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Isthmus of the corpus callosum – An anatomical investigation

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A R T I C L E I N F O

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A B S T R A C T

Introduction: The corpus callosum, a principal commissural fibre-bundle of the brain, connects the two cerebral hemispheres, facilitating interhemispheric communication, cognitive and emotional processes. The anatomical definition of the isthmus of the corpus callosum remains unclear in literature with limited studies focusing on this region. This research addresses this gap by providing a detailed anatomical description of the isthmus of the corpus callosum in a South African cadaveric sample.

Methods: Digital photographs of thirty embalmed cadaver brains were analysed and measurements of the corpus callosum and isthmus were taken, as seen on a midsagittal section.

Results: The results revealed no significant differences in isthmus measurements when comparing the sex of the cadavers. The average length of the isthmus accounted for approximately 16.66 % of the total length of the corpus callosum. The isthmus constituted approximately 17.92 % of the corpus callosum surface area. Females tend to have a larger isthmus relative to the size of their corpus callosum. The prevalence of a posterior notch on the superior border of the corpus callosum was found to be approximately 46.66 % in the studied sample, with males showing a slightly higher prevalence.

Conclusion: Since the isthmus constituted almost 20 % of the total surface area of the corpus callosum, as seen on midsagittal sections, it should be acknowledged as a fifth part. It should further be included in the undergraduate neuroanatomy curriculum and textbooks, which is currently lacking this information. This research recommends expanding the sample size, encompassing diverse demographics, employing fresh cadavers, and utilize three-dimensional imaging to understand the isthmus of the corpus callosum and its relevance to neuropsychiatric conditions and brain morphology.

1. Introduction

The principal commissural fibre-bundle of the brain, the corpus callosum (CC), consists of myelinated commissural fibres that interconnect the left- and right cerebral hemispheres and is situated deep to the median longitudinal fissure. The CC plays a crucial role in interhemispheric communication and is responsible for a wide range of functions including sensory integration, motor coordination as well as cognitive and emotional processes.

The exact anatomy of the isthmus of the CC has not been clearly defined in the reported literature and is currently lacking in anatomy textbooks [1]. In most of the existing literature only four parts of the CC is mentioned, namely the. Rostrum, genu, body, and splenium (from anterior to posterior) [1–3]. Although mention of the isthmus is made by Musiek [2], it is not included as a fifth part but rather referred to a "region" between the body and splenium.

Occasionally, a fifth component is mentioned, termed the isthmus [4]. Goldstein and co-authors [5] describe the isthmus as the narrowed region between the body and splenium in the posterior aspect of the CC. Since there are no macroscopic anatomical landmarks that clearly delimit distinct callosal areas in a midsagittal cross-section, several geometric partitioning schemes have been designed to subdivide the CC. Witelson [6] described the anatomy of the isthmus and segmented the CC into seven regional subdivisions with isthmus to be the posterior one-third minus the posterior one-fifth region of the CC (as seen in Fig. 1).

In a study by Sullivan and co-workers [7], the ratio of male- and female brain sizes to the size of the CC consistently showed that males had larger CCs, when compared to their brain-size. Witelson [6] observed that in the age range of 25–68 years, callosal size seemed to decrease, specifically in males. However, it remained constant in females. Compared to Vermeulen and co-authors [8] who investigated a South African population and found that differences in several areas of the CC between the sexes and ages exist. This includes observations such

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as a thinner isthmus with increasing age.

The CC has been the target of extensive studies indicating that its morphology may be related to dyslexia [9], Tourette's syndrome [10], Down's syndrome [11], depression [12], bipolar disorders [8] and schizophrenia [8,13]. Clinical conditions that may involve the isthmus of the CC include agenesis of the CC and CC lesions [14], and neuropsychiatric disorders [15,16].

It is important to note that these conditions can have variable presentations and associated symptoms. The specific impact on the isthmus and overall brain function will depend on the extent and nature of the underlying condition. Thus, it is crucial to thoroughly investigate and describe the anatomy of the isthmus (including its variations) to create a reference framework for comparison to abnormal isthmus anatomy. Therefore, the purpose of this article is to establish a detailed anatomical description of the isthmus of the CC in a South African cadaveric sample by measuring the size of the isthmus according to the parameters described by Witelson [6]. Further noting the prevalence of the posterior notch in the superior border of the CC and the amount of surface area lost in the isthmus if the posterior notch is present.

2. Materials and methods

Embalmed cadaver brains were collected from the Department of Anatomy (the custodians of the cadavers), School of Medicine, Faculty of Health Sciences at the University of Pretoria. A sample of 25 embalmed adult South African cadaveric brains were retrospectively collected from digital photographs and a further five brain specimens were harvested providing to a total sample size of 30 cadaver brain specimens (15 males and 15 females). All the brains were removed from the cadavers by means of a typical horizontal craniotomy. A midsagittal cut was then made with a brain knife to obtain equal left- and right halves of the brain. Digital images of each brain's midsagittal sections were taken using a digital camera and the best side was selected afterwards for data collection.

To standardise the procedure, each of these sectioned brain specimens were placed 30 cm perpendicular to the digital camera. Only cadavers over the age of 18 with no visible trauma or pathology to the cerebral hemispheres were included in the study. Brain specimens that underwent surgery, were inadequately embalmed, or displayed any pathology in the region of the CC was excluded from the study.

2.1. Ethical considerations

The dissections and collection of digital photographs are subject to the ethical guidelines outlined in the Helsinki Declaration of 1964 and its later amendments. Ethical clearance was obtained from the Faculty of Health Sciences Research Ethics Committee (REC 259/2023) at the University of Pretoria before the commencement of this study. Additional permission was obtained from this Committee for the retrospective use of digital photographs previously used in another brain study (REC 3/2021). The research was carried out under the direction of the Department of Anatomy and the National Health Act (of 2003) of South Africa.

All information collected from the cadavers were anonymised by allocating unique identifiers to each brain specimen. The risk and potential consequences associated with this research are modest. In addition to offering chances for learning in academic domains, this study may also lay the groundwork for future research and offer insight into human variations in this area, as well as how variations and anomalies effect communities. "The authors hereby confirm that every effort was made to comply with all local and international ethical guidelines and laws concerning the use of human cadaveric donors in anatomical research."

2.2. Segmentation of the corpus callosum

The digital images were uploaded to a computer for data collection using ImageJ software (LOCI, University of Wisconsin). Each image was imported, scaled, and orientated in this software before the measurements were done. The CC on a midsagittal section was carefully identified and traced using the free-hand tool in ImageJ according to the landmarks and criteria published by Witelson [6] and Tanaka- Arakawa and co-authors [17].

The CC was divided using the line tool in ImageJ into seven subregions as illustrated in Fig. 1. The borders of these subregions were calculated using the length of the CC. The midpoint in length was established after which the CC was divided into thirds and subsequently into fifths. By subtracting the distance of the posterior fifth from the posterior third of the CC, the region/part (isthmus) could be established (Region 6 in Fig. 1).

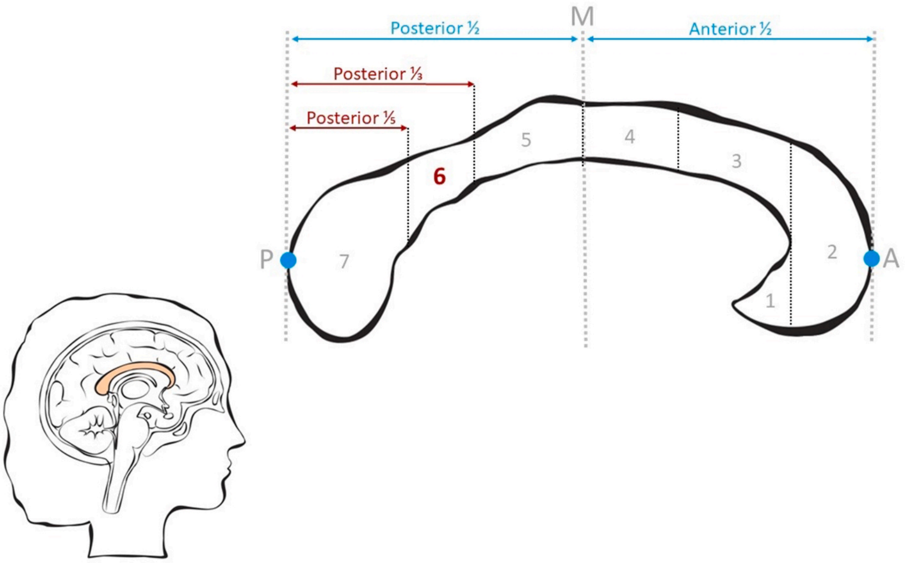

Fig. 1. Diagram showing the regional subdivisions of the corpus callosum numbered 1 to 7 (1- rostrum, 2-genu, 3-rostralbody, 4-anterior midbody, 5-posterior midbody, 6-isthmus, 7-splenium). 'A' represents the most anterior point, 'P' represents the most posterior point and 'M' represents midpoint in the length of the corpus callosum. (Adapted from Witelson, 1989 and Tanaka-Arakawa et al., 2015).

2.3. Measurements of the CC and isthmus

The following measurements were taken on the medial surface of each of the midsagittal brain images using the measurement tool in ImageJ:

- Length of the CC (cm) - to help establish one-third and one-fifth posteriorly from the most anterior point of the CC to the most posterior point (Fig. 2a).
- Length of the isthmus (cm) as seen in Fig. 2b.
- Surface area of the CC (cm^2) by outlining the CC with the free hand tool (Fig. 2c).
- Surface area of the isthmus (cm^2) by outlining the isthmus with the free hand tool (Fig. 2d).
- Height of the isthmus at its midpoint (cm) as seen in Fig. 2e.

Each midsagittal section was further observed for the presence or absence of a posterior notch in the area of the isthmus of the CC. The posterior notch is an indentation on the dorsal contour of the CC which are sometimes visible in the regions of the body and isthmus of the CC [4]. If the posterior notch was present on the specimen, the surface area lost in the isthmus was then calculated by deducting the actual surface area of the CC from the surface area measured (cm^2) if the posterior notch was not present on CC (Fig. 2f).

2.4. Statistical analyses

Statistical analyses were done in IBM SPSS software program (Version 29) for Windows (SPSS Inc., Chicago, Illinois). Descriptive statistics included the mean, median, range and standard deviations of each measurement. Prevalence (presence/absence) were described using percentage values. Interferential statistics included a normality test for the data (Shapiro-Wilk test), Paired Samples t-Tests, Pearson Chi-squared tests as well as Intraclass Correlation tests.

3. Results

To test if the data collected from the measurements were normally distributed, a Shapiro-Wilk test was conducted. Since all the p-values obtained in this test were above 0.05, they are considered normally or symmetrically distributed and are summarised in Table 1.

3.1. Measurements of the isthmus and the CC

The descriptive statistics for each of the measurements done are summarised in Table 2. The length of the isthmus was further compared to the length of the CC, as a percentage value. The average length of the isthmus accounted for 16.66 % of the overall length of the CC, while the average surface area of the isthmus constitutes 17.92 % of the overall surface area of the CC.

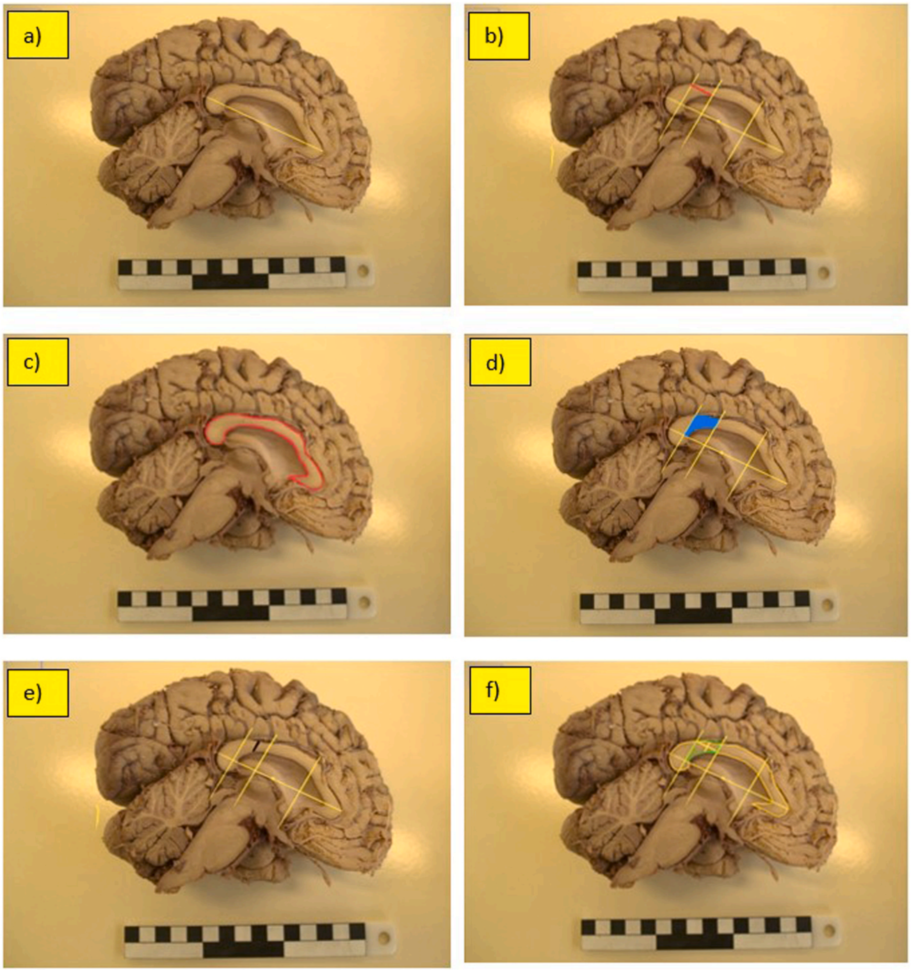

Fig. 2. Digital photographs illustrating the measurements taken in relation to the isthmus of the corpus callosum (CC). **a)** length of the CC (yellow line), **b)** length of isthmus (red line), **c)** surface area of the CC (red outline), **d)** surface area of the isthmus (blue area), **e)** the height of the isthmus at midpoint (black line), **f)** surface area of the CC measured that would have been lost if the posterior notch was not present (green area). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 1
Shapiro Wilk test outcome for all measurements done indicating normally distributed data.

Measurements	Significance (p-value)
Length of CC (cm)	0.76
Length of isthmus (cm)	0.76
Height of isthmus at midpoint (cm)	0.51
Surface area of CC (cm^2)	0.14
Surface area of isthmus (cm^2)	0.65

CC: Corpus callosum, cm: centimetres.

Table 2
Descriptive statistics summarised for each measurement conducted.

Measurements	Mean	SD	Minimum	Maximum	Range	Median
Length of CC (cm)	9.02	0.87	7.21	11.00	3.79	9.00
Length of isthmus (cm)	1.50	0.14	1.12	1.83	0.63	1.50
Height of isthmus at midpoint (cm)	0.82	0.24	0.39	1.31	0.92	0.79
Surface area of the CC (cm^2)	9.29	1.76	6.69	12.68	5.98	9.44
Surface area of the isthmus (cm^2)	1.67	0.54	0.72	2.63	1.91	1.60

CC: Corpus callosum, SD: standard deviation, cm: centimetres.

The data obtained from the measurements were further compared based on the biological sex of the cadavers (males vs females) with Paired Samples t-Tests. Although differences were noted in the measurements between the sexes, none of these are statistically significant since all the p-values are above 0.05, as seen in Table 3.

3.2. *Prevalence of the posterior notch*

The prevalence of a posterior notch on the dorsal contour of the CC was observed and documented. Table 4 indicates that in this sample, males tend to have the posterior notch present (30 %) compared to females with a notch present in 16. 66 %. The prevalence of the posterior notch was further compared to the sex of the cadaver with a Pearson Chi-squared test with an outcome of $p = 0.136$. This means that even though there is a difference in the prevalence of the posterior notch between males and females, this difference is not statistically significant.

If the posterior notch was present in the isthmus, a further calculation was done to determine the extent of the surface area that was lost. This surface area lost was calculated as a percentage value in comparison to the surface area of the isthmus. On average, the posterior notch removed approximately 28.75 % of the isthmus surface area. In males this lost surface area was 29.96 % compared to females with a lost area of 26. 56 %. On average, if the notch is present, it tends to be larger in males compared to females. To test correlation, a paired sample *t*-Test was done to compare the lost surface area to the sex of the cadaver with an outcome of $p = 0.218$ – meaning that the difference between the sexes is evident but not statistically significant.

Table 3
Outcome of Paired Student t-Tests conducted on the measurements based on the sex of the cadaver.

Measurements	Sex of cadaver	Mean	SD	p-value
Length of CC (cm)	Male	9.132	0.814	0.36
	Female	8.912	0.931	
Length of isthmus (cm)	Male	1.522	0.135	0.36
	Female	1.484	0.155	
Height of isthmus at midpoint (cm)	Male	0.836	0.241	0.76
	Female	0.813	0.248	
Surface area of the CC (cm^2)	Male	9.778	1.844	0.06
	Female	8.803	1.584	
Surface area of the isthmus (cm^2)	Male	1.667	0.504	0.97
	Female	1.672	0.561	

CC: Corpus callosum, SD: Standard deviation, cm: centimetres.

Table 4
Prevalence of the posterior notch summarised according to the biological sex (male and female) of the cadaveric sample.

	Notch present n (Percentage)	Notch absent n (Percentage)
Males	9 (30 %)	6 (20 %)
Females	5 (16.66 %)	10 (33.33 %)
Total sample	14 (46.66 %)	16 (53.33 %)

3.3. *Comparing area of the isthmus to the CC area*

The surface area of the isthmus was further compared to the surface area of the CC, as seen on a midsagittal section through the brain. On average the isthmus constitutes 17.92 % of the CC (17.03 % in males and 18.80 % in females), indicating that the isthmus tends to be larger in females compared to males in this study.

Intraclass correlation coefficient (ICC) tests were done to determine the reliability and repeatability of the measurements. An ICC value of 0.74 was obtained for the intra-observer error. Indicating a good reliability and repeatability of researcher's measurements compared to an ICC value of 0.71 for the interobserver error - indicating a good reliability and repeatability.

4. Discussion

A considerable amount of literature has been published on the CC [8,18–20] and the parameters of the CC in which the isthmus lies have been researched, however, there is a relatively small body of literature that reports the isthmus of the CC [6,21]. Anatomically the isthmus is the area between the body and splenium, connecting the posterior parts of the cerebral hemispheres, and is where white matter fibres connecting the parietal regions converge [22]. The physiological function of the isthmus is unknown although some studies speculate that it plays a role in lateralization relating motor and sensory information between the two hemispheres [23].

However, there is a lack of consensus in the literature which has created room for further investigation into the general anatomy of the CC. This research brings to light the importance in establishing the anatomy of the isthmus to identify variations which may exist. Fibres originating in the motor cortex are assumed to cross the CC through the anterior midbody, whereas somaesthetic and posterior parietal fibre bundles cross the CC through the posterior midbody [24]. Other researchers also subdivided the CC into different regions [25–29]. However, it should be noted that most studies rely on Witelson's original classification [6], including the current study.

The effects of variance in midsagittal morphology on encephalograms and cerebral angiographies was explored in an earlier investigation at the Montreal Neurological Institute in Canada [30]. According to the report, the prominence of the indentation on the superior surface of the posterior portion of the CC's body was caused by the wide diversity in the anatomy of the CC [31].

To the author's knowledge, no studies on the anatomy of the isthmus of the CC in a South African population could be identified in the literature. Thus, the present study used quantified measures to describe the isthmus of the CC and aimed to establish correlations between the sexes, in a normally distributed dataset. Furthermore, the prevalence of the posterior notch in the superior border of the CC and the amount of surface area lost in the isthmus if the posterior notch is present, was determined.

4.1. Measurements of the isthmus and CC

This study obtained an average length of the isthmus of 0.76 cm, average height of the isthmus as 0.51 cm with a total surface area of 0.65 cm^2. The mean length of the CC was larger than the reported measurements of Witelson [6] as mentioned by Shah and co-authors [32] as well as Guner and co-workers [33] who claimed that the sex, brain volume, and age could lead to different measurements in cadaver samples. The values of these exact measurements, however, could not be compared to other studies since quantifying them have not been the main objective of studies and requires further research on the subject for critical engagement. Differences can be attributed to the sample size (30 vs 50), population group (Canada) and source of the sample, as summarised in Table 4. The Canadian population is reported to have a smaller cranial size than the South African population [34]. It is well known that cranial sizes between population groups differ [35]. The present study did not account for age and cranial size due to the limited sample size. However, it has been reported that older individuals have thinner CC and thus smaller isthmi [36] (Table 5).

The present study did not find significant differences in the length, height, and surface area of the isthmi between males and females. However, Steinmetz and co-authors [37] found that females have a larger proportional isthmus segment of the CC. This may reflect a sex-specific difference in the inter-hemispheric connectivity and functional organization of the temporoparietal association cortex [37]. Another reason for the difference between the two studies may be attributed to the age, population group and source of the brains (MRI vs cadaver) and possibly sexual dimorphism.

In the existing study, the average length of the isthmus accounts for 16.66 % of the overall length of the CC. In this study, male and female isthmi were pooled, thus, no correlation between male and female cadaveric brains could be made. However, slight differences were observed for all the measurements when comparing the biological sex of the cadavers.

4.2. Prevalence of the posterior notch

According to Witelson [6], a “notch” is described as a focused concavity in the dorsal surface that is at least 1 mm deep from the surface of the CC. Additionally, the pericallosal artery becomes rather tortuous as it courses along the superior border of the CC, causing an undulating of the CC. The overall surface area of the CC may be influenced by this as the total surface area could possibly decrease [3,4]. In the current study the posterior notch was present in 60 % ($n = 9$) of the male specimens and in 33.33 % ($n = 5$) of the female brain specimens. This suggests that just less than half of this sample (46.66 %) presents with a posterior notch as seen in 14 cadavers. No correlation between the prevalence of the posterior notch and the sex of the cadaver could be established ($p = 0.218$) and this could be accounted for by the limited sample in this study.

An analysis of the surface area lost when comparing the posterior notch to the isthmus indicated a 29.96 % reduction in males and a 26.56 % reduction in females. Additionally, when the posterior notch was present, it removed approximately 28.75 % of the isthmus surface area.

Table 5
Comparison of demographics between the current study and reported studies.

	Witelson (1989)	Gruner et al. (2023)	Current study
Sample Size	50	80	30
Sample Method	Cadavers	MRI and cadavers	Digital imaging of cadavers
Countries where study was conducted	Canada	Turkey	South Africa

4.3. Comparing the area of the isthmus to the CC area

In this study, the isthmus constituted 17.92 % of the surface area of the CC. This percentage was 17.03 % in males and 18.80 % in females. Given that the isthmus constitutes nearly 20 % of the CC’s dimensions, it is crucial to acknowledge its significance and incorporate it into neuroanatomy textbooks and the undergraduate neuroanatomy curriculum. Additionally, conducting additional research on the isthmus with a more extensive sample size becomes imperative. This study proved to be highly reliable and repeatable based on the outcomes of the Intraclass Correlation (ICC) tests with values of 0.71 and 0.74.

4.4. Limitations of the study and future recommendations

One of the primary limitations of this study is the relatively small sample size as well as a predominantly white South African population sample due to the limited availability of diverse cadaveric brain specimens. This may limit the generalisability of the findings to a broader population.

The difficulty in measuring a three-dimensional structure in two dimensions is an inherent limitation that impacts the precision and completeness of the analysis. However, a two-dimensional view was chosen as these midsagittal sections are mainly used in neuroanatomy textbooks to describe the CC and its parts. Therefore, reinforcing the fact that the isthmus should be recognised and included as part of the CC in textbooks. Furthermore, all measurements obtained in this study only reflected the size of the CC as seen in a midsagittal section and is not representative of the entire size of the CC.

The authors fully understand the CC is a three-dimensional fibre-bundle, which will be best investigated with radiographic digital analysis such as tractography in brain MRI’s. While every effort was made to minimize these limitations through careful data acquisition and analysis techniques, readers should be aware of the potential constraints.

Future research should aim to include a larger and more diverse range of brain specimens including a broader range of age groups, population groups and geographic locations, to ensure that findings can be generalized more broadly. The use of fresh cadaver brains should be considered since a shrinking factor exists (0.07) in embalmed brains which may affect the results of a study. Furthermore, incorporating advanced three-dimensional tractography is a promising avenue for future research. These imaging techniques offer a richer understanding of spatial relationships and facilitate precise measurements in ways that two-dimensional imaging cannot.

5. Conclusion

In conclusion, this study has addressed the aim of establishing a detailed anatomical description of the isthmus of the CC in a South African cadaveric sample by measuring the size of the isthmus according to the parameters described by Witelson [6]. The findings revealed that there are differences in the measurements when comparing male and female cadaver CCs, but not statistically significant. The average length of the isthmus accounts for 16.66 % of the length of the CC. The isthmus constitutes 17.92 % of the surface area of the CC, when viewed in a midsagittal section. It was observed that females have a larger isthmus in relation to the size of their CC. The presence of the posterior notch in males and females is almost 50 %. However, it should be noted that when the notch is present, it tends to be larger in males. Therefore, the isthmus should be acknowledged and included in the undergraduate neuroanatomy curriculum and textbooks as a fifth part of the CC, found between the body and the splenium.

Declaration statements

The authors have no relevant financial or non-financial interest to disclose. The authors have no competing interests to declare that are relevant to the content of this article. All authors certify that they have no affiliations or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The authors have no financial or proprietary interests in any material discussed in this article.

Ethical declaration

All procedures performed in studies involving cadavers were following the ethical standards of the Faculty of Health Sciences Research Ethics Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. This study was approved by the Faculty of Health Sciences Research Ethics Committee of the University of Pretoria (REC 259/2023).

Data availability statement

The dataset is available from the corresponding author with a reasonable request.

Ethics in publishing

The authors state that every effort was made to follow all local and international ethical guidelines and laws that pertain to the use of human cadaveric donors in anatomical research.

Financial interests

The authors have no relevant financial or non-financial interests to disclose. No funding was received for conducting this study. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest or non-financial interest in the subject matter or materials discussed in this manuscript. The research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Yukta Maharajh: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis, Data curation. **René Human-Baron:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Formal analysis, Conceptualization. **Gerda Venter:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Formal analysis, Conceptualization.

Declaration of competing interest

The authors have no competing interests to declare that are relevant to the content of this article.

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