeled as pin-heads, evolutionary missing links, or were displayed as being members of indigenous cultures. Although the predominant intention of sideshows was to generate income, a large proportion of promotors projected their shows to be sources of viable knowledge. Within this context, knowledge was gained through gauging difference between oneself and those exhibited, with the intention of reaffirming what was deemed normal by society. According to Russell, "sideshows ensured and encourage[d] 'normal' spectators to feel both superior and fortunate that they had been born and raised without 'deformities'" (Russell, 2001).

The prominent physician and anthropologist, Rudolf Virchow (1821-1902), hypothesized that the microcephalic was representational of a "return to the simian form" ('Microcephaly, 1933). Despite the popularity of this view, comparative anatomical studies determined that the brains of microcephalics did not resemble those of monkeys. The popularity and inclusion of this theory might have greatly impacted the believability of microcephalics as missing links within side shows. Interestingly, Virchow also held controversial views about Neanderthals, characterizing them as pathological *Homo sapiens* (Schultz, 2008).

In addition to side shows, individuals with microcephaly were made public through reports by a Russian psychiatrist by the name of Ivan Pavlovich Merzheevskii (1838-1908) (Molgilner, 2013). He worked with Jean-Martin Charcot (1825-1893), otherwise

known as the father of neurology, as well as with a French psychiatrist by the name of Valentin Magnan (1835-1916). Together, Magnan and Merzheevski presented a report on microcephaly at the Paris Anthropological Society in 1872, yet the nature of the paper is to be determined (Vein, 2011).

Microcephaly was also brought to the public's attention through the work of Cesare Lombroso (1835-1909). Lombroso was an Italian physician and criminologist whose work remains controversial to this day. He displayed various individuals with microcephaly, to whom he ascribed behavioral correlations. These examples included l'uomo coniglio, il scimmin, and l'ummo uccello, three men whose behaviors were compared to rabbits, monkeys and birds, respectively ('Micrencephaly', 1922).

Lombroso's interest in microcephaly, as well as that of many other criminologists, was related to crimes committed by people that had the classical features of microcephaly, such as a small head and a sloping forehead. According to Havelock Ellis (1890), some of these cases perplexed law enforcement and judiciaries, because officials had divided opinions regarding whether or not to deem these individuals criminally insane or to amongst those who committed crimes of passion. In one particular case, a 15 year old boy with a small head and sloping forehead, developmental delay and intellectual disabilities murdered his sister with a hammer, allegedly as a conflict management strategy to bullying by his peers and his sister, while showing no remorse following his actions. Although the case was deemed by the jury and judge to be manslaughter, a doctor involved with the case considered it to be the result of insanity. Ellis, on the other hand, believed this case to rest somewhere amongst the crossroads between criminal insanity and instinctive criminality.

Theorists of the late 19th and early 20th century proposed that microcephaly was the result of premature synostosis, or fusion, of cranial bones (Tredgold, 1922). The earliest report of this occurrence came from the French neurologist and psychiatrist by the name of Jules Baillarger (1809-1890), who was also well-known for his categorization of bipolar disorder (Berrios, 2008, 'Microcephaly', 1933). Another popular theory was that microcephaly represented a retardation of an infant's development. This was justified through observations correlating a small-head with cognitive abnormalities. This theory then was later challenged when cases of radiogenic microcephaly were brought to light. These cases were thought to result from an environmental insult, specifically "x-ray irradiation during pregnancy" ('Microcephaly, 1933).

4 TYPES OF MICROCEPHALY

4.1 PRIMARY MICROCEPHALY

Insight gathered through historical observations of microcephaly has resulted in it being referred to in terms of primary and secondary forms. When microcephaly is observed at the time of birth it is often denoted as primary microcephaly, yet this category is also used to describe cases of microcephaly that are brought on by a genetic causes. Environmental insults, like Cytomegalovirus (CMV), can also result in a small head at birth (Abuelo, 2007). Primary microcephaly can either be isolated, syndromic or accompanied by other anomalies. Isolated microcephaly, also known as "true" microcephaly or microcephaly vera, was initially observed in 1885 by neuroscientist and anatomist, Carlo Giocomini (Mocida, 2009, Falk et al., 2009). More recently, this condition has been relabeled "autosomal recessive primary microcephaly" and is commonly referred to as *MCPH* in medical literature. The locus associated with this type of microcephaly is termed *MCPH1*, or *Microcephalin* (Abuelo, 2007). In addition to the mutation at this locus, mutations at many other loci (MCPH1-17) are associated with microcephaly. The genes affiliated with these loci include WDR62 (Bhat et al., 2011, Bacino et al., 2012, Montgomery et al., 2014), *Microcephalin* (Abuelo, 2007, Bhat et al., 2011), CDK5RAP2 (Bacino et al., 2012, Montgomery et al., 2014, Murray et al., 2012), CEP152 (Bacino et al., 2012, Montgomery et al., 2014), ASPM (Horvath et al., 2006, Passemard et al., 2016, Bond et al., 2002, Ahn et al., 2011), CENPJ (Bond et al., 2005, Montgomery et al., 2014) and STIL (Bhat et al., 2011, Montgomery et al., 2014).

Table 1 | MPCH Loci and their Associated Genes

MPCH Loci and their Associated Genes		
Name of Loci	Associated Gene	References
MCPH1	*Microcephalin*	(Abuelo, 2007), (Bhat et al., 2011), (Duerinckx and Abromowicz, 2017)
MCPH2	WDR62	(Bhat et al., 2011), (Bacino et al., 2012), (Montgomery et al., 2014), (Duerinckx and Abromowicz, 2017)
MCPH3	CDK5RAP2	(Bacino et al., 2012), (Montgomery et al., 2014), (Murray et al., 2012), (Duerinckx and Abromowicz, 2017)
MCPH4	KNL1 (CASC5)	(Duerinckx and Abromowicz, 2017)
MCPH5	*ASPM*	(Horvath et al., 2006), (Passemard et al., 2016), (Bond et al., 2002), (Ahn et al., 2011), (Duerinckx and Abromowicz, 2017)
MCPH6	CENPJ	(Bond et al., 2005), (Montgomery et al., 2014), (Duerinckx and Abromowicz, 2017)
MCPH7	STIL	(Bhat et al., 2011), (Montgomery et al., 2014), (Duerinckx and Abromowicz, 2017)
MCPH8	CEP135	(Hussain et al., 2012), (Duerinckx and Abromowicz, 2017)
MCPH9	CEP152	(Bacino et al., 2012), (Montgomery et al., 2014), (Duerinckx and Abromowicz, 2017)
MCPH10	ZNF335	(Duerinckx and Abromowicz, 2017)
MCPH11	PCH1	(Duerinckx and Abromowicz, 2017)
MCPH12	CDK6	(Duerinckx and Abromowicz, 2017)
MCPH13	CENPE	(Duerinckx and Abromowicz, 2017)
MCPH14	SASS6	(Duerinckx and Abromowicz, 2017)
MCPH15	MFSD2A	(Duerinckx and Abromowicz, 2017)
MCPH16	ANKLE2	(Duerinckx and Abromowicz, 2017)
MCPH17	CIT	(Duerinckx and Abromowicz, 2017)

Of these seventeen genes, the CDK5RAP2 gene is affiliated with the third variant of the *MPCH* loci, *MCPH3*. As with *MCPH1*, mutations of this sort can be caused by consanguineous partnerships. Children with *MCPH3* often experience developmental delay, sensorineural hearing loss, seizures and intellectual disabilities (Alfares, A. et al, 2017). While this gene is of interest to researchers, it has not been studied as extensively as some of the other genes affiliated with microcephaly and its relation to consanguinity and other comorbidities is still to be determined.

The abnormal spindle-like microcephaly associated gene, otherwise referenced as *ASPM*, which has been associated with the *MCPH5* locus, has been of much interest to researchers because it has been found in different cultural groups (Bond et al., 2002). This gene is expressed during the early stages of development and plays a role in the proliferation of neural stem cells within the Central Nervous System (CNS) (Ahn et al., 2011, Horvath et al., 2006). This gene has been observed to cause microcephaly when mutations cause it to become under-expressed. On the contrary, overexpression of the *ASPM* gene has been observed in glioblastomas (Horvath et al., 2006). Interestingly, *ASPM* mutations do not impact the hippocampus, thus long-term memory remains undisturbed, further suggesting that it impacts cells proliferating from the subventricular zone, since *ASPM* mutations are associated with other cognitive disabilities, such as schizophrenia, a cell cycle disease with neuropsychiatric implications (Passemard et al., 2016, Rivero et al., 2006).

4.2 SECONDARY MICROCEPHALY

Secondary forms of microcephaly are often caused by environmental factors such as exposure to teratogens and viruses, malnutrition, trauma during pregnancy (Abuelo,

2004). Despite their genetic causal factors, conditions such as Angelman syndrome and Rett syndrome that carry the risk of microcephaly are categorized as secondary microcephaly due to the later onset of microcephaly (Abuelo, 2007). Instances such as these have led some investigators to categorize microcephaly based upon the age of onset.

Secondary microcephaly can also be caused by ionizing radiation, which is one of the negative consequences of nuclear fallout as occurred at Chernobyl. Wertlecki et al. (2014) assessed for the prevalence of isolated microcephaly among births impacted by Chernobyl. Isolated microcephaly was found in females, an observation that was also observed in Hungary. Despite their findings, the researchers suggested that some of the cases of microcephaly were not have the direct result of ionizing radiation, but may have been instances of microcephaly brought on by the consumption of alcohol during pregnancy, or other causes (Wertlecki et al, 2014).

Evidence has shown a difference between the types of microcephaly observed in high-income and low-income countries. A higher proportion of cases in low-income countries are due to infectious agents, like cytolomegalovirus (CMV) and the Zika virus (Devakumar et al, 2017). The prevalence of infectious agents resulting in microcephaly within more developed countries is much lower. For example, within New York, New York, only 16% of cases were caused by infectious agents and only 6% were caused by infectious agents in Germany (Devakumar, et al., 2017). The prevalence of microcephaly in underdeveloped countries is yet to be determined and requires further research.

5 THE CORPUS CALLOSUM

The predominant focus of this study is on the corpus callosum of individuals with microcephaly. The corpus callosum is a large white matter structure that is only found in placental mammals, making it a very interesting focal point for students of evolutionary biology (Aboitiz and Montiel, 2003). Studies have shown that the size of the corpus callosum is directly proportional to the extent of interhemispheric connections (Josse et al., 2008). Just as in other placental mammals, the corpus callosum is the largest white matter structure found within the human brain. This commissure assists in facilitating communication between the left and right hemispheres of the brain. The corpus callosum is comprised of a genu, which is located anteriorly, followed by a rostrum, body and a splenium at the posterior end (Vannucci et al., 2017).

The topography of the corpus callosum is not static amongst species, with notable differences existing between rodents and macaques (Aboitiz and Montiel, 2003). In most species, the size of the corpus callosum is proportional to the overall size of the brain, especially the cerebral hemispheres. Exceptions to this trend include the corpus callosum of aquatic mammals, which has been found to be smaller in relation to overall brain size. This has been hypothesized to be the result of convergent evolution that is related to aquatic habitats (Manger et al., 2010).

5.1 DEVELOPMENT AND FUNCTION

The corpus callosum is comprised of the axons stemming from neurons that are found within layers II, III, and IV of the cerebral cortex, while oligodendrocytes and

astrocytes make up the majority of glial cells in the corpus callosum (Unni et al., 2012). Layers IV and VI are associated with the thalamus, a part of the brain most sensory pathways project (Kumar et al., 2017, Barth and Kuhlman, 2013). Somatosensory projections, including those that are associated with nociception, are processed by the thalamus. While the axons in the corpus callosum are not made up of the axons projecting to and from the thalamus, the corpus callosum plays a vital role in interpreting, categorizing and reacting to nociception and other sensory experiences (Yen and Lu, 2013).

The formation of the corpus callosum begins in utero and occurs in an anterior to posterior fashion (Barkovich and Norman., 1988). The rostrum is the last portion of the corpus callosum to form(Jarred, A. et al., 2017). Despite formation of the most anterior portion of the corpus callosum occurring first, it is the last portion to myelinate (Thompson, 2011). Formation occurs between the 74^{th} and 115^{th} days post-conception, the process of myelination begins around four postnatal months and continues throughout adolescence and into adulthood (Dávila-Guitiérrez, G., 2002, Narberhaus, A. et al., 2008, Phillaps, K. A. and Sherwood, C. C., 2012).

In utero, the most crucial period of corpus callosal growth occurs during the third trimester. Studies on very preterm (VPT) infants have shown thinning and smaller overall size of the structure due to an interruption of this important developmental period (Narberhaus, A., et al., 2008, Thompson et al., 2011). One study found that the part of the corpus callosum that was most affected in VPT infants was the posterior two-thirds, which includes the isthmus, splenium and a portion of the body. The shape of the pre-term corpus callosum was described as being more circular, which is a feature that is also

seen in patients with fetal alcohol syndrome (FAS) and Williams syndrome (Thompson et al., 2011). Other studies have shown a reduction in the size of the anterior region of the corpus callosum in VPT children as well (Narberhaus, A. et al., 2008).

5.2 ABNORMAL CORPUS CALLOSUM DEVELOPMENT

Studies on anomalies of corpus callosum structure have added depth to our understanding of its vulnerability. Variations of the corpus callosum were originally thought to be isolated, however, MRI studies were able to show relationships between corpus callosum and brain abnormalities (Hetts et al., 2006, Crawley et al., 2014). Many studies focused on agenesis of the corpus callosum, a condition in which this structure is completely missing, and hypogenesis of the corpus callosum, a condition in which portions of the corpus callosum fail to develop (Barkovich and Norman, 1988, Hetts et al, 2006).

Abnormalities of the corpus callosum can arise due to a genetic predisposition to a certain characteristic, or genetic vulnerability susceptible to environmental insult. When malformations arise due to environmental insult, the developmental stage can play a greater role than the insult itself (Barkovich and Norman, 1988). Malformations of the corpus callosum can often be found in association with anomalies of neuronal migration, which include the lissencephalic and schizencephalic phenotypes.

Table 2 | Corpus Callosum Connectivity in Relation to Associated Function

Corpus Callosum Connectivity and Associated Function		
Areas of Connectivity for the Rostrum		
Region of Cerebrum	*Associated Function*	*Resources*
Posterior Prefrontal	Top-down construction of syntactic categories, enhanced distinction between self and other in	Witelson, 1989; Meyer et al., 2018; Shuwerk et al., 2014; Shin et al., 2018, Koritzky et al, 2013; Xiao and Zhang, 2018

	Theory of Mind (TOM), enhanced decision-making in movement, recent time perception, negative affect in relation to noiception	
Inferior Premotor	Peripersonal space coding	Witelson, 1989; Fogassi et al., 1996
Areas of Connectivity for the Genu		
Region of Cerebrum	*Associated Function*	*Resources*
Prefrontal	Modulates enhanced motivation (desire/dread), inhibition, impulse control, supporting the cognitive control of memory	Witelson, 1989; Richard and Berridge, 2013; Cohen-Zimerman et al., 2017; Liu et al., 2018
Areas of Connectivity for the Rostral Body		
Region of Cerebrum	*Associated Function*	*Resources*
Premotor	Inhibition of visuomotor association, body language, the enactment effect	Witelson, 1989. Ianì et al., 2018; Parmigiani and Cattaneo 2018
Supplementary Motor	Speech production/initiation, rhythm and beat perception, processing of emotional tones, auditory imagery (speech, sounds and music),	Witelson, 1989; Narayana et al., 2012; Price, 2000; Lima et al., 2016
Areas of Connectivity for the Anterior Midbody		
Region of Cerebrum	*Associated Function*	*Resources*
Motor	Controls movement, learning movement, singing perception	Witelson, 1989; Georgopoulos and Carpenter, 2015; Kawai et al., 2015; Lévêque and Schön, 2015
Areas of Connectivity for the Posterior Midbody		
Region of Cerebrum	*Associated Function*	*Resources*
Somatosensory	Fine-tuning of movement, precision in motor control, habituation, indicator of negative affect	Witelson, 1989; Borich et al., 2015; Klingner et al, 2011
Posterior Parietal	Spatial navigation, perceptual decision making, attention, route planning/reaching, multisensory integration	Witelson, 1989; Mohan et al., 2018; Schiffino et al., 2014
Areas of Connectivity for the Isthmus		
Region of Cerebrum	*Associated Function*	*Resources*
Superior Temporal	Auditory association, speech, word meaning, coding meaning, speech perception, tone processing	Witelson, 1989; Price, 2010; DeWitt and Rauschecker, 2013; Mancini et al., 2017; Schremm et al., 2018
Posterior Parietal	Visual short-term memory	(Witelson, 1989; von Allmen et al., 2014

Areas of Connectivity for the Splenium		
Region of Cerebrum	*Associated Function*	*Resources*
Occipital	Vision	Witelson, 1989
Inferior Temporal	Visuo-spatial working memory, visual imagery, primary word recognition, word retrieval	Witelson, 1989; Hamamé et al., 2012; Hitomi et al., 2013; Price, 2010
Posterior Cingulate	Processing optic flow, sustaining conscious information, body ownership, retrieval of autobiographical memories, self-reflection	Knyazeva, 2013; Field et al., 2015; Guterstam et al., 2015; Herbet et al., 2014; Maddock et al., 2001; Johnson et al., 2006

6 METHODS

6.1 STUDY COHORT

MRI measurements were obtained from pediatric patients seen at WellSpan Pediatric Neurology in York, PA. under the direction of Todd Barron M.D. A total of 18 microcephalic patients were selected. These images were imaged at WellSpan over a five-year interval from 2012 to 2017. The microcephalic patients were selected clinically due to an abnormally small head size for age (<2 percentile), and then whom each underwent an MRI scan. There were eleven female patients and seven male patients in the study cohort. The female patients ranged from 0.5 to 5.5 years of age, while the male patients ranged from 0.3 to 3 years of age. All scans were interpreted as abnormal or microcephalic. Nine patients were considered to have primary microcephaly, three were considered to have secondary microcephaly and the remaining five exhibited microcephaly of an unknown origin.

6.2 MRI IMAGING AND DATA ACQUISITION

MRI images were collected with or without contrast enhancement using either a 1.5 or 3.0 Tesla General Electric whole-body imager. The images depended primarily on the clinical status of the patient, with a heavy predominance of T1-weighted images. Imaging parameters depended upon the age of the patients. For patients under eight years old, the thickness for sagittal and axial measurements was 4 mm skip 0.4 mm, whereas the thickness of the 3D coronal images measured 2 mm skip 0. For patients over the age of eight, coronal, axial and sagittal measurements thickness measured 5 mm skip 0.5

(Vannucci et al., 2017 and Vannucci et al. 2011). In order to obtain the best quality images, some infants required sedation.

6.3 MRI MEASUREMENTS

For the purpose of this study, a total of 24 measurements were taken from each MRI image. In the mid-sagittal plane, 11 measurements were taken of the corpus callosum. Included measurements were the height and width of both the genu and splenium, the total length of the corpus callosum, the height of four predetermined locations within the body and rostrum of the corpus callosum, and finally the entire corpus callosum area. These measurements were obtained using an electronic ruler. Seven other measurements were taken in the sagittal plane, including maximum width and maximum height. Four measurements were taken in the axial plane and three measurements were taken in the coronal plane. These measurements were used to help calculate total brain volume as previously described (Vannucci et al., 2011). These measurements were repeated 18 times. Some measurements were repeated to ascertain error.

Figure 1 | Diagram of Corpus Callosum Measurements

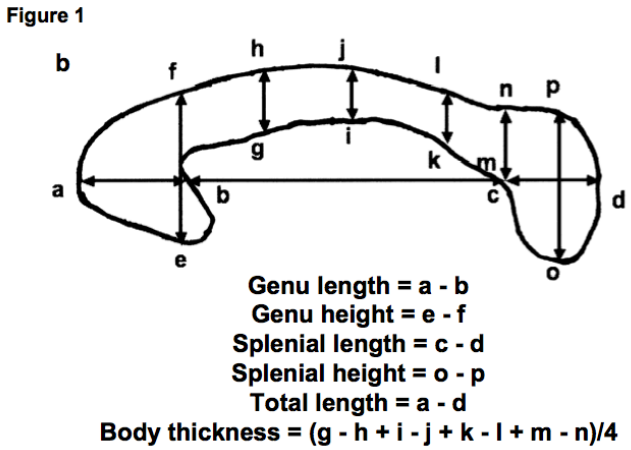

Figure 2 | Measurement Acquisition from MRI

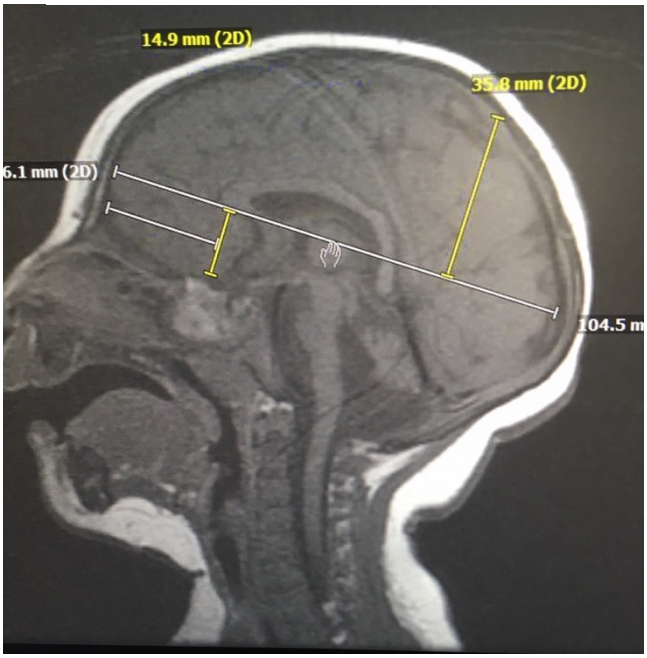

Table 3 | Table Representing Specific Corpus Callosum Measurements Obtained

Corpus Callosum Measurements		
Abbreviation	Corpus Callosum Figure	Associated Measurement
CC1	Genu Length	a-b
CC2	Splenial Length	c-d
CC3	Total Length	a-d
CC4	Genu Height	e-f
CC5	Body (a)	g-h
CC6	Body (b)	i-j
CC7	Body (c)	k-l
CC8	Body (d)	m-n
CC5-CC8	Body Thickness	$\frac{(g-h)+(i-j)+(k-l)+(m-n)}{4}$
CC9	Splenial Height	o-p
CCA (in cm^3)	Corpus Callosum Area	Area = πab *Equation 1 | Area of an Ellipsoid* Volume (cm^3)= $\frac{4}{3}\pi abc$ *Equation 2-Volume of an Ellipsoid* Volume (cm^3) = $\frac{\frac{4}{3}\times\pi\times r(length)\times r(width)\times r(height)}{1{,}000}$ *Equation 3-Volume of an Ellipsoid in Cubic Centimeters* =((4/3)*(PI())*(Length/2)*(Width/2)*(Height/2))/1000 *Equation 4- Volume of and Ellipsoid in Cubic Centimeters (EXCEL)*

6.4 STATISTICAL TESTING

Statistical testing was conducted using the "*R*" statistical program available for free online, as well as in Microsoft Excel. A series of two sample unpaired *t*-tests were carried out to compare each microcephalic individual to designated controls. The *p* value obtained assisted in confirming or denying statistical significance between two variables. Separate *t*-tests were run for each of the 24 measurements obtained. Due to the small

sample size, the rnorm feature was used, with an *n* value set to 15. The number 15 was used because too large a number (i.e. 100) yielded all statistically significant results. The *p* values were recorded and then compared to normocephalic controls. The cerebral hemispheric volume was then scaled for each individual microcephalic and the associated control group. Three ratios were obtained and a series of two sample unpaired *t*-tests were carried out to compare each microcephalic individual to the corresponding control group. The *p* values obtained confirmed or denied statistical significance.

7 RESULTS

7.1 DESCRIPTIONS OF INDIVIDUAL PATIENTS ACCORDING TO INDIVIDUAL DIAGNOSES

7.1.1 PRIMARY

Patient one is a female aged 5.5 years. The patient was diagnosed with epilepsy and a cognitive disability. Genetic testing revealed a T>A transversions resulting in a amino acid changes from cysteine to serine, further swapping sulfur atoms with an oxygen atoms. The nucleotide position was 829 and the codon was 277. This resulted in an SCN1A genetic defect, a defect common amongst individuals with epilepsy. Microcephaly of the patient was classified as primary. MRI imaging for this patient was considered unremarkable. As displayed in the associated table (see below) the genu length was considered significant and was found at the lowest end of the range when compared to the control group. Genu height was below the normal range and highly significant. The splenial length was not significant and fit within the range, but the splenial height was outside of the range and highly significant. When scaled in relation to cerebral hemispheric volume, the genu was above the range and highly significant, leading to the conclusion that it was larger in relation to the overall cerebral hemisphere when compared to the control group. In relation to overall cerebral hemispheric volume, the splenium was within the range, was still statistically significant. The total length of the corpus callosum was statistically insignificant and within the range. The anterior $1/4^{th}$, anterior-mid $1/4^{th}$, and posterior $1/4^{th}$ of the corpus callosum body were found to be

statistically insignificant and fit within the range, yet the posterior-mid 1/4th of the body possessed a p value of high significance and fit within the range. The body thickness possessed high significance, yet it fell within the range. In relation to overall cerebral hemispheric volume, the body was within the range, yet it was still statistically significant. The corpus callosum area was statistically insignificant and within the range.

Patient 2 is a male of 1 year. The patient was diagnosed with severe developmental delay and MRI imaging displayed evidence of lissencephaly that is not of the Miller-Decker type. Genetic testing did not locate any defect, making the reason for lissencephaly questionable. Microcephaly of the patient was classified as primary. The entire body and body thickness were found to be above the range and both measurements held high statistical significance when compared to age and sex matched controls. The splenial height was also above the range and highly significant, however the splenial length was not significant and fell within the normal range The genu length did not possess statistical significance and fit within the range, while the genu height was above the range and highly significant. Both the genu and the splenium were not smaller in relation to the overall cerebral hemispheric volume when compared to the control group. The total length was at the lowest end of the range, but still possessed high statistical significance. When scaled to cerebral hemispheric volume, the corpus callosum body was below the range and highly significant, while the isthmus and splenium were highly significant and fit within the normal range when compared to the control group.

Patient three is a female aged 5.1 years. She was diagnosed with developmental delay, epilepsy and had a SCN1A gene defect. MRI scans for this patient were unremarkable. Microcephaly of the patient was classified as primary. When compared to the control

group, the genu length was below the range and highly significant. The genu height was highly significant, yet was at the lowest end of the range. When scaled to the overall cerebral hemispheric volume, the genu fit within the normal range and was not significant. The splenial length was below the range and highly significant, yet the splenial height was not significant and fit within the range. When scaled to overall cerebral hemispheric volume, the splenium was within the range and was statistically significant. The anterior 1/4th of the corpus callosum body was found to be highly significant and below the range. The anterior-mid 1/4th of the corpus callsom body and the posterior 1/4th were within the range and were not statistically significant. The posterior-mid 1/4th of the corpus callosum did have a significant p value, however the measurement fit within the range at the lowest end of the spectrum. The body length was within the normal range, while the body thickness was above the range. The size of the corpus callosum body was well below the range and highly significant when scaled to overall cerebral hemispheric volume. The corpus callosum area fell at the low end of the range and was statistical significance.

Patient four is a female aged 2 years. She was diagnosed with CHARGE syndrome and displayed evidence of developmental delay. MRI images of the patient displayed evidence of periventricular leukomalacia, which is the loss of brain tissue around the ventricles. Microcephaly of the patient was classified as primary. The genu length was below the range and highly significant when compared to the control group, while the genu height was significant and below the range. When scaled to overall cerebral hemispheric volume, the genu was above the range and highly significant, making it larger in relation to overall cerebral hemispheric volume when scaled to the control

group. When scaled to overall cerebral hemispheric volume, the body did not possess statistical significance and fell within the range. Interestingly, the splenium was smaller when scaled to overall cerebral hemispheric volume, was highly statistical significant and below the range. The corpus callosum area held high statistical significance and was below the range. All other measurements were not statistical significance and fell within the normal range.

Patient seven is a female aged 0.5 years. The patient was diagnosed with epilepsy, showed evidence of developmental delay and genetic testing showed evidence of a *CASK* mutation. The *CASK* gene is considered an X-linked intellectual disability gene (Srivastava et al., 2016). Mutations of the *CASK* gene are more severe in females than in males. *CASK* mutations in females frequently result in microcephaly, while rarely resulting in microcephaly in males (Takanashi et al., 2010). MRI imaging showed cerebellar and pontine hypoplasia. Microcephaly of the patient was considered primary. All measurements were highly significant when compared to the control group. The splenial height above the normal range, while the rest of the measurements were below the range. When scaled to overall cerebral hemispheric volume, the genu and body were within the range and did not possess statistical significance when compared to the control group. The splenium, when scaled to overall cerebral hemispheric volume, was well below the range and highly significant, making it when scaled to overall cerebral hemispheric volume when compared to the control group.

Patient thirteen was a male aged 1.1 years. The patient was diagnosed with developmental delay, failure to thrive and hypertonia. Genetic testing found several heterozygotic changes in *ASPM*. MRI images displayed evidence of a diffusely decreased

white matter volume and mildly enlarged lateral ventricles, which suggested mild atrophy, especially in the frontal regions. The patient was born with a small head at birth and microcephaly was considered to be of the primary type. The genu height and length were highly significanct and fell below the normal range. The splenial height and length were highly significance and fell below normal the range. The overall thickness of the corpus callosum body fell below the range and was highly significant. The measurements for the corpus callosum body were all highly significant. The anterior-mid 1/4th of the corpus callosum fell towards the low end of the range, while the other three measurements fell below the normal range. The overall corpus callosum area was highly significant and fell below the range. The total length of the corpus callosum fell towards the low end of the range. When scaled overall cerebral hemispheric volume, the genu and body were well below the range and highly significant, making them smaller in relation to overall cerebral hemispheric volume when compared the control group. The splenium, when scaled to overall cerebral hemispheric volume was well above the range and highly significant. The splenium was larger when scaled to overall cerebral hemispheric volume when compared to the control group

Patient sixteen was a male aged 1.3 years. The patient was diagnosed with hypotonia, developmental delay and failure to thrive. Genetic testing found evidence of a 16p13.11 chromosomal duplication, which explained the dysmorphic features of the patient's face. MRI images wer considered normal. Microcephaly was considered to be of the primary type. When compared to the control group, the length of the splenium was fell within the range and was not statistically significance. The height of the splenium was highly significant (p value <0.005) and fit above the range. The genu length was highly

significant and fell below the range, while the genu height was highly significant and fit within the range. When scaled cerebral hemispheric volume, the genu fell towards the high end was within the range, the body was above the range and the splenium was below the range when compared to the control group. All three of these portions possessed high statistical significance. Taking the previous t-tests into account, it appears as if the body and genu the corpus callosum was larger when scaled to overall cerebral hemispheric volume and the splenium was smaller in relation to overall cerebral hemispheric volume when compared to the control group. All of the measurements for the body of the corpus callosum fit within the range, however, the anterior 1/4th of the corpus callosum body was highly significant. The overall body thickness was highly significant and fell towards the low end of the range when compared to the control group. The corpus callosum length and corpus callosum area were highly significant and both fell below the range.

Patient seventeen was a female aged 0.83 years. The patient was diagnosed with developmental delay, hypotonia, congenital heart disease (CHD) and facial dysmorphism. Genetic testing revealed long continuous stretches of homozygosity, or identical alleles. This most likely related to being born to a consanguineous pair. An initial MRI scan was unremarkable, but further testing with a CT scanner displayed evidence of calcifications. Microcephaly of the patient was considered primary. When compared to the control group, the genu height and length were both highly significant and fell below the range. The length of the splenium was highly significant ($p<0.005$) and fell below the range, while the height of the splenium was statistically significant ($p<0.05$) and fit within the range. The posterior ½ and the anterior 1/4th of the corpus callosum body held high statistical significance and fell below the range. The anterior-mid 1/4th of the corpus

callosum body was not significant and fit within the range at the low end of the spectrum. The body thickness was highly significant and fell below the range. The overall corpus callosum length and area both carried high statistical significance and fell below the range. Although the genu length and height, splenium length fell below the range and the overall body thickness was below the range, when the corpus callosum was scaled to cerebral hemispheric volume, it was found the genu, body and splenium were larger in when compared to the control group, having high statistical significance and falling above the range.

Patient eighteen was a male aged 3 years. This patient was diagnosed with developmental delay and epilepsy due to Angelman Syndrome. The corpus callosum appeared dysplastic in MRI images. Microcephaly of the patient was classified as primary in type. The overall corpus callosum area fell below the range when compared to the control group and the measurements were highly significant (p value <0.005). The total length was below the range and highly significant. The length of the splenium was below the range and highly significant, while the height of the splenium was not statistically significant (p value >0.05) and fell within the range at the low end of the spectrum. The genu height was below the range and highly significant and the genu length was not statistically significant and fell within the range. When scaled to cerebral hemispheric volume, the genu and splenium were above the range and highly significant, making them larger than the overall cerebral hemispheric volume when compared to age and sex matched controls. The overall body thickness of the corpus callosum was not statistically significant and fell within the range. The anterior 1/4th and the posterior ½ of the corpus callosum body were not statistically significant and fell within the range at the

low end of the spectrum, but the anterior-mid 1/4th of the corpus callosum was highly significant and was above the range. When scaled to cerebral hemispheric volume, the body was not significant and fell within the range.

7.1.2 SECONDARY

Patient six is a male aged 1.5 years. Diagnoses included congenital cytomegalovirus, with associated cerebral palsy, epilepsy and evidence of a cognitive disability. MRI imaging of the patient showed severe cystic white matter changes. Microcephaly of the patient was classified as secondary. When compared to age and sex matched controls the genu length was highly significant and fell below the range, while the genu height was highly significant and fell within the range. The splenial length was below the range and highly significant, while the splenial height was highly significant and interestingly fell above the range. The splenium was larger when scaled to overall cerebral hemispheric volume when compared to the control group, possessing both high statistical significance and falling above the range. The anterior 1/4th of the corpus callosum body was found to fit within the lowest portion of the spectrum and was highly significant, while the anterior 1/4th of the body was found the be statistically significant and within the range. The posterior-mid 1/4th of the body did not hold statistical significance and fell within the range, while the posterior 1/4th of the body was highly significant and fell towards the low end of the range. The body of the corpus callosum when scaled to overall cerebral hemispheric volume was smaller when compared to age and sex matched controls, possessing high statistical significance and falling below the range. The total length of the corpus callosum fell below the range and was highly significant and the corpus callosum area was highly significant and fell below the range.

Patient eleven was a female aged 0.5 years. The patient carried a variety of diagnoses, including prematurity, intrauterine growth restriction (IUGR) and respiratory distress syndrome (RDS). An MRI study revealed a corpus callosum that ranged from normal to thin, as well as slightly enlarged ventricles. Microcephaly of the patient was considered to be secondary. When compared to the control group, the genu length was highly significant and fell below the range, while the genu height was not significant and fit within the range. The splenial length was not significant and fell within the range and the splenial height was not statistically significant and was above the range. The anterior $1/4^{th}$ of the corpus callosum body was found to be highly significant and fell below the range. The posterior-mid $1/4^{th}$ of the corpus callosum was found to be within the range at the low end of the spectrum, but a standard t-test still indicated a high statistical significance. Both the anterior-mid $1/4^{th}$ of the corpus callosum and posterior $1/4^{th}$ of the corpus callosum were not significant , yet the anterior-mid $1/4^{th}$ of the corpus callosum fit within the range, while the posterior $1/4^{th}$ was did not fit and was below the range. The overall body thickness of the corpus callosum was highly significant and below the range. The total length of the corpus callosum, as well as the corpus callosum area were below the range and highly significant. The entire corpus callosum was larger when scaled to overall cerebral hemispheric volume, having high statistical significance and falling above the range.

Patient twelve was a female aged 1.5 years. The patient carried a diagnosis of hemiparesis due to an intra-uterine stroke. MRI images displayed evidence of left frontal and temporal encephalomalacia. Microcephaly of the patient was considered to be of the secondary type. All corpus callosum measurements were well below the range and highly

significant when compared to the control group. The splenial height was well below the range. When compared to the control group, the splenium and the genu both were larger when scaled to overall cerebral hemispheric volume , possessing both high statistical significance and falling above the range. In contrast, the body of the corpus callosum was smaller when scaled to overall cerebral hemispheric volume, falling below the range and holding high statistical significance.

7.1.3 UNKNOWN

Patient five is a male aged 0.3 years. The patient was diagnosed with epilepsy but any other affiliated comorbidity was unknown. MRI images displayed evidence of hypoplasia of the cerebral hemispheres and the cerebellum. Microcephaly of the patient was classified as unknown. The genu height was found the be significant and below the range when compared to age and sex matched controls, while the genu length possessed high statistical significance and fell below the range. The splenial length was found to be highly significant and within the range, while the splenial height was not statistically significant and fell within the range. The area of the splenium was well below the range and results from a two sample t-test indicated high statistical significance when assessing the size of the genu when scaled to overall cerebral hemispheric volume. The anterior ½ of the corpus callosum body was highly significant and fell below the range, while the posterior half fell within the range and was not statistically significant. The total length of the corpus callosum was interestingly above the range and highly significant. The corpus callosum are was below the range and possessed high statistical significance. The genu of the corpus callosum was smaller when scaled to overall cerebral hemispheric volume when compared to the control group. It was both below the range and highly significant

(p value >0.005). The body thickness was highly significant and fell below the range. The length of the body was interestingly above the range. When scaled to cerebral hemispheric volume, it was both above the range and highly significant. This is most likely due to the above average length of the corpus callosum body, rather than the width.

Patient eight is a female aged 0.67 years. The patient was diagnosed with mild developmental delay. Genetic testing revealed a normal genetic makeup. MRI imaging was considered unremarkable. Microcephaly of the patient was considered to be of an unknown type. When compared to age and sex matched controls it was found that the genu length and height were both highly significant, however the genu length was below the range, while the genu height was within the range at the low end of the spectrum. The genu length and height were both situated within the range, yet the value for the splenial height was deemed statistically significant, while the splenial length bared no statistical significance. The total length of the corpus callosum was not significant and fit within the range. The anterior 1/4th of and the posterior-mid 1/4th of the corpus callosum body were highly significant, but fell within the range. The anterior-mid 1/4th of the corpus callosum body was not significant and fit within the range and the posterior ¼ of the corpus callosum body was highly significant and fell below the range. The body thickness held a statistical significance, but fell within the range. The corpus callosum area was highly significant and below the range. The genu was smaller when scaled to the overall cerebral hemispheric volume when compared to age and sex matched controls, possessing high statistical significance and falling below the range. The splenium was larger when scaled to the overall cerebral hemispheric volume when compared the control group, being highly significant and above the range. In contrast, the body of the corpus callosum was

not statistically significant and was within the range.

Patient nine was a female aged 0.5 years. The patient was diagnosed with developmental delay and hypotonia. Genetic testing yielded normal results. MRI imaging showed cerebellar and pontine hypoplasia, as well as a thin corpus callosum. Microcephaly of the patient was considered of an unknown type. The genu length of the corpus callosum held high statistical significance, but fell within the range at the low end of the spectrum. All other measurements were highly significant and fell below the range. The genu and body of the corpus callosum were larger in relation to overall cerebral hemispheric volume when compared to the control group, highly significant and above the range, while the splenium was not statistically significant and was within the range.

Patient ten was a female aged 1.15 years. The patient was diagnosed with developmental delay with regression. Genetic testing appeared normal. An MRI revealed evidence of normal to mildly large lateral ventricles and subarachnoid space (SAS), which suggested mild cerebral atrophy. Microcephaly of the patient was considered to be of an unknown type. When compared to the control group, the genu height and length were highly significant, but the length was below the range and the height fit within the range at the low end of the spectrum. The splenial length was above the range and highly significant, while the splenial height was highly significant and within the range at the low end of the spectrum. The anterior 1/4th of the corpus callosum body was highly significant and below the range. The remaining 3/4^{ths} of the corpus callosum body fit within the range and did not possess statistical significance. The overall body thickness fit within the range and was not statistically significant. The total length of the corpus callosum and the corpus callosum area were below the range and possessing highly

significant. When scaling corpus callosum size in relation to cerebral hemispheric volume, all corpus callosum measurements were within the range and not significant when compared to the control group.

Patient fourteen was a female aged 1.0 years. The patient was diagnosed with epilepsy and hypertonia. MRI imaging showed severe global hypoplasia, which included hypoplasia of the corpus callosum. Although the patient was born with a small head at birth, microcephaly of the patient was considered to be unknown. When compared to the control group, all measurements were highly significant and fell below the range. The entire corpus callosum was larger when scaled to overall cerebral hemispheric volume when compared to the control group, holding both high statistical significance and falling above the range.

Patient fifteen was a male aged 1.4 years. The patient was diagnosed with epilepsy and had a behavioral disorder of an unknown type. MRI images were unremarkable. Microcephaly of the patient was of an unknown type. When compared to the control group, the splenial height and length were both found to fit below the range and both possessed high statistical significance. The genu length fit within the range and the height fell below the range. Despite this, both measurements were highly significant when a t test was performed. The genu and splenium were smaller when scaled to overall cerebral hemispheric volume when compared to the control group, having high statistical significance and falling below the range. The overall thickness of the corpus callosum was highly significant and fell below the range. The anterior $1/4^{th}$ and posterior-mid $1/4^{th}$ of the corpus callosum body possessed high statistical significance and fell below the range. The posterior $1/4^{th}$ of the corpus callosum fit within the range and did not possess

statistical significance and the anterior-mid portion of the corpus callosum was statistically significant (p value <0.05), but fit within the range. The body of the corpus callosum was larger when scaled to overall cerebral hemispheric volume when compared to the control group, having high statistical significance and falling above the range. The corpus callosum area was well below the range and had high statistical significance (p value <0.005) and the total length of the corpus callosum was below the range and highly significant.

7.2 RESULTS OF INDIVIDUAL PATIENTS

Table 4 | Results by Patient

Patient 1			
Variable	Microcephalic Value (1)	Normocephalic Value (s)	P Value
CC1	10.1	10.1 - 14.6	**0.008**
CC2	10.2	8.6 - 11.3	0.5936
CC3	58.7	55.5 – 68.9	0.1308
CC4	11.1	13.8 – 20.6	**<0.001**
CC5	7.1	4.2 – 9.3	0.368
CC6	5.4	4.3 – 8	0.5458
CC7	5.1	4.1 – 9.6	**0.002**
CC8	6.8	4.1 – 10.5	0.1502
CC9	11.1	12.6 – 19.9	**<0.001**
Body Thickness	6.1	4.25 – 8.52	**<0.001**
CCA	4.37	4.27 – 6.26	0.07
CHV1	11.58	5.95 - 9.7	**<0.001**
CHV2	30.48	25.99 – 50.21	0.3575
CHV3	60.90	54.25 – 95.77	0.2742

Patient 2			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	8	7.8 – 11.7	0.3359
CC2	7.2	5.0 – 9.7	0.4914
CC3	48	53.6 – 64.4	**0.005**
CC4	11.9	7.0 – 19.2	0.2821
CC5	9.7	2.2 – 6.4	**<0.001**
CC6	6.4	1.4 – 5.2	**<0.001**
CC7	8	2.0 – 6.0	**<0.001**
CC8	9.9	2.0 – 7.9	**<0.001**
CC9	21.6	13.4 – 18.4	**<0.001**
Body Thickness	8	2.0 – 6.32	**<0.001**
CCA	11.61	1.85 – 4.96	**<0.001**
CHV1	12.02	8.73 – 32.4	0.2629
CHV2	17.34	32.44 – 87.35	**<0.001**
CHV3	74.02	15.97 – 85.28	**0.01**

Patient 3			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	9.3	10.1-14.6	**<0.001**
CC2	8.1	8.6-11.3	**<0.001**
CC3	55.7	55.5-68.9	**0.01**
CC4	14.1	13.8-20.6	**<0.001**
CC5	4.6	4.2-9.3	**<0.001**
CC6	5.7	4.3-8	0.4786
CC7	4.3	4.1-9.6	**<0.001**
CC8	9.3	4.1-10.5	0.06935
CC9	14.8	12.6-19.9	0.1521
Body Thickness	5.97	4.25-8.52	**<0.001**
CCA	4.02	4.27-6.26	**0.001**
CHV1	8.19	5.95-9.7	0.235
CHV2	28.65	25.99-52.1	**0.02**
CHV3	60.24	54.25-95.77	0.19

Patient 4			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	7.8	9.0-13.8	**<0.001**
CC2	9.2	5.5-12.9	0.8696
CC3	58.2	52.7-65.4	0.105
CC4	12.3	13.1-19.4	**0.01**
CC5	4.2	1.7-6.7	0.2269
CC6	4.1	1.5-6.5	0.6748
CC7	4.4	1.3-6.9	0.9669
CC8	5.6	1.9-6.9	0.9573
CC9	13.7	6.0-14.2	0.1005
Body Thickness	4.57	1.55-6.15	0.6898
CCA	2.57	2.72-5.07	**<0.001**
CHV1	9.37	5.0-11.9	**<0.001**
CHV2	48.35	31.89-58.43	0.1953
CHV3	105.40	51.54-218.35	**<0.001**

Patient 5			
Variable	Microcephalic Value	Normocephalic Value(s)	P Value
CC1	2.7	3.1-7.5	**0.02**
CC2	2.5	3.2-6.7	**0.001**
CC3	53.6	39.1-43.9	**<0.001**
CC4	8.6	8.8-13.2	**<0.001**
CC5	2.6	3.2-4.4	**<0.001**
CC6	1.4	2.1-3.2	**<0.001**
CC7	2.2	1.3-3.2	0.1071
CC8	2.7	1.4-4.6	0.4568
CC9	8.7	6.9-11.3	0.5632
Body Thickness	2.22	2.67-2.75	**0.005**
CCA	0.39	1.5-1.9	**<0.001**
CHV1	23.45	8.84-27.65	0.1787
CHV2	54.87	42.07-53.42	**<0.001**
CHV3	72.79	10.42-39.63	**<0.001**

Patient 6			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	8.2	9.1-14.0	**0.001**
CC2	4.1	6.5-10.5	**<0.001**
CC3	52.3	54.6-63.3	**<0.001**
CC4	14.7	12.9-18.4	**0.004**
CC5	4.8	4.8-6.5	**<0.001**
CC6	5.8	3.5-6.1	**0.01**
CC7	4.5	3.0-4.7	0.07399
CC8	3.3	4.6-8.9	**0.002**
CC9	16.3	10.1-14.7	**<0.001**
Body Thickness	4.6	3.05-4.07	**0.01**
CCA	2.28	3.87-4.99	**<0.001**
CHV1	9.17	6.69-13.47	0.1037
CHV2	58.42	53.53-71.12	**<0.001**
CHV3	63.32	36.29-86.78	**<0.001**

Patient 7			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	7	5.9-10.6	**0.004**
CC2	3.4	5.6-11.3	**<0.001**
CC3	44.1	50.7-62.9	**<0.001**
CC4	8.3	11.7-12.9	**<0.001**
CC5	2.6	3.9-5.1	**<0.001**
CC6	2.9	3.0-4.3	**<0.001**
CC7	3.1	3.0-5.9	**<0.001**
CC8	2.7	2.9-7.6	**<0.001**
CC9	17.9	9.1-12.0	**<0.001**
Body Thickness	2.82	3.85-5.40	**<0.001**
CCA	1.05	2.27-4.37	**<0.001**
CHV1	10.43	7.83-14.43	0.5045
CHV2	37.04	31.51-46.22	0.1244
CHV3	43.96	59.32-138.63	**0.005**

Patient 8			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	7.4	8.3-10.6	**<0.001**
CC2	8.1	7.3-11.3	0.08902
CC3	55.4	50.7-62.9	0.3225
CC4	12	11.7-17.3	**0.004**
CC5	3.6	3.4-5.1	**<0.001**
CC6	3	2.6-5.9	0.3106
CC7	3.4	3.0-4.3	**0.003**
CC8	3.3	4.7-7.8	**<0.001**
CC9	11.8	9.0-14.8	**0.02**
Body Thickness	3.325	3.85-5.4	**0.007**
CCA	1.68	2.81-4.37	**<0.001**
CHV1	11.68	7.83-10.45	**<0.001**
CHV2	40.83	31.94-50.11	0.3427
CHV3	48.05	59.32-90.23	**<0.001**

Patient 9			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	5.9	3.1-10.6	**<0.001**
CC2	4	4.6-11.3	**<0.001**
CC3	45.6	42.3-62.9	**<0.001**
CC4	5.7	8.8-12.9	**<0.001**
CC5	2.3	3.0-5.1	**<0.001**
CC6	1.6	1.8-5.9	**<0.001**
CC7	1.1	2.3-3.9	**<0.001**
CC8	1	2.9-7.6	**<0.001**
CC9	5	6.9-11.7	**<0.001**
Body Thickness	1.5	2.75-5.40	**<0.001**
CCA	0.42	1.55-4.37	**<0.001**
CHV1	25.59	0.07-0.14	**<0.001**
CHV2	99.67	31.51-46.22	**<0.001**
CHV3	83.02	59.32-138.63	0.9219

Patient 10			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	7.9	8.3-11.0	**<0.001**
CC2	9.7	8.2-9.5	**<0.001**
CC3	52.6	54.0-62.1	**<0.001**
CC4	12.6	12.2-17.3	**<0.001**
CC5	3.2	3.4-5.8	**<0.001**
CC6	4.5	2.6-6.3	0.1262
CC7	4.4	3.4-6.8	0.4344
CC8	5.3	4.7-9.9	0.1513
CC9	9.7	9.0-14.8	**<0.001**
Body Thickness	4.35	3.85-7.20	0.785
CCA	2.17	2.81-4.46	**<0.001**
CHV1	9.23	7.69-10.45	0.3245
CHV2	42.2	31.33-50.11	0.3164
CHV3	100	46.42-104.72	**<0.001**

Patient 11			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	4	5.9-10.6	**<0.001**
CC2	6.8	5.6-11.3	0.3211
CC3	44	50.7-62.9	**<0.001**
CC4	12.3	11.7-12.9	0.9523
CC5	3.5	3.9-5.1	**<0.001**
CC6	4.4	3.0-5.9	0.8369
CC7	3	3.0-4.3	**<0.001**
CC8	2.8	2.9-7.6	0.155
CC9	12.1	9.2-12.0	0.06568
Body Thickness	3.42	3.85-5.40	**0.001**
CCA	1.28	2.27-4.37	**<0.001**
CHV1	19.02	7.83-14.43	**<0.001**
CHV2	45.53	31.51-46.22	**0.03687**
CHV3	52.39	59.32-138.63	**0.006**

Patient 12			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	7.1	6.9-13.8	**<0.001**
CC2	4	7.3-12.9	**<0.001**
CC3	49.8	54.0-62.1	**<0.001**
CC4	9.6	9.5-17.2	**<0.001**
CC5	1.4	1.7-5.8	**<0.001**
CC6	1.5	1.4-6.5	**<0.001**
CC7	1.6	1.3-6.8	**<0.001**
CC8	1.7	1.8-9.9	**<0.001**
CC9	4.7	6.0-14.2	**<0.001**
Body Thickness	1.55	2.0-6.3	**<0.001**
CCA	0.69	2.74-5.07	**<0.001**
CHV1	13.29	6.69-12.9	0.1824
CHV2	97.97	156.52-259.51	**<0.001**
CHV3	104.44	11.32-36.17	**<0.001**

Patient 13			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	1.9	6.1-12.7	**<0.001**
CC2	2.4	5.0-10.5	**<0.001**
CC3	47.6	53.6-64.4	**0.003**
CC4	2.7	7.0-19.2	**<0.001**
CC5	2.1	2.2-6.4	**0.001**
CC6	1.4	1.4-6.3	0.475
CC7	1.9	2.0-5.8	**<0.001**
CC8	1.6	2.0-8.9	**<0.001**
CC9	5.2	7.3-14.7	**<0.001**
Body Thickness	1.75	2.00-6.32	**<0.001**
CCA	0.15	1.85-4.99	**<0.001**
CHV1	173.79	6.69-32.40	**<0.001**
CHV2	64.98	174.70-298.11	**<0.001**
CHV3	140.13	11.33-36.17	**<0.001**

Patient 14			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	4.9	8.3-10.5	**<0.001**
CC2	3.1	7.7-9.5	**<0.001**
CC3	46	54.3-62.1	**<0.001**
CC4	6.8	12.2-17.3	**<0.001**
CC5	2.1	4.1-5.2	**<0.001**
CC6	2.2	2.6-4.4	**<0.001**
CC7	1.9	3.4-3.9	**<0.001**
CC8	1.5	4.7-7.0	**<0.001**
CC9	7.1	9.0-14.8	**<0.001**
Body Thickness	1.92	3.85-4.75	**<0.001**
CCA	0.46	2.81-4.46	**<0.001**
CHV1	28.24	7.69-10.45	**<0.001**
CHV2	85.59	37.09-50.11	**<0.001**
CHV3	179.8	55.05-90.23	**<0.001**

Patient 15			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	7.7	9.1-12.7	**<0.001**
CC2	7.2	6.5-10.5	**0.004**
CC3	55.2	57.2-64.4	**<0.001**
CC4	13.4	12.9-19.2	**<0.001**
CC5	4	4.6-6.5	**<0.001**
CC6	3.8	3.5-6.3	**0.01**
CC7	2.8	3.5-5.8	**<0.001**
CC8	5.1	3.1-8.9	0.6975
CC9	9.6	11.8-14.7	**<0.001**
Body Thickness	3.92	4.20-6.30	**<0.001**
CCA	1.77	4.05-4.99	**<0.001**
CHV1	72.02	7.24-14.59	**<0.001**
CHV2	39.36	4.66-5.80	**<0.001**
CHV3	64.53	501.24-996.38	**<0.001**

Patient 16			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	5.7	9.1-12.7	**<0.001**
CC2	7.9	5.0-10.5	0.01996
CC3	52.3	53.6-64.4	**<0.001**
CC4	10.8	7.0-19.2	**<0.001**
CC5	3.5	2.6-6.5	**<0.001**
CC6	3.9	1.4-6.3	0.9542
CC7	3.7	2.0-5.8	0.23
CC8	5.8	2.0-8.9	0.1144
CC9	15.7	9.6-14.7	**<0.001**
Body Thickness	4.225	2.0-6.3	**<0.001**
CCA	2.03	2.31-4.99	**<0.001**
CHV1	18.68	6.96-20.24	**<0.001**
CHV2	39.35	7.69-21.83	**<0.001**
CHV3	49.16	226.57-460.85	**<0.001**

Patient 17			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	6.3	8.3 – 10.6	**<0.001**
CC2	4.5	9 – 14.8	**<0.001**
CC3	40.2	53.8 – 62.9	**<0.001**
CC4	7.2	11.7 – 17.3	**<0.001**
CC5	2.4	3.4 – 5.1	**<0.001**
CC6	2.8	2.6 – 5.9	0.06639
CC7	2.8	3.5 – 4.3	**<0.001**
CC8	3.9	4.7 – 7.8	**<0.001**
CC9	9.6	9 – 14.8	**0.03**
Body Thickness	2.97	3.85 – 5.4	**<0.001**
CCA	0.83	3.64	**<0.001**
CHV1	21.23	8.73 – 10.45	**<0.001**
CHV2	64.38	54.93 – 65.63	0.2931
CHV3	81.05	12.63 -18.26	**<0.001**

Patient 18			
Variable	Microcephalic Value	Normocephalic Value (s)	P Value
CC1	10.3	9.3-14.8	0.1868
CC2	7.7	9.7-12.6	**<0.001**
CC3	60.3	63.5-72.6	**<0.001**
CC4	12.9	15.8-20	**<0.001**
CC5	6.1	3.1-7.9	0.6995
CC6	6.6	4.0-6.4	**<0.001**
CC7	3.9	3.1-6.5	0.1316
CC8	5.6	6.9-9.5	0.06004
CC9	11.2	10.7-18.9	0.1016
Body Thickness	5.55	3.62-6.9	0.7258
CCA	3.44	4.27-6.26	**<0.001**
CHV1	11.3	6.83-11.43	**<0.001**
CHV2	31.1	26.83-46.68	0.4675

8 DISCUSSION

Microcephaly is symptom that can represent a variety of cell cycle disruptions that either occur during gestation or after gestation. In many of the cases, the corpus callosum was smaller in relation to overall cerebral hemispheric volume, however, this result was not consistent for each individual. Similarly, in a majority of the cases the corpus callosum measurements fell below or at the low end of the range of the control groups, yet the particular measurements varied by case. This is largely due to the limitations of this study, which included a small overall sample size, small sample sizes for each age group and different associated diagnoses. Despite this, the results of this study do show us that glial cells are compromised in microcephaly.

Considering the necessity of astrocytes for the formation of muscle memory, the 16p13.11 duplication may have impacted the differentiation of RGPs into astrocytes, thus resulting in the patient's diagnosis of hypotonia (Falleh et al., 2012). This may have also been due to disruptions in the development of oligodendrocytes, since actyl-CoA is the precursor for acetylcholine, a neurotransmitter vital to motor neurons and skeletal tissue. Developmental delay may also have been caused by a disruption to astrocytes, as well as oligodendrocytes, for both of these cell types are needed for myelination. If myelination does not occur during infancy, development will be impacted.

The corpus callosum length fell below the range and were highly significant ($p < 0.005$). The was largely attributed to the length of the genu, which fell below the range and was statistically significant. These results were very interesting considering that age

of the infant. In contrast, the genu height, although highly significant, was did not fall below the range, yet the height of the splenium was found to be larger than the measurements within the range and statistically significant. In light of the hypotonia diagnosis, this is very interesting, as the posterior third of the corpus callosum was smaller in relation to overall cerebral hemisphere as well.

Insert paragraph about cerebellum and cognition in relation to hypotonia.

Contrary to microcephaly, lissencephaly, as seen in patient two, results from disruptions in neuronal migrations (Mochida, 2019). Although comparisons of corpus callosum size alone were above the range when compared to the control group, they were well below the range when scaled to the overall cerebral hemispheric volume of the patient. Since the type of microcephaly was primary, it suggests that the cell cycle was greatly disrupted during gestation. In comparison to the lissencephalic brains, gyrencephalic brains typically house basal radial glial cells. These cells are found within the outer subventricular zone. Since these cells are not found within lissencephalic brains, it is possible that inter-kinetic nuclear migration was disrupted, causing the asymmetrical division of radial glial cells into basal radial glial cells to become interrupted (Romero et al., 2018).

Various patients within the cohort have developmental delay. Disruptions in the proliferation of glial cells can inhibit the myelination of neuronal pathways that allow for movement and its security through habituation. With a lower volume of white matter tissues, the resistance necessary for muscle memory takes much more effort to achieve. Since motor development is relative to social interaction, this places the limbic system as an important part of understanding right and wrong in relation to movement. Studies have

found connections between the cerebellum, a part of the brain that historically was related strictly to movement, and the cingulate gyrus. The anterior portion of the cingulate gyrus is a part of the posterior prefrontal cortex, to which the genu plays a vital role (Schmahmann, 2019, Moreno-Rius, 2019). A decreased volume of white matter within the genu would make it more difficult to ascribe positive connotations to specific movements, such as grasping, crawling. This, along with the various volumetric declines in other regions of the corpus callosum could relate directly to delayed development.

In patient nine, all corpus callosum measurements were highly significant. Of interest, the corpus callosum body was both highly significant and below the range. The body of the corpus callosum contains axons that communicate between various motor cortices in the left and right hemispheres (Witelson, 1989, Parmigiani and Cattaneo 2018. Georgopoulos and Carpenter, 2015; Kawai et al., 2015, Borich et al., 2015). Thinning in this region could indicate a failure for the proper neural pathways allowing for movement to develop. The splenium of patient nine was also underdeveloped, possessing high statistical significance and falling below the range. This splenium houses axons from the posterior cingulate cortex which plays a role in our ability to perceive our body as distinctly our own (Guterstam et al., 2015). This in addition to the thin body could explain the presence of hypotonia in patient nine.

The posterior region of the corpus callosum body as well as the splenium in patient thirteen were both highly significant and below the range, potentially providing sound reasoning for the presence of hypotonia. When compared to the control group, these regions were also small in relation to the overall cerebral hemispheric volume. The underdevelopment of these regions of the corpus callosum may also assist in

understanding the presence of developmental delay in this patient. Unlike patient nine, genetic testing found several heterozygotic changes in the *ASPM* gene, a common microcephaly related gene referred to as *MCPH5 (*Horvath et al., 2006, Passemard et al., 2016, Bond et al., 2002, Ahn et al., 2011, Duerinckx and Abromowicz, 2017). *ASPM* mutations have been shown to have no impact on the cells in the hippocampus (Passemard et al., 2016, Rivero et al., 2006). This suggests that the cells proliferating from the subventricular zone were impacted in patient thirteen, however more testing would need to be done to be absolutely certain.

9 CONCLUSION

The results of this study indicated that the corpus callosum is impacted by microcephaly. Since the corpus callosum is comprised primarily of axons that are heavily myelinated, the results suggested that white matter cell tissues, as well as grey matter cell tissues are impacted by microcephaly. Although it can be concluded that both cell tissue types are impacted by microcephaly, it is still uncertain which tissues are impacted the most. Further research that focusing on oligodendrocytes and astrocytes, two glial cell tissues found in high volumes within the corpus callosum, will be useful to our understanding of which tissues are impacted more severely by microcephaly.

Research on microcephaly is valuable to the study of neurodevelopmental disorders. Very little is still known about the mechanisms responsible for brain growth and development and research on microcephaly assists in our understanding of many genes that help make brain growth and development possible. The corpus callosum provides researchers with a wealth of information that assists in our understanding of densely myelinated tracts. Oligodendrocytes and astrocytes, two white matter cell tissues found within the corpus callosum still remain grossly understudied.

Since the human brain has been shown to increase in size over the course of evolution, more research on microcephaly will prove beneficial to the study of hominid brain evolution. A deeper understanding of how our brains came to exist as they do today will improve our ability to react accordingly when disorders of the brain arise. More research on microcephaly and the corpus callosum will prove valuable to the detection, treatment

and prevention of neurodevelopmental, neurodegenerative and neuropsychiatric disorders.

10 APPENDICES

APPENDIX A – GLIAL CELLS

Astrocytes play a pivotal role in regulating blood flow to and from neurons by creating the blood-brain barrier (Lundgaard I et al., 2013). Astrocytes are found in close proximity to the 'end feet' of blood vessels, where they aid in the tightening and expansion of the blood vessels to regulate which nutrients make their way to the neurons (Frank 2013). The BBB protects the brain from toxins and helps transport things such as oxygen and glucose to the brain.

The corpus callosum is predominantly comprised axons that are insulated by glial cells. In order for tissue to form, cells need to bind together. Astrocytes and Oligodendrocytes, two glial cell types, work together to assist in connecting neurons together, while also allowing for the transport of nutrients to the brain from the blood. GLUT1 genes support glucose transport from the blood. Astrocytes take in GLUT1 from the blood and use this to create ATP, which is essential for energy production in cells. Connexins assists in the formation of gap junctions between astrocytes and oligodendrocytes. These gap junctions assist in the transport of lactate from astrocytes to oligodendrocytes. Lactate, along with glucose, assists in the production of acytel-CoA. ATP and acytel-CoA help produce lipids, which then assist in the production of myelin within oligodendrocytes, which is essential for myelination, the process by which a neuron becomes insulated. Myelination is essential for the smooth transmissions of nerve impulses from neuron to neuron and helps prevent the scattering of voltage. This, eventually, assists in the production of neural networks within the brain (Krasnow and Attwell, 2016).

Oligodendrocytes and astrocytes begin to form after neurogenesis. They form from

radial glial progenitor cells (RGPs). RGPs undergo a type of cell division called asymmetric cell division, within which the RGPs split into a new cell and another RGP cell (Kageyama et al., 2019) . The NDE1 gene plays a pivotal role in inter-kinetic nuclear migration, a function necessary for mitosis (Kageyama et al., 2009). If mitosis fails to occur, brain growth is disrupted.

APPENDIX B – THE POSTERIOR CINGULATE CORTEX

The posterior cingulate cortex is the "backmost part of the cingulate cortex" (Zhang et al, 2017). It has been found to play a dominant role in acts that help us to recognize and perceive ourselves as separate and distinct from others. Interhemispheric connectivity of the posterior cingulate cortex occurs through the splenium of the corpus callosum (Knyazeva, 2013). The posterior cingulate cortex has been found to become activated during the retrieval of autobiographical memories (Maddock et al., 2001). In addition, various other activities that involve self-reflection or acknowledgement of the self in relation to others have become related to increased activity within the posterior cingulate cortex (Johnson et al., 2006). Studies have shown that psilocybin impacts activity within posterior cingulate cortex, further relating this change in activity to 'ego dissolution'(Tagliazucchi et al., 2016). Essentially, this may be related to the role that the posterior cingulate cortex plays in perceptions of body ownership and self-location (Guterstam et al., 2015).

Most interestingly, studies that have used the dopamine and serotonin agonist LSD have found that the serotonin 2A receptor, 5HT-$_{2A}$, is "highly expressed in high-level association cortices, including the anterior cingulate cortex (ACC), posterior cingulate cortex (PCC) and insula" (Kaelen et al., 2016). Studies of this nature used the serotonin 2A receptor antagonist, ketanserin, to assess the function of 5HT-$_{2A}$, specifically during altered states of consciousness. These studies, however, have assisted in furthering our understanding of this specific serotonin receptor.

APPENDIX C – TRAUMA AND THE CORPUS CALLOSUM

Studies have shown that childhood trauma, including neglect, can cause implications to the development of the corpus callosum. While some studies have shown there to be abnormalities in the anterior and posterior mid-body portions of the corpus callosum in those that experienced sexual and physical maltreatment in childhood, one particular study neglect can cause a reduction in the overall size of the corpus callosum. In this particular study, this effect was shown to be greater within the brains of male participants (Cyprien, F. et al., 2011, Teicher, M. H. et al., 2004). These studies display the crucial role that environmental insult can play in the development of the corpus callosum. With this being noted, it is unknown as to whether some experience such an effect to a greater extent due to a genetic predisposition to such structural differences, or whether variation may be related to the absence and presence of particular genes of interest.

Variations in corpus callosum size, shape and structure have also been seen in various psychiatric pathologies. It is hypothesized that a reduction in the size of the corpus callosum significantly contributes to the symptoms associated with various mood disorders due to the mild to severe impairments of interhemispheric connectivity. One study found there to be an overall reduction in the posterior third portion of the corpus callosum in those who had attempted suicide. Interestingly, this trend was not found within the group of participants that had a history of depression without suicidality. Since fibers from this part of the corpus callosum connect primary sensory, parietal association, and primary motor areas, it was suggested that this reduction potentially plays a role in difficulties with conflict management (Cyprien et al., 2011). Other studies have shown there to be abnormalities in the corpus callosum of individuals diagnosed with bipolar

disorder (Gifuni et al., 2017). A reduction in size of the corpus callosum has also been observed in patients diagnosed with autism (Harden, A. et al., 2009).

APPENDIX D– INTER AND INTRA OBSERVER ERROR

After all measurements were taken, eight measurements were repeated to assess for inter and intra observer error. A problem arose when measurements were obtained for the genu height. The genu height did not consistently fit within the range, nor did it consistently fall below the range or wind up above the range. It is possible that this may very well have been an error in the repeat measurement, rather than in the initial measurements

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