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DEPARTMENT OF ANATOMY

SURFACE ANATOMY AND SUBCORTICAL ARCHITECTURE OF THE OCCIPITAL LOBE

PHD DOCTORAL THESIS
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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΕΡΓΑΣΤΗΡΙΟ ΑΝΑΤΟΜΙΑΣ

ΕΠΙΦΑΝΕΙΑΚΗ ΑΝΑΤΟΜΙΑ ΚΑΙ ΥΠΟΦΛΟΙΩΔΗΣ ΑΡΧΙΤΕΚΤΟΝΙΚΗ ΤΟΥ ΙΝΙΑΚΟΥ ΛΟΒΟΥ

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΧΡΗΣΤΟΣ ΚΟΥΤΣΑΡΝΑΚΗΣ, ΝΕΥΡΟΧΕΙΡΟΥΡΓΟΣ

ΑΘΗΝΑ 2021

The approval of the doctoral dissertation by the Medical School of the National Kapodistrian University of Athens does not imply approval of the views of the author. (Law 5343/1932, article 202, paragraph 2).

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Dedicated

To my parents Kostas and Kiki Koutsarnakis who gave me everything

And to Ifigeneia who means everything

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CURRICULUM VITAE

Personal Details

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Professional Details

GMC Number: 6124389

License to Practice: Yes

Specialist Registration (Neurosurgery): Yes (since 7/2016)

Committees - Societies

International Association for Mapping the Brain: Member of the Scientific Committee (Specialty: Neurosurgery - White Matter Neuro-anatomy)

European Association of Neurosurgical Societies – EANS: Individual Member (IM) Delegate (Voted on 7/2020)

Greek Neurosurgical Society: Elected Member - Scientific committee on Surgical Neuro-Oncology (3 -member committee)

Member of the Greek American Neurosurgical Society (GANS)

European Association of Neurosurgical Societies – EANS: Section Member Neuro-Oncology

Current posts

5/2020 -	***Attending Neurosurgeon in Radiosurgery** – Cyber knife Department, Iatropolis Medical Center, Athens, Greece*
11/2016-	***Neurosurgeon, Research Associate**, interest in Surgical Neuro-Oncology, Brain Mapping and Skull Base Neurosurgery Department, University of Athens, Evangelismos Hospital, Athens, Greece.*

11/2016-	***Head*** *Athens Microneurosurgery Lab - University of Athens. Director: Prof. George Stranjalis*
1/2019 -	***Lecturer - MSc in Clinical and Experimental Neurosurgery*** *(Medical School National and Kapodistrian University of Athens, Athens Greece) Topic: White matter and Skull Base Anatomy*

Previous posts

2017-2019	***Lecturer - MSc in Applied Neuroanatomy*** *(Medical School National and Kapodistrian University of Athens, Athens Greece, Directors: Prof E. Johnson – Prof G. Stranjalis) Topic:* ***:*** *White matter and Skull Base Anatomy*
8/2016-10/2016	***Senior Specialist Registrar*** *Department of Pediatric Neurosurgery, Royal Hospital for Sick Children, Edinburgh, UK.*
8/2015-8/2016	***Post CCT Senior Clinical Fellow-Senior Specialist Neurosurgical Registrar (training post) interest in Surgical Neuro-Oncology and Skull Base*** *Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK*
1/2015- 8/2015	***Research Associate-Scientific Coordinator in Neuroanatomy*** *Neurosurgery Department, University of Athens, Evangelismos Hospital. Chair: Prof. Damianos Sakas*
2/2014- 12/2015	***Research Fellow*** *Athens Microneurosurgery Lab - University of Athens. Director: Prof. George Stranjalis*

Education

10/2016-6/2018	***MSc in Surgical Anatomy (with distinction-funded by the Greek Medical Council)****–Department of Anatomy – National and Kapodistrian University of Athens, Director: Prof P. Skandalakis* *Thesis title: "Defining the relationship of the optic radiation to the roof and floor of the ventricular atrium. A focused microanatomic study" published in Journal of Neurosurgery.*
8/2015-10/2016	***Senior Clinical Fellow-Senior Specialist Neurosurgical Registrar (Training post)*** *Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK*

2/2014-12/2014	***Research Fellow** Microneurosurgery Lab - University of Athens. Director: Prof. George Stranjalis*
2/2014	***Successfully passed the Neurosurgery Specialty License Exams. (FRCS equivalent)***
1/2012-1/2014	***Senior resident** Neurosurgery Department-University of Athens, Evangelismos Hospital, Chair: Prof. Damianos. E. Sakas*
6/2009-12/2011	***Resident** Neurosurgery Department-University of Athens -Evangelismos Hospital, Chair: Prof. Damianos. E. Sakas*
9/2008-2/2009	***Resident** Neurology Department-251 Air force Military Hospital, Athens Greece (during 1 year obligatory national service)*
7/2006-2/2008	***Resident** Department of General and Vascular Surgery Elpis Hospital, Athens Greece*
5/2005-6/2006	***Research Fellow** (Brain trauma Microdialysis) Neurosurgery Department-University of Athens -Evangelismos Hospital, Chair: Prof. Damianos. E. Sakas*
4/2005	***Intercollegiate MRCS (Ed)***
9/1998-2/2005	***Medical Degree** - **University of Athens –Faculty of Health Sciences Department of Medicine** (Overall Mark 7, 15/10)*

Fellowships

Senior Clinical Fellow, interest in Skull base and Surgical Neuro-Oncology (2015-2016) Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK

Research Fellow, Skull base and White Matter Anatomy (2014-2015), Athens Microneurosurgery Laboratory, Academic Department of Neurosurgery, Evangelismos Hospital, Athens, Greece.

Research Fellow, Brain Microdialysis (2005-2006), Academic Department of Neurosurgery, Evangelismos Hospital, Athens, Greece.

Editor - Reviewer

Brain and Behavior (IF = 2,091) - Reviewer

Reviews in the Neurosciences (IF = 3,358 – 5 year IF = 3,39) - Reviewer

Communications Biology (Nature) - Reviewer

Brain Sciences – Topic Editor

Surgical Neurology International (IF=1) – Reviewer

Journal of Clinical Medicine (IF =1, 88) – Reviewer

Journal of Integrative Neuroscience (IF=1, 19) - Reviewer

Invited Speaker

- ***Fifth Annual Course on Brain Mapping: A worldwide video Symposium (20-21/3/2021)***

Topic: *Language and Middle & Inferior longitudinal fasciculi*

- ***2nd International Webinar of the Hellenic Neurosurgical Society on Neuro-oncology (27-28/2/21)***

Topic: *Intra-operative Brain Mapping*

- ***Webinar organized by Advantis Medical Imaging (22/12/20)***

Topic: *"Clinical applications of DTI and fMRI in Neuro-oncology: Neurosurgeon's perspective*

Invited speakers: Christos Koutsarnakis, Foteini Christidi

- ***1st Webinar of the Hellenic Neurosurgical Society on Stereotactic Radiosurgery (28-29/11/20)***

Topic: *The role of the Neurosurgeon in Stereotactic Radiosurgery treatment.*

- ***Fourth Annual Course in White Matter Surgery and Brain Mapping (4-5/3/2020) Anatomy Lab, Charring Cross, Imperial College London and National Hospital for Neurology and Neurosurgery, Queen Square, London***

Topics *1) SLF and AF: Anatomy and importance in tumor resection*

2) How to set up a white matter anatomy laboratory

3) Round table: Language Models with fMRI, DTI, psychology

- ***Santo-Rhino II. Santorini Skull Base Meeting (26-28/9/2019)***

Topic: *It's the Anatomy. Skull Base- An open Perspective*

- ***1st GANS Meeting - Greek-American Neurosurgical Society (4-6/8/2019)***

Topic: *Understanding Hodotopy. The role of the white matter dissection technique in modern Neurosurgery*

- ***33rd Annual Congress of the Hellenic Neurosurgical Society & 4th Congress of SEENS Southeast Europe Neurosurgical Society (27-30/6/2019)***

Topic: *Skull Base Approaches. Cavernous sinus, Petrosectomy, Retrosigmoid.*

- ***Annual Medical Symposium of Evangelismos Hospital (2/3/2018)***

Topic: *The added value of Applied Neuroanatomy in Neurosurgery.*

- ***31st National Neurosurgical Conference (15-18/6/2017)***

Topic: *White matter fiber tract anatomy and radiographic correlation.*

- ***29th National Neurosurgical Conference***

Topics *1) Introduction to White Matter Dissection.*

2) Idiopathic Intracranial Hypertension: A systematic review of the efficacy and complication profile of the available surgical interventions.

- ***Scottish Neurosurgical training meeting (November 2016 Perth, Scotland)***

Topic: *Temporal lobe anatomy*

Teaching Experience

***1-2/6/2021** Invited Faculty 1st Athens Skull base Hands –on Course organized by the Hellenic Neurosurgical Society*

***17/5/2021-21/5/2021** Organizer-Convenor 6th International Neurosurgical Anatomy and White Matter Dissection course organized by The National Neurosurgical Society, the Academic Neurosurgical Department of Evangelismos Hospital and under the auspices of EANS. Scientific Director: George Stranjalis*

***4-5/3/2020** Invited Faculty 4th annual course in white matter surgery and Brain Mapping. Anatomy Lab, Charring Cross, Imperial College London and The National Hospital for Neurology and Neurosurgery, Queen Square, London. Convenor: Mr. George Samandouras*

***6/11/2019-8/11/2019** Invited Faculty Neurosurgical Approaches to the Cranial Compartments.– Neurosurgery Course organized by the Royal College of Surgeons Edinburgh, UK. Convenor Mr. Ioannis P. Fouyas.*

***6/5/2019-10/5/2019** Organizer-Convenor 5th International Neurosurgical Anatomy and White Matter Dissection course organized by The National Neurosurgical Society, the Academic Neurosurgical Department of Evangelismos Hospital and under the auspices of EANS. Scientific Director: George Stranjalis*

***3/10/2018-5/10/2018** Invited Faculty Neurosurgical Approaches to the Cranial Compartments. Applied Neuroanatomy – Neurosurgery Course organized by the Royal College of Surgeons Edinburgh, UK. Convenor Mr. Ioannis P. Fouyas.*

***7/5/2018-11/5/2018** Trainer in the 4th International Neurosurgical Anatomy and White Matter Dissection course organized by The National Neurosurgical Society, the Academic Neurosurgical Department of Evangelismos Hospital and under the auspices of EANS. Scientific Director: George Stranjalis*

***31/10/2017-2/11/2017** Invited Faculty Neurosurgical Approaches to the Cranial Compartments. Applied Neuroanatomy – Neurosurgery Course organized by the Royal College of Surgeons Edinburgh, UK. Convenor Mr. Ioannis P. Fouyas.*

***29/5/2017-2/6/2017** Trainer in the 3rd International Neurosurgical Anatomy and White Matter Dissection course organized by The National Neurosurgical Society, the Academic Neurosurgical Department of Evangelismos Hospital and under the auspices of EANS. Scientific Director: George Stranjalis*

***18/4/2016-22/4/2016** Invited faculty in the 2nd International Neurosurgical Anatomy and White Matter Dissection course organized by The National Neurosurgical Society, the Academic Neurosurgical Department of Evangelismos Hospital and under the auspices of EANS. Scientific Director: George Stranjalis*

***20/4/2015-23/4/2015** Trainer in the 1st International Neurosurgical Anatomy and White Matter Dissection course organized by The National Neurosurgical Society, the Academic Neurosurgical Department of Evangelismos Hospital and under the auspices of EANS Scientific Director: George Stranjalis*

28/05/2014-30/05/2014 *Trainer in the 3rd National Course in Neurosurgical Approaches to the Cranial Compartments Organized by The School of Medicine, University of Athens. Convenor: Prof. G. Stranjalis.*

29/05/2013-31/05/2013 *Trainer in the 2ndNationalCourse in Neurosurgical Approaches to the Cranial Compartments Organized by The School of Medicine, University of Athens. Convenor: Prof. G. Stranjalis.*

2012 (Autumn Semester) *Tutor in Clinical Semiology, MSc in ICU and Emergency Nursing, University of Athens, School of Medicine*

2011 (Autumn Semester) *Tutor in Clinical Semiology, MSc in ICU and Emergency Nursing, University of Athens, School of Medicine*

Patents

A new access kit for the first placement and revision procedure of the ventricular catheter using the "over the wire" technique.

Patented by the Hellenic Industrial Property Organization (2014).

Prizes

- *The cerebral isthmus: Definition, fiber tract anatomy and functional considerations.*

1st Prize for the best oral presentation on the 29th National Neurosurgical Conference

- *Surface Anatomy of the temporal lobe with emphasis on the topographic architecture of the temporal pole*

1st Prize for the best Poster Presentation on the 4th Congress of SEENS - Southeast Europe Neurosurgical Society (27-30/6/2019)

Languages

Greek (native)

English (Certificate of Proficiency, University of Michigan)

IELTS (2015) (academic module overall score: 8 /9)

Memberships

EANS

Greek –American Neurosurgical Society (GANS)

Hellenic Neurosurgical Society

Athens Medical Association

ADVISORY COMMITTEE

Maria Piagkou, *Associate Professor, Department of Anatomy, National and Kapodistrian University of Athens, Medical School (Supervisor)*

George Stranjalis, *Professor, Department of Neurosurgery, National and Kapodistrian University of Athens, Medical School*

Theodoros Troupis, *Professor, Department of Anatomy, National and Kapodistrian University of Athens, Medical School*

THESIS PUBLICATIONS

Mapping the human middle longitudinal fasciculus through a focused anatomo-imaging study: shifting the paradigm of its segmentation and connectivity pattern

Kalyvas A, Koutsarnakis C, Komaitis S, Karavasilis E, Christidi F, Skandalakis G, Liouta E, Papakonstantinou O, Kelekis N, Duffau H, Stranjalis G. (equally contributing first authors)

Brain Struct Funct. 2020 Jan;225(1):85-119. doi: 10.1007/s00429-019-01987-6.

Mapping the superficial morphology of the occipital lobe: proposal of a universal nomenclature for clinical and anatomical use.

Koutsarnakis C, Komaitis S, Drosos E, Kalyvas AV, Skandalakis GP, Liakos F, Neromyliotis E, Lani E, Kalamatianos T, Stranjalis G.

Neurosurg Rev. 2019 Nov 22. doi: 10.1007/s10143-019-01212-2.

Sledge runner fasciculus: anatomic architecture and tractographic morphology.

Koutsarnakis C, Kalyvas AV, Skandalakis GP, Karavasilis E, Christidi F, Komaitis S, Velonakis G, Liakos F, Emelifeonwu J, Giavri Z, Kalamatianos T, Kelekis N, Stranjalis G.

Brain Struct Funct. 2019 Apr; 224(3):1051-1066

PRESENTATIONS

6th International Neurosurgical Anatomy and White Matter Dissection course (Athens17-21/5/2021)

Topic: Basic Anatomo-functional concepts on the Ventral and Dorsal Language Pathways

Fifth Annual Course on Brain Mapping: A worldwide video Symposium (20-21/3/2021)

Topic: Language and Middle & Inferior longitudinal fasciculi

Fourth Annual Course in White Matter Surgery and Brain Mapping (4-5/3/2020) Anatomy Lab, Charring Cross, Imperial College London and National Hospital for Neurology and Neurosurgery, Queen Square, London

Topics 1) SLF and AF: Anatomy and importance in tumor resection

2) How to set up a white matter anatomy laboratory

1st GANS Meeting - Greek-American Neurosurgical Society (Athens 4-6/8/2019)
Topic: Understanding Hodotopy. The role of the white matter dissection technique in modern Neurosurgery

ABSTRACT

OBJECTIVE

To study and record the surface anatomy and subcortical architecture of the occipital lobe, since detailed knowledge of its axonal connectivity is still vague. Regarding the surface anatomy, the morphological pattern of the lateral, medial and basal occipital sulci has been studied whereas in regard to the subcortical architecture the morphology, spatial relationship and axonal connectivity of the fiber tracts residing in the occipital lobe have been meticulously explored.

MATERIALS & METHODS

Thirty –three (33) adult, cadaveric hemispheres fixed in a 10-15% formalin solution for a period of at least 8 weeks were studied. The arachnoid membrane and vessels of the area of the occipital lobe were cautiously removed and the sulcal morphology was systematically recorded. Following the removal of the arachnoid membrane and vessels, all specimens underwent the Klingler's procedure (freeze–thaw process) and were subsequently investigated using the fiber dissection technique and the microscope (Carl Zeiss OPMI). The dissection tools used consisted of fine metallic periosteal elevators, various sized anatomical forceps, and micro-scissors. Numerous photographs were obtained during cadaveric dissections to illustrate the regional cortical and subcortical anatomy of interest.

RESULTS

With regard to the surface anatomy of the occipital lobe we recorded the lateral occipital sulcus and the intraoccipital sulcus in 100% of the specimens whereas the anterior occipital sulcus in 24%, and the inferior occipital sulcus in 15%of cases. In the medial occipital surface, the calcarine fissure and parieto-occipital sulcus were always present. Finally, the basal occipital surface was always indented by the posterior occipitotemporal and posterior collateral sulci. A sulcus not previously described in the literature was identified on the supero-lateral aspect of the occipital surface in 85% of cases. We named this sulcus "marginal occipital sulcus" after its specific topography.

With respect to the subcortical architecture of the occipital lobe, special attention has been given to the detailed description of a novel fasciculus named as the "sledge runner fasciculus" after its peculiar shape. This tract was consistently identified as a distinct white matter pathway lying under the U fibers of the medial occipital lobe, exhibiting an oblique dorsomedial–ventrolateral direction and connecting the areas of the anterior cuneus, anterior lingula, isthmus of the cingulum and posterior parahippocampal gyrus. To our knowledge this is the first study in the pertinent literature to describe the morphology, correlative anatomy and axonal connectivity of this fiber pathway.

Furthermore, emphasis was placed to the anatomy, morphology and axonal connectivity of the middle longitudinal fasciculus. This white matter tract has been consistently identified as a discrete group of fibers travelling medial to the fibers of the arcuate fasciculus and found to participate in the connectivity of the temporal pole to the parietal and occipital lobes. The tract was further subdivided into three segments according to their special axonal connectivity.

CONCLUSION

By using the white matter dissection technique – Klingler preparation, we were able to provide a detailed description of the white matter tracts that traverse the occipital lobe and indeed participate in the axonal connectivity and functional integration of the human brain. Hence, the sledge runner fasciculus is consistently involved in the axonal connectivity of cerebral areas that are believed to be strongly implicated in the cognitive ability of spatial navigation and visuospatial imagery whereas the middle longitudinal fasciculus seems to participate in the connectivity of functional hubs sub serving the integration of acoustic information.

ΠΕΡΙΛΗΨΗ

ΣΚΟΠΟΣ

Σκοπός της παρούσας έρευνας είναι η διεξοδική μελέτη και καταγραφή της επιφανειακής τοπογραφικής ανατομίας και της υποφλοιώδους αρχιτεκτονικής του ινιακού λοβού. Σχετικά με την επιφανειακή ανατομία έχει μελετηθεί το πρότυπο κατανομής και μορφολογίας των αυλάκων της έξω, έσω και κάτω επιφάνειας του ινιακού λοβού καθώς και οι παραλλαγές αυτού. Σε ότι αφορά την υποφλοιώδη αρχιτεκτονική, έχει διερευνηθεί η τοπογραφία, μορφολογία και συγκριτική ανατομία των δεματίων της λευκής ουσίας που εντοπίζονται στον ινιακό λοβό.

ΜΕΘΟΔΟΣ

Η επιφανειακή ανατομία καθώς και η υποφλοιώδης αρχιτεκτονική του ινιακού λοβού μελετήθηκε σε τριάντα- τρία (33) εγκεφαλικά ημισφαίρια μονιμοποιημένα σε διάλυμα φορμόλης 10-15% για τουλάχιστον 8 εβδομάδες. Εφόσον αφαιρεθεί η αραχνοειδής μήνιγγα και τα αγγεία έχει καταγραφεί λεπτομερώς η τοπογραφία και μορφολογία των ελίκων και αυλάκων του ινιακού λοβού ενώ στη συνέχεια τα εν λόγω παρασκευάσματα μελετήθηκαν με τεχνική διαχωρισμού της λευκής ουσίας κατά Klingler με στόχο την διερεύνηση της υποφλοιώδους ανατομίας του ινιακού λοβού. Τα εργαλεία που χρησιμοποιήθηκαν κατά τις ανατομικές παρασκευές είναι χειρουργικές μικρολαβίδες, μικροψαλίδια και μικροαποκολλητήρες διαφόρων ειδών καθώς και χειρουργικό μικροσκόπιο τύπου Carl Zeiss OPM Plus.

ΑΠΟΤΕΛΕΣΜΑΤΑ

Σχετικά με την επιφανειακή ανατομία, στην έξω/πλάγια επιφάνεια του ινιακού λοβού αναγνωρίσθηκαν η έξω ινιακή αύλακα (lateral occipital sulcus) και η ενδο-ινιακή αύλακα (intra-occipital sulcus) στο 100% των παρασκευασμάτων ενώ η πρόσθια ινιακή αύλακα και η κάτω ινιακή αύλακα σε 24% και 15% αντίστοιχα. Στην έσω επιφάνεια του ινιακού λοβού η πληκτριαία σχισμή και η βρεγματο-ινιακή αύλακα αναγνωρίσθηκαν ευκρινώς σε όλα τα παρασκευάσματα όπως και στην κάτω ινιακή επιφάνεια στην οποία εντοπίζονται τα άπω τμήματα της κρόταφο-ινιακής και παράπλευρης αύλακας αντίστοιχα. Στην άνω επιφάνεια του ινιακού λοβού καταγράφηκε στο 85% των παρασκευασμάτων μια νέα αύλακα που δεν έχει ταυτοποιηθεί στην σχετική βιβλιογραφία και την οποία ονομάσαμε «επιχείλια αύλακα» του ινιακού λοβού εξαιτίας της τοπογραφίας της.

Σε σχέση με την υποφλοιώδη αρχιτεκτονική του ινιακού λοβού ιδιαίτερη έμφαση δόθηκε στη λεπτομερή περιγραφή της μορφολογίας και συνδεσιμότητας ενός νέου δεματίου, του δεματίου «δίκην ελκήθρου» (sledge runner fasciculus). Το συγκεκριμένο αυτοτελές δεμάτιο εντοπίστηκε σε όλα τα παρασκευάσματα στην έσω επιφάνεια του ινιακού λοβού ακριβώς κάτω από τις επιφανειακές συνδετικές ίνες, επιδεικνύοντας μια λοξή κατεύθυνση και συμμετέχοντας στην συνδεσιμότητα περιοχών του προσθίου σφηνοειδούς λοβίου, προσθίου τμήματος της γλωσσοειδούς έλικας, ισθμού του προσαγωγίου και οπίσθιου τμήματος της παραιπποκάμπειας έλικας. Η συγκεκριμένη μελέτη αποτελεί την πρώτη διεθνώς καταγεγραμμένη προσπάθεια ανατομικής περιγραφής της αρχιτεκτονικής του δεματίου «δίκην ελκήθρου».

Επίσης, έγινε λεπτομερή ανατομική περιγραφή του μέσου επιμήκους δεματίου (middle longitudinal fasciculus) σε σχέση με την μορφολογία του και την συνδεσιμότητα του. Το μέσο επίμηκες δεμάτιο εντοπίστηκε αμιγώς ως ένα αυτοτελές δεμάτιο ινών λευκής ουσίας ακριβώς κάτω από την ομάδα ινών του τοξοειδούς δεματίου και με κατεύθυνση από τον κροταφικό πόλο προς τον βρεγματικό και ινιακό λοβό. Αναγνωρίσθηκαν τρία συγκεκριμένα τμήματα του δεματίου τα οποία κατηγοριοποιήθηκαν σε σχέση με το πρότυπο συνδεσιμότητας τους.

ΣΥΜΠΕΡΑΣΜΑΤΑ

Με την βοήθεια της τεχνικής διαχωρισμού της λευκής ουσίας κατά Klingler έγινε δυνατή η λεπτομερής περιγραφή της αρχιτεκτονικής των δεματίων που εντοπίζονται στο ινιακό λοβό και τα οποία συμμετέχουν στην συνδεσιμότητα και ως εκ τούτου στην λειτουργική απαρτίωση του ανθρώπινου εγκεφάλου. Πιο συγκεκριμένα το δεμάτιο δίκην ελκήθρου φαίνεται να συμμετέχει στην σύνδεση περιοχών που συσχετίζονται και ευοδώνουν την επιτυχημένη πλοήγηση του ατόμου στο χώρο ενώ το μέσο επίμηκες δεμάτιο φαίνεται να συσχετίζεται με την απαρτίωση των ακουστικών ερεθισμάτων, εφόσον οι περιοχές που συνδέει παρουσιάζουν αυτήν την λειτουργική εξειδίκευση.

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION TO THE SUPERFICIAL ANATOMY OF THE OCCIPITAL LOBE

The occipital lobe has attracted particular scientific interest since the second half of the 19th century. Indeed, different techniques have been implemented to approach the anatomo-functional correlates of this highly eloquent area. Initially, Brodmann (1909), Economo and Koskinas (1925) focused on the cytoarchitectonic organization. The classification of the occipital cortex into Brodmann areas 17, 18 and 19 applies to date.(1) During the following years, neurophysiological studies in non-human primates picked up the torch. These studies identified distinct functional units in the occipital cortex. In the era of functional imaging, the interest shifted towards the delineation of equivalent areas in the human brain. This led to the identification of analogous areas in the human occipital lobe and to the notion that no strict anatomo-functional correlation exists (2-5).

Cunningham and Elliot Smith were the first to conduct anatomical studies during the late 19th and early 20th century(6, 7). For many decades, the efforts to achieve a more precise understanding of the anatomy of the occipital lobe, were mainly limited to the description of the most prevalent landmarks such as the calcarine fissure and the parieto-occipital sulcus. In the mid and late 20th century, less prominent structures such as the lunate sulcus which corresponds to the Affenspalte of the non-human primate brain, drew special attention(8). It wasn't until 1990 that Ono and colleagues presented a detailed description of the occipital area in their textbook "Atlas of the cerebral sulci"(9). Since then a limited number of studies attempted to systematically record and categorize the morphological features of the occipital region.

However, the available literature on the surface morphology of the occipital lobe remains vague on mainly two topics. First, there is a lack of a unified classification and universally accepted definitions, as is the case in the frontal, temporal and parietal areas. This is evident in modern neuroanatomical textbooks that are devoid of a thorough description of this area referring to it as irregular and highly variable. Second, the nomenclature used in different studies regarding the occipital region is often inconsistent, overlapping and conflicting and thus creates further confusion to the reader.

We therefore set out to accomplish a systematic and detailed description of the morphology and topography of the occipital lobe through a focused anatomic study and to compare our findings to current literature with the overarching goal to pave the way for a universally accepted terminology for clinical and anatomical use.

1.2 INTRODUCING THE SLEDGERUNNER FASCICULUS

The recent revival of the white matter fiber dissection technique -first described by Klingler- and its incorporation not only to neuroanatomical education but also to neurocognitive research, in combination with the advent of sophisticated neuroimaging methods such as functional magnetic resonance imaging (fMRI) and diffusion tensor imaging (DTI) have led to a more profound understanding of the brain connectivity and anatomo-functional organization (10-12) (13, 14) (15) (16) (17) (18) (19, 20) (21, 22) (23). The coining of the modern concept of brain hodotopy (deriving from the Greek words hodos meaning road, pathway and topos meaning place) moves away from the classical localizationist view and introduces a new model of perceiving cerebral function not only as a cortical phenomenon but as an integral cortico-subcortical epiphenomenon (24, 25) (26) (27) (28) (29) (30) (31) (32). In other words, apart from an intact cortical organization, the integrity of the white matter axonal connectivity is essential to cerebral physiology and function.

Since brain anatomy and function are tightly and reciprocally connected, a special interest has aroused over the past few years regarding the intricate morphology and architecture of white matter pathways previously described in core neuroanatomical texts, aiming not only to refine anatomical knowledge but mainly to improve our understanding of cerebral connectivity and function (11, 12) (19, 20) (33) (34). Recent literature has thus revisited the subcortical anatomy of various, eloquent and non-eloquent fiber tracts by using white matter dissections and DTI techniques with the overarching goal to combine the extracted evidence with functional data, thus providing a refined concept of brain organization (10) (11, 12) (35-38) (15, 16) (39) (17) (18) (19, 20) (21, 22, 24, 25) (26, 27) (33) (34) (40, 41) (23)

In this regard, we opted to investigate, through cadaveric fiber microdissections and an vivo DTI study, the structural architecture of a recently identified fiber tract known as the “sledge runner fasciculus” (42) (43) (44) (45) (Gungor et al. 2017; Vergani et al. 2014; Baydin et al. 2017; Beyh et al. 2017). This white matter pathway has been allegedly implicated in the axonal connectivity of high level cortical areas, such as the parahippocampal place area (PPA) and posterior cingulate or retrosplenial cortex (PCC-RSC), which represent key hubs of the neural circuit underlying the cognitive ability of spatial navigation and visuospatial imagery (46) (47-51) (52) (53, 54) (55) (56) (57) (45). Indeed, meticulous neuropsychological assessment of patients harbouring posterior circulation infarcts with posterior parahippocampal and/or retrosplenial area damage indicates increasing difficulty or even inability of these individuals to identify large scale scenes, such as landscapes or cityscapes, and further inability of proper self-navigation and way finding in familiar environments (56) (58) (59) (60) (61) (62) (63) (64) (65) (66). In this study, we provide anatomic and imaging data on the topography, morphology and axonal connectivity of the sledge runner fasciculus (SRF) using the Klinger's dissection technique and DTI tractography on publicly available dataset from the Human Connectome Project. Our overarching goal is to clarify the intricate subcortical architecture of this recently identified white matter tract believed to subserve spatial navigation and visuospatial imagery.

1.3 INTRODUCING THE MIDDLE LONGITUDINAL FASCICULUS

Anatomical investigations by early scientists have sparked interest in cerebral subcortical anatomy and paved the way for a fundamental change in our perception of the white matter; from being regarded as an amorphous mass, to actually represent a complex network of tracts that interconnect adjacent and distant cortical and subcortical areas (67). Later, the introduction of Klingler's technique refined the anatomical investigation of white matter microstructure through the fixation of brains in a formalin solution followed by a freeze-thaw process, which facilitates meticulous dissections and enhances the delineation of fiber pathways (13, 14). Further, the recent advent of diffusion-weighted magnetic resonance imaging has allowed for a fast and non-invasive investigation of the white matter architecture *in vivo* and has provided valuable insights on the intrinsic white matter anatomy and its 3D representation (10, 68-72).

From a functional standpoint, evidence from stroke studies combined with data stemming from pathologic processes mainly affecting white matter structures, such as multiple sclerosis, have led to the appreciation of a broad clinical significance of the cerebral white matter (73, 74). Keeping with this, functional neuroimaging (75-78) and human brain mapping studies (32, 79-83) reflect the concept of a cortico-subcortical correlation and integration, thus emphasizing on a hodotopical network approach to understand higher cerebral processing (31, 84). To this end, advances in decoding the anatomical basis of cerebral processing along with the availability of the non-invasive diffusion tensor imaging (DTI) technique, led to a special research interest on the white matter architecture and brain connectivity. Due to specific technical limitations of DTI and tractography, data had to be validated through classical anatomic descriptions of white matter tracts (85, 86) or alternatively be compared to relevant studies on non-human primates (87). However, especially with regard to novel tracts, neither of the two aforementioned approaches seems to be accurate (88, 89). Hence, the Klingler's technique is currently considered the gold standard method through which DTI results can be verified (16).

We therefore opted to study through a combined approach entailing white matter anatomic dissections and DTI tractography the architecture of a fiber tract known as the Middle Longitudinal Fasciculus (MdLF). Although this bundle was originally described in macaque monkeys by Seltzer and Pandya in 1984 (90), it was not until 2009 that Makris et al provided preliminary supporting DTI evidence of its existence and connectivity in the human brain (91). Further DTI studies that aimed to enhance our knowledge on MdLF subcortical architecture introduced ambiguity instead by suggesting more sophisticated but at the same time conflicting connectivity patterns (92-97). In the same vein, discrepancy remains even in the two available studies that employed microanatomic techniques to explore the morphology and inherent configuration of the MdLF (98, 99).

Our objective was therefore to clarify the debatable anatomical characteristics of the MdLF through focused dissections augmented by a tailored DTI protocol. Dissections was the core analysis approach of our study and DTI was used as a complementary method which was applied on an independent sample of healthy adults from the publicly available dataset of the Human Connectome Project (http://humanconnectome.org). In addition, we provide a review of the pertinent anatomo-tractographic literature with the overarching goal to compare our findings with current data and further provide insights on the MdLF structure to function relationship.

CHAPTER 2:
MATERIALS & METHODS

2.1 MATERIALS AND METHODS: GENERAL CONSIDERATIONS

For the purposes of the current study a total of thirty (30) healthy adult hemispheres belonging to the Department of Anatomy of the Medical School of the University of Athens and the Microneurosurgery Laboratory of the Department of Neurosurgery of Evangelismos Hospital have been studied. All specimens have been obtained from specialized centers for the preparation and provision of anatomical specimens after self-consent or consent from the next-of-kin. Approval from the Bioethics Committee of the National and Kapodistrian University of Athens has been obtained (21.05.2019 – Reference Number 118).

All specimens have been processed through the Klingler's technique that entails fixation in 15% formaldehyde, removal of the dura, the arachnoid and the vessels and freezing in -15 C for a period of at least 15 days. Subsequently, the hemispheres remain under running water for a period of several hours. Due to the freezing procedure, the formaldehyde crystals naturally divide the white matter fibers and allow for an easier and more effective dissection process under the surgical microscope.

The superficial anatomy of the areas typically corresponding to the primary motor, premotor and non-primary motor cortex –as described above- have been meticulously observed and recorded prior to the dissection process. Hence, the morphology of the central sulcus, the precentral sulcus, the precentral gyrus, the posterior frontal area, the paracentral lobule and the posterior part of the medial frontal gyrus has been recorded.

Following this, the hemispheres have been dissected in both lateral to medial and medial to lateral tandem fashion under an OPMI Zeiss Plus surgical microscope and using various fine surgical micro-instruments including microforceps, microscissors and microdissectors. During the lateral to medial stage of the dissection process the anatomy of the Frontal Longitudinal System(FLS) the Frontal Aslant Tract(FAT) and the Frontostriatal/Frontocaudate tract(FCT) has been revealed. In the medial to lateral phase of the dissections the fibers of the dorsal component of the Superior Longitudinal Fasciculus(SLF I) and the Corticotegmental tract(CTT) as well as the fibers of the Corticospinal Tract(CST) have been revealed and recorded. The particularities and technical aspects of the dissection of each fiber tract are extensively described in the following paragraphs.

During each stage of the dissection multiple pictures from various angles have been obtained to adequately illustrate the relevant anatomy.

2.2 DISSECTION TECHNIQUE: SLEDGERUNNER FASCICULUS

Twenty (20) normal, adult, cadaveric cerebral hemispheres (11 right hemispheres – 9 left hemispheres) obtained from 20 different cadavers previously fixed in a 10% -15% formalin solution for a minimum period of 8 weeks, were investigated. Following careful removal of the arachnoid membrane and vessels, all specimens underwent the Klingler’s procedure (freeze-thaw process) and were subsequently investigated using the fiber dissection technique and the microscope (Carl Zeiss OPMIR Plus, Carl Zeiss AG, Oberkochen, Germany) (13, 14) (18) (23).

Given that the Sledge Runner fasciculus lies in the depth of the medial and medio-basal occipital lobe (42) (43) (44), we opted to perform regional (confined to the occipital lobe), microanatomic dissections in a medial to lateral direction in all twenty (20) hemispheres.

The regional sulcal anatomy consisting of the parieto-occipital sulcus (demarcating the precuneus and isthmus of the cingulate gyrus from the cuneus), calcarine fissure (demarcating the cuneus from the lingual gyrus) and their common stem (demarcating the lingual and posterior parahippocampal gyri from the isthmus of the cingulate gyrus) the collateral sulcus (demarcating the parahippocampal from the fusiform gyrus) and sub-parietal sulcus (demarcating the isthmus of the cingulate gyrus from the precuneus) were readily identified in all specimens (Fig. 1). The fiber microdissections were initially focused on the area of the cuneus and lingual gyrus and were further extended to the adjacent cerebral region of the cingulate isthmus, posterior half of the precuneus and posterior part of the parahippocampal gyrus with the aim to study and record the morphology, topography and dimensions of the sledge runner fasciculus (Fig. 2). Special emphasis was also placed on the correlative anatomy of the sledge runner fasciculus with the sulci gyri, adjacent white matter pathways and ventricular compartments.

The dissection tools used consisted of fine metallic periosteal elevators, various sized anatomical forceps, and micro-scissors (23, 34) (Koutsarnakis et al. 2015; Koutsarnakis et al. 2016). Numerous photographs were obtained during cadaveric dissections in order to illustrate the regional cortical and subcortical anatomy of interest. Of note is that the dissection photos included in this study have not been edited by picture enhancing software so that they closely resemble the anatomy encountered during standard fiber micro-dissections in the setting of a microneurosurgery laboratory (23, 34) (35-38).

2.3 DISSECTION TECHNIQUE: MIDDLE LONGITUDINAL FASCICULUS

Twenty adult, normal, cadaveric cerebral hemispheres (9 right hemispheres-11 left hemispheres) obtained from 20 different cadavers previously fixed by immersion in a 10–15% formalin solution for a minimum period of 8 weeks were included. Following careful removal of the arachnoid membrane and vessels, the specimens were initially refrigerated at temperatures between -10 to -15 for 15 days and were then allowed to thaw under running water for several hours (Klingler or freeze-thaw procedure).

Subsequently, all cerebral hemispheres were investigated using the fiber dissection technique and the operating microscope (Carl Zeiss OPMIR Plus, Carl Zeiss AG, Oberkochen, Germany) (Klingler 1935; Klingler and Ludwig 1956; Koutsarnakis et al. 2015; Martino et al. 2011; Ture et al. 2000).

According to current literature, the MdLF runs in the lateral aspect of the hemisphere and participates in the axonal connectivity of the superior temporal gyrus (STG) and the parietal and occipital lobes (92) (95) (98) (96) (100) (93, 94). We therefore performed lateral to medial anatomic dissections with special emphasis on the aforementioned area. In order to better illustrate the subcortical correlative anatomy, we further dissected the entire temporal lobe, insula and fronto-parietal operculum. Prior to the dissection process, the sulcal and gyral anatomy of the lateral aspect of the hemisphere was recorded in detail.

CHAPTER 3: RESULTS

3.1 RESULTS: SUPERFICIAL ANATOMY

The superficial morphology of the occipital lobe was categorized into 4 different sub-regions based on the findings of previous studies, allowing for a better understanding of the most prominent and consistent anatomical landmarks of this highly variable area. Our results are summarized in Table 1.

3.1.1 AREA OF THE OCCIPITAL POLE

The occipital pole represents the most posterior aspect of the hemisphere and the area of convergence of the superior and inferior occipital gyri. The distance measured between the occipital pole and the pre-occipital notch varied from 40 to 56mm (average 48mm). Four sulci and one gyrus were systematically recorded in the area of the occipital pole (Fig1).

More specifically:

Lunate sulcus

The lunate sulcus is a crescent-shaped, vertical oriented sulcus with its concavity facing the occipital pole. It was recorded in 64% (21/33) of the specimens. In 54% (18/33) of them it was identified as a deep and continuous sulcus while in 9% (3/33) it was interrupted and shallow. In 6% (2/33) of cases it was seen to originate either from the inferior part of the transverse sulcus or from the posterior part of the lateral occipital sulcus. In 9% the lunate sulcus gave rise to a small branch, which was seen to run posteriorly and perpendicular to the main stem. This branch typically emerged from the mid-portion of the lunate sulcus. In 6% (2/33) of the hemispheres the sulcus was encountered on the basal occipital surface.

Transverse occipital sulcus

The transverse occipital sulcus is a relatively constant (present in 29/33 of the studied hemispheres) vertical sulcus, typically arising at the end of the intraoccipital sulcus. The intraoccipital-transverse sulcal meeting point divides this sulcus into a superior and inferior segment. The mean length of the superior and inferior sulcal segments was 19mm 21mm respectively. In 60% of cases the sulcus did not exhibit any branches, while in 40% it was recorded to have 1 to 4 branches running perpendicular to the main

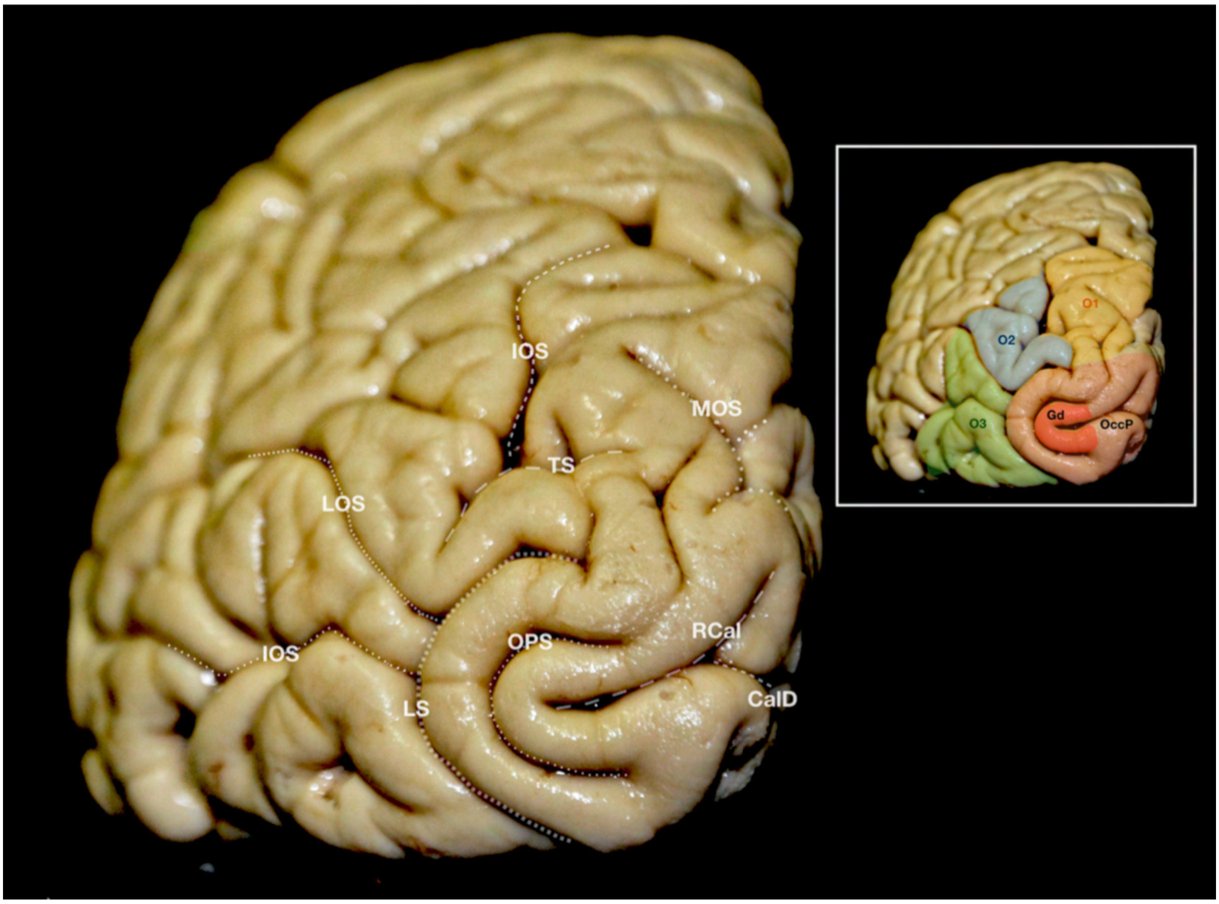

FIG3.1 Surface Anatomy of the Occipital Pole.

A posterior view of a left cerebral hemisphere illustrating the superficial anatomy of the occipital pole. The bifid termination of the calcarine sulcus, namely the retrocalcarine sulcus can be identified. Anterior to the retrocalcarine sulcus, the occipitopolar, lunate and transverse sulci are demarcated with their concavities facing towards the pole. The marginal occipital, intraoccipital, lateral occipital and inferior occipital sulci are also illustrated.

Inset: The gyral morphology on the same specimen is illustrated. The Superior(O1), Middle(O2) and Inferior Occipital Gyri are highlighted in orange, blue and green color respectively. The area of the Occipital Pole is highlighted in light orange color. The Gyrus Descendens, delineated by the occipitopolar and retrocalcarine sulci, is highlighted in dark orange color. CalD = Distal part of the Calcarine Sulcus; GD = Gyrus Descendens; IOS = Inferior Occipital Sulcus; LOS = Lateral Occipital Sulcus; LS = Lunate Sulcus; MOS = Marginal Occipital Sulcus; O1 = Superior Occipital Gyrus; O2 = Middle Occipital Gyrus; O3 = Inferior Occipital Gyrus; OccP = Occipital Pole; OPS = Occipitopolar sulcus; RCal = Retrocalcarine Sulcus; TS = Transverse Occipital Sulcus. Reprinted from Koutsarnakis et al. Permission granted from Springer-Verlag GmbH Germany, part of Springer Nature, Neurosurgical Review

stem and usually merging with the lunate or the marginal occipital sulcus. The transverse occipital sulcus was observed to intersect the lateral occipital sulcus in 12% (4/33) and the lunate sulcus in 3% (1/33) of the hemispheres. It was seen to extend to the superomedial aspect of the occipital lobe in 6% of cases (2/33).

Retrocalcarine sulcus

This sulcus appears as the terminal bifurcation of the calcarine fissure. It was detected in 12% (4/33) of cases, exhibiting a left side preponderance of 75% (3/4 cases). It was encountered either anterior to the occipital pole on the medial aspect (75%) or at the level of the apex of the occipital pole (25%).

Occipitopolar sulcus

The occipitopolar sulcus was identified in 24% (8/33) of the studied hemispheres. This small crescent-shaped sulcus appears as a short and shallow indentation encountered posterior and parallel to the lunate sulcus.

Gyrus descendens

The gyrus descendens was detected in 9% (3/33) of the hemispheres, when both the retrocalcarine and occipitopolar sulci were present. This gyrus appears as a thin cortical strip between the two aforementioned sulci, lying just anterior to the apex of the occipital pole.

3.1.2 ANATOMY OF THE MEDIAL OCCIPITAL SURFACE

The medial aspect of the occipital lobe is delineated anteriorly by the parieto-occipital sulcus and superiorly by the free margin of the hemisphere (or the marginal occipital sulcus when it is present). Inferiorly, the medial and basal surface of the occipital lobe seem to be in continuity. Therefore, the superior part of the lingual gyrus resides in the medial surface while its inferior part to the basal surface. The medial occipital surface includes the cuneal and lingual gyri. The calcarine fissure and the parieto-occipital sulcus are the most consistent and prominent landmarks in this area. (Fig2)

Calcarine Sulcus

The calcarine sulcus is a consistent sulcus and originates at the level of the isthmus of the cingulate gyrus. It was seen to exhibit a postero-superior trajectory, reaching the area of the occipital pole. Four different morphological patterns were observed (Fig6) with the most common being that of an “M shaped” (23/33) or reverse V-shaped (6/33) morphology. An incomplete (1/33) as well as an “S- shaped” (3/33) pattern were also encountered. The calcarine sulcus appeared as a complete and continuous sulcus in 91% (30/33) of the studied hemispheres. In one case, the sulcus was interrupted and consisted of two individual sulci. A number of 1-5 rami were recorded to branch off the stem of the calcarine fissure in 67% (22/33) of the cases. These branches, known as the paracalcarine sulci, travel for a short distance on the lingual and/or the cuneal gyri.

The calcarine sulcus was observed to meet the parieto-occipital sulcus in all studied cases. This sulcal meeting point known as the Cuneal Point, defines the transition between the proximal and distal part of the calcarine sulcus. In 6% (2/33) of cases the caudal collateral sulcus bents towards and meets the distal part of the calcarine sulcus. In 79% (20/33) of the specimens the calcarine sulcus reaches and projects to the lateral cerebral surface. In 12% (4/33) it was recorded to exhibit a bifid termination, giving rise to the retrocalcarine sulcus.

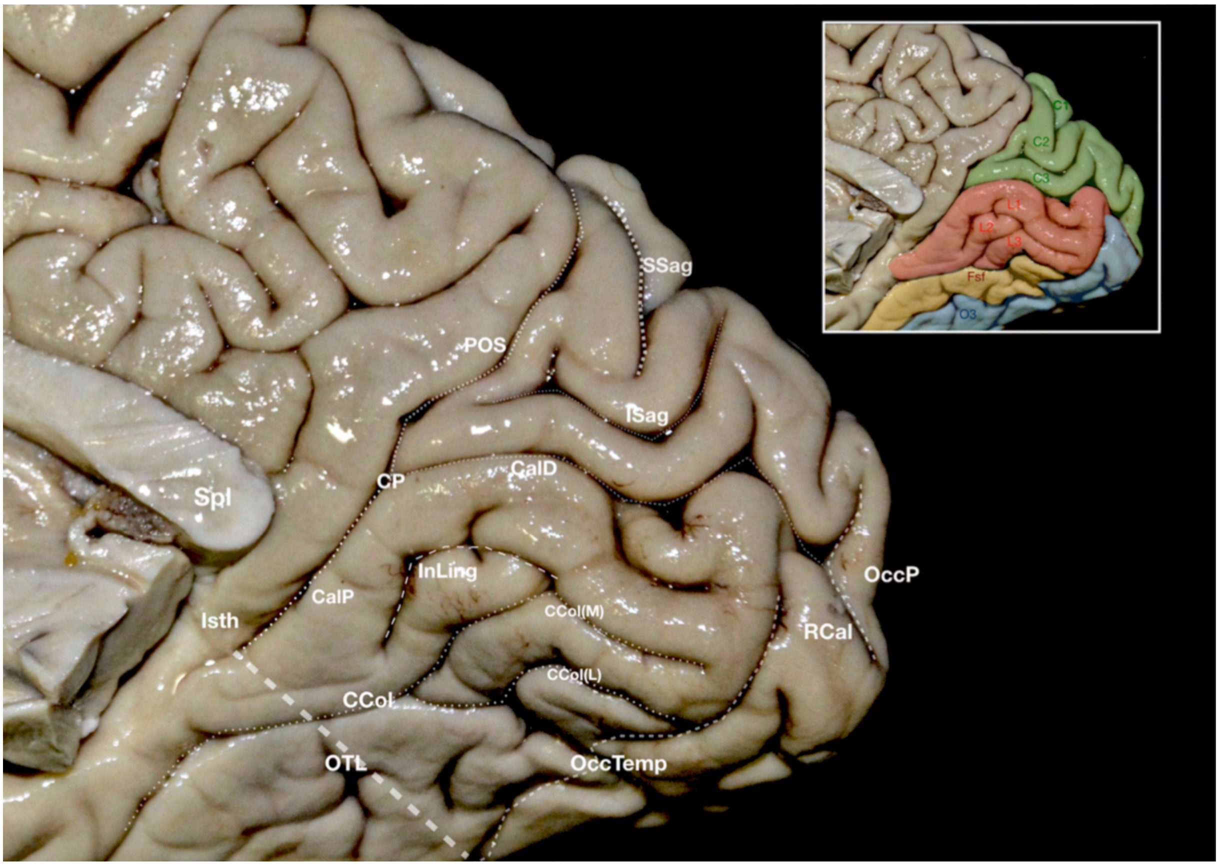

FIG 3.2. Surface Anatomy of the Medial and Basal Occipital area.

Medial view of a right cerebral hemisphere. The Occipitotemporal line, that is the anterior border of the basal Occipital surface, connecting starting point of the proximal part of the Calcarine sulcus to the Preoccipital Notch is illustrated. The Parieto-occipital and the Calcarine Sulci can be easily identified. Their intersection, known as the Cuneal Point, divides the Calcarine Sulcus into a proximal and a distal part. A superior and an inferior sagittal sulcus divide the cuneus into three gyri. Inferior to the calcarine sulcus, the Lingual Gyrus is indented by an intralingual sulcus that arises from the posterior part of the collateral sulcus, namely the Caudal Collateral Sulcus. Lateral to the Collateral Sulcus the Posterior Occipitotemporal Sulcus is seen. These two sulci demarcate the Fusiform Gyrus.

Inset: The gyral morphology is illustrated with the green color for the Cuneus, red color for the Lingual Gyrus, orange color for the Posterior Fusiform Gyrus and blue color for the Inferior Occipital Gyrus(O3). The Cuneus is divided by the sagittal sulci into a superior(C1), middle(C2) and inferior(C3) cuneal gyrus. Likewise, the intralingual sulcus divides the lingula into a superior(L1), a middle(L2) and an inferior(L3) lingual gyrus.

C1 = Superior Cuneal Gyrus; C2 = Middle Cuneal Gyrus; C3 = Inferior Cuneal Gyrus; CalD = Distal Part of the Calcarine Sulcus; CalP = Proximal Part of the Calcarine Sulcus; CCol = Caudal Collateral Sulcus; CCol(L)= Lateral branch of the caudal collateral sulcus; CCol(M) = Medial branch of the caudal collateral sulcus; CP = Cuneal Point; Fsf = Posterior Fusiform Gyrus; InLing = Intralingual Sulcus; ISag = Inferior Sagittal Sulcus of the Cuneus; Isth = Isthmus of the Cingulate Gyrus; L1 = Superior Lingual Gyrus; L2 = Inferior Lingual Gyrus; O3 = Inferior Occipital Gyrus; OccP = Occipital Pole; OccTemp = Posterior Occipitotemporal Sulcus; OTL = Occipitotemporal Line; POS = Parieto-occipital Sulcus; RCal = Retrocalcarine Sulcus; Spl = Splenium of the corpus callosum; SSag = Superior Sagittal Sulcus of the Cuneus. Reprinted from Koutsarrnakis et al. Permission granted from Springer-Verlag GmbH Germany, part of Springer Nature, Neurosurgical Review

Parieto-occipital Sulcus

The parieto-occipital sulcus (POS) is a constant (100% of the studied hemispheres) sulcus, seen to originate in the retro-splenial area. It exhibits a postero-superior trajectory reaching the lateral surface in 91% (30/33) of cases. In 7 hemispheres, the external perpendicular fissure was seen to intersect with the intraparietal-intraoccipital sulcal meeting point. In 82% (27/33) of the specimens the POS was recorded to exhibit 1 to 5 sulcal branches directed towards the cuneus.

Cuneal Sulci

The cuneal sulci were prominent and deep in 91% (30/33) of the specimens while in the remaining 9% (3/33) they were shallow, randomly orientated and fragmented, thus creating a non-typical anatomy. In 24% (8/33) of the hemispheres, two (2) cuneal sulci were identified whereas in 12% (4/33) three (3) or more sulci were obvious (Fig5). The most frequent of these sulci, was the inferior sagittal sulcus, which runs parallel and slightly superior to the distal part of the calcarine fissure (Fig2, Fig5). In one case this sulcus was seen to emerge as a dorsal branch of the calcarine fissure. The second most consistent sulcus encountered was the superior sagittal sulcus, exhibiting a trajectory that was parallel or oblique with regard to the parieto-occipital sulcus.

Interestingly, in 85% (28/33) of the studied specimens we identified and recorded, for the first time in the relevant literature, a sulcus seen to run in a parallel trajectory to the interhemispheric fissure and to reside at the margin of the cuneus and the superior occipital gyrus. It exhibits a straight, H-shaped or T-shaped configuration and its mean length is 33mm (range 28-37mm). We named this sulcus the “marginal occipital sulcus” after its specific topography (Fig7).

Lingual Gyrus

The lingual gyrus is demarcated superiorly by the calcarine fissure and inferiorly by the trunk or the medial branch of the posterior collateral sulcus. In 91% (30/33) of the specimens the lingual gyrus exhibits a continuous morphology while in 9% (3/33) it was interrupted by 1 or 2 intralingual sulci. When present, these sulci divide the lingual gyrus into a superior and inferior segment (Fig2).

FIG3.3. Surface Anatomy of the Lateral Occipital Surface.

Posterolateral view of a right cerebral hemisphere. The Preoccipital Notch as well as the External Perpendicular Fissure demarcate the occipital from the parietal and temporal lobes. The Intaparietal – Intaoccipital sulcus transition point is defined by the lateral projection of the External Perpendicular Fissure. The Lateral Occipital Sulcus and the Intraoccipital Sulcus intersect with the Transverse Occipital Sulcus. The Inferior Occipital Sulcus runs parallel to the inferior margin of the hemisphere and meets the Lunate Sulcus. Posterior to the Lunate sulcus, the Occipitopolar and Retrocalcarine sulci are identified close to the occipital pole. The Anterior Occipital Sulcus in this specimen is seen to run vertically to the occipitotemporal transition area.

Inset: The Gyral morphology of the lateral aspect of the occipital lobe is illustrated: The Superior(O1), Middle(O2) and Inferior(O3) occipital gyri are highlighted in yellow, blue and green color respectively.

The Superior (O1) and Inferior(O3) gyri can be seen merging in the area of the occipital pole(white arrow), while the Middle occipital gyrus presents with a more retracted configuration.

AOS = Anterior Occipital Sulcus; EPF = External Perpendicular Fissure; InOS = Inferior Occipital Sulcus; IOS = Intraoccipital Sulcus; IPS = Intraparietal Sulcus; LOS = Lateral Occipital Sulcus; LS = Lunate Sulcus; OPS = Occipitopolar Sulcus; PON = Preoccipital Notch; RCal = Retrocalcarine Sulcus; TS = Transverse Occipital Sulcus.

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3.1.3 ANATOMY OF THE BASAL OCCIPITAL SURFACE

The basal occipito-temporal surface is a large area divided by the arbitrarily defined occipito-temporal line into a temporal and an occipital part. This straight imaginary line connects the starting point of the proximal part of the calcarine fissure to the preoccipital notch (101-104). The preoccipital notch corresponds to a deep indentation of the inferolateral border of the hemisphere, located approximately 5cm anterior to the occipital pole and separating the temporal from the occipital lobe.(102, 105). Laterally, the basal occipital surface extends up to the inferior margin of the hemisphere while medially it is continues as the medial occipital surface. In this area two prominent sulci and three gyri can be identified, namely the posterior occipitotemporal sulcus, the posterior collateral sulcus, the ventral aspect of the lingual gyrus, the posterior fusiform gyrus and the ventral part of the inferior occipital gyrus. (Fig4)

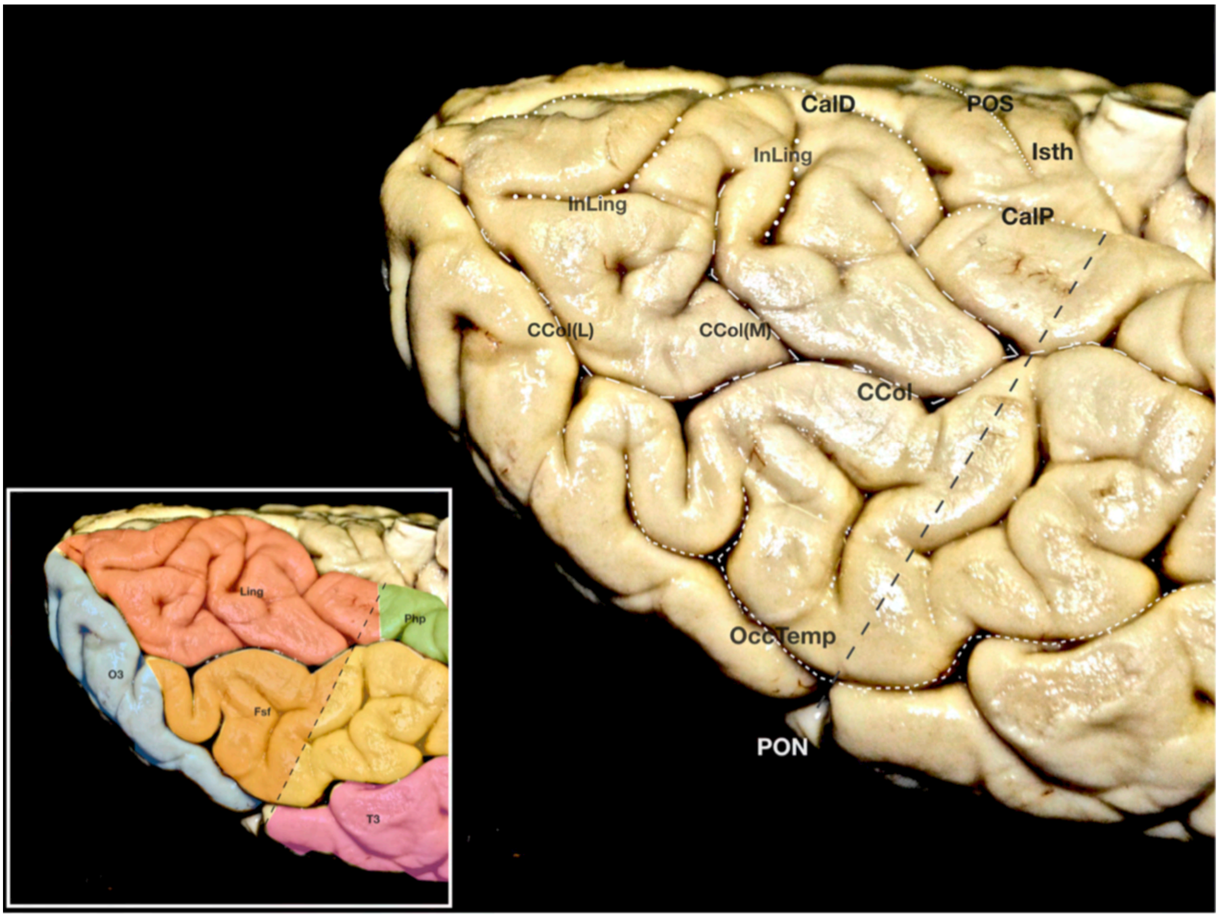


FIG 3.4. Standard superficial anatomy of the basal occipital surface.

Inferior view of a left cerebral hemisphere. The basal surface of the occipital lobe is anteriorly delineated by the Occipitotemporal line (black dashed line) connecting the starting point of the proximal Calcarine sulcus to the Preoccipital Notch. The Caudal Collateral Sulcus gives off a medial and a lateral branch. The posterior occipitotemporal sulcus is seen. In this specimen two vertical intralingual sulci travel on the surface of the lingual gyrus.

Inset: The gyral morphology of the basal temporo-occipital area is illustrated. The lingual gyrus(red), the posterior fusiform gyrus(orange), the inferior occipital gyri(blue), the parahippocampal gyrus(green), the anterior fusiform gyrus(yellow) as well as the inferior temporal gyrus(purple) are depicted.

CCol = Caudal Collateral Sulcus; CCol(L) = Lateral branch of the Caudal Collateral Sulcus; CCol(M) = Medial Branch of the Caudal Collateral Sulcus; Fsf = Fusiform Gyrus; InLing = Intralingual sulcus; Isth =

Isthmus of the cingulate sulcus; Ling = Lingual Gyrus; O3 = Inferior Occipital Gyrus; OccTemp = Occipitotemporal Sulcus; Php = Parahippocampal gyrus; PON = Preoccipital Notch; T3 = Inferior Temporal Gyrus. Reprinted from Koutsarrnakis et al. Permission granted from Springer-Verlag GmbH Germany, part of Springer Nature, Neurosurgical Review

Posterior Occipitotemporal Sulcus

The occipito-temporal sulcus is a constant and prominent horizontal sulcus indenting the basal temporo-occipital surface. It can be divided into an anterior (temporal) and a posterior (occipital) part by the temporo-occipital line. The posterior part had a complete and continuous sulcal trajectory in 67% (22/33) of the specimens while in the remaining 33% (11/33) it was interrupted. In one hemisphere, the occipitotemporal sulcus appeared as the posterior continuation of the inferior temporal sulcus. In 24% (8/33) of cases the sulcus was seen to deviate medially meeting the caudal collateral sulcus. A maximum of 4 rami were recorded to branch off the sulcus, with the single-branch pattern being the most common one.

FIG 3.5. Gyral patterns of the Cuneus. Medial views of two left hemispheres.

LEFT: The calcarine and parieto-occipital sulci demarcate the cuneus. In this specimen only one sulcus running parallel to the calcarine, that is the inferior sagittal sulcus, can be identified. This sulcus divides the cuneus into two gyri: a superior cuneal and an inferior cuneal gyrus. INSET: The superior(C1) and inferior(C3) cuneal gyri are highlighted in green and red color respectively.

RIGHT: In this specimen two sulci, a superior sagittal and an inferior sagittal sulcus can be identified dividing the cuneus into a superior, middle and an inferior cuneal gyri. INSET: The superior(C1), middle(C2) and inferior(C3) cuneal gyri are highlighted in green, yellow and red color respectively.

POS = Parieto-occipital Sulcus; CalS = Calcarine Sulcus; Isag = Inferior Sagittal Sulcus of the Cuneus; SSag = Superior Sagittal Sulcus of the Cuneus; C1 = Superior Cuneal Gyrus; C2 = Middle Cuneal Gyrus; C3 = Inferior Cuneal Gyrus. Reprinted from Koutsarrnakis et al. Permission granted from Springer-Verlag GmbH Germany, part of Springer Nature, Neurosurgical Review

Caudal Collateral Sulcus

The caudal segment of the collateral sulcus runs on the medial aspect of the basal occipital surface. It either travels as a continuous sulcus or it bifurcates into a medial and lateral branch. The “continuous pattern” was seen in 67% (22/33) of the studied hemispheres while the “bifurcated pattern” was present in 33% (11/33) of them. We recorded up to 8 rami branching off the main trunk (continuous sulcal pattern) or the terminal branches of the posterior collateral sulcus. These branches most commonly indent the area of the lingual gyrus and are referred to as the “intralingual sulci”.

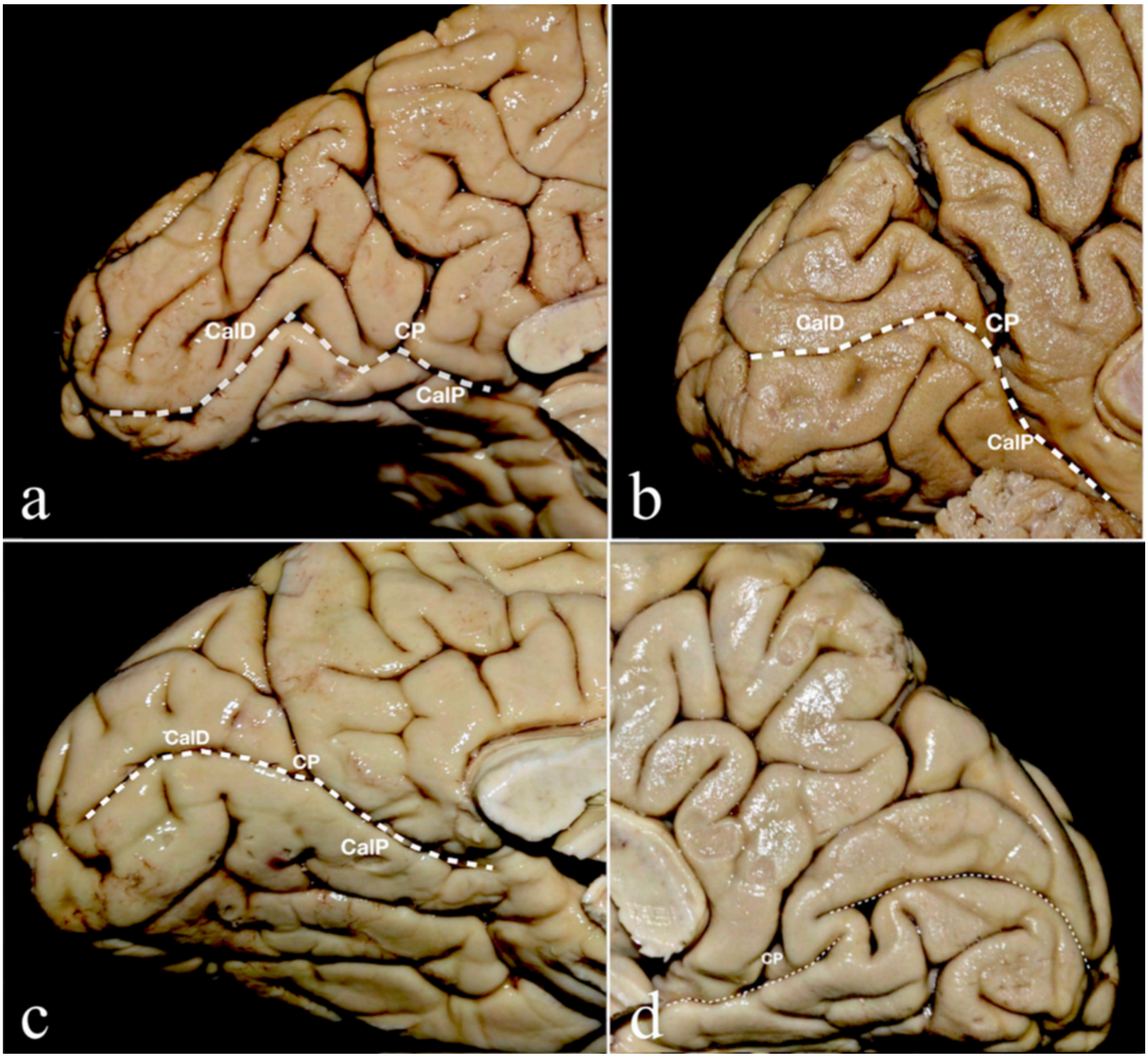


FIG3.6. Morphological patterns of the Calcarine Sulcus.

Medial view of three (3) left and one (1) right hemisphere illustrating the different patterns of the calcarine sulcus.

a: An M-shaped calcarine sulcus is seen. This configuration is the most prevalent consisting of two curves that point superiorly. The anterior curve points towards the Cuneal Point.

b: Here the calcarine sulcus has a reverse-V shaped with one curve pointing to the Cuneal Point.

c: An S-shaped calcarine sulcus consisting of a posterior and an anterior bend is illustrated.

d: A non-continuous pattern of the calcarine sulcus is depicted. This morphology is the least prevalent.

CalD = Distal Part of the Calcarine Sulcus; CalP = Proximal Part of the Calcarine Sulcus; CP = Cuneal Point. Reprinted from Koutsarrnakis et al. Permission granted from Springer-Verlag GmbH Germany, part of Springer Nature, Neurosurgical Review

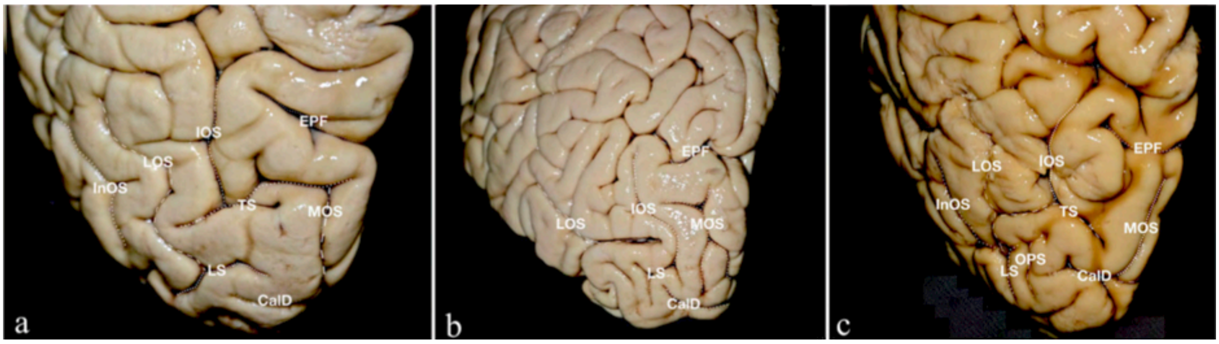


FIG7. Morphological patterns of the Marginal Occipital Sulcus. Posterosuperior views of three (3) left hemispheres.

a: Typical superficial anatomy of the occipital convexity. The Intraoccipital, Lateral occipital and Inferior occipital sulci can be identified. The Intraoccipital sulcus intersects with the Transverse occipital sulcus while the Lateral occipital sulcus meets the lunate sulcus. A T-shaped Marginal Occipital Sulcus is documented. A small sulcus connecting the Marginal occipital and the Transverse occipital Sulcus is also depicted.

b: In this specimen the Intraoccipital sulcus intersects with the lunate sulcus while the Transverse Occipital Sulcus is absent. Here the Marginal Occipital Sulcus has an “H” shape.

c: In this hemisphere, the Marginal Occipital Sulcus takes a straight trajectory and meets the distal part of the Calcarine sulcus. A prominent Occipitopolar sulcus is also apparent.

CalD = Distal part of the Calcarine Sulcus; EPF = External Perpendicular Fissure; InOS = Inferior Occipital Sulcus; IOS = Intraoccipital Sulcus; LOS = Lateral Occipital Sulcus; LS = Lunate Sulcus; MOS = Marginal Occipital Sulcus; OPS = Occipitopolar Sulcus; TS = Transverse Occipital Sulcus. Reprinted from Koutsarrnakis et al. Permission granted from Springer-Verlag GmbH Germany, part of Springer Nature, Neurosurgical Review

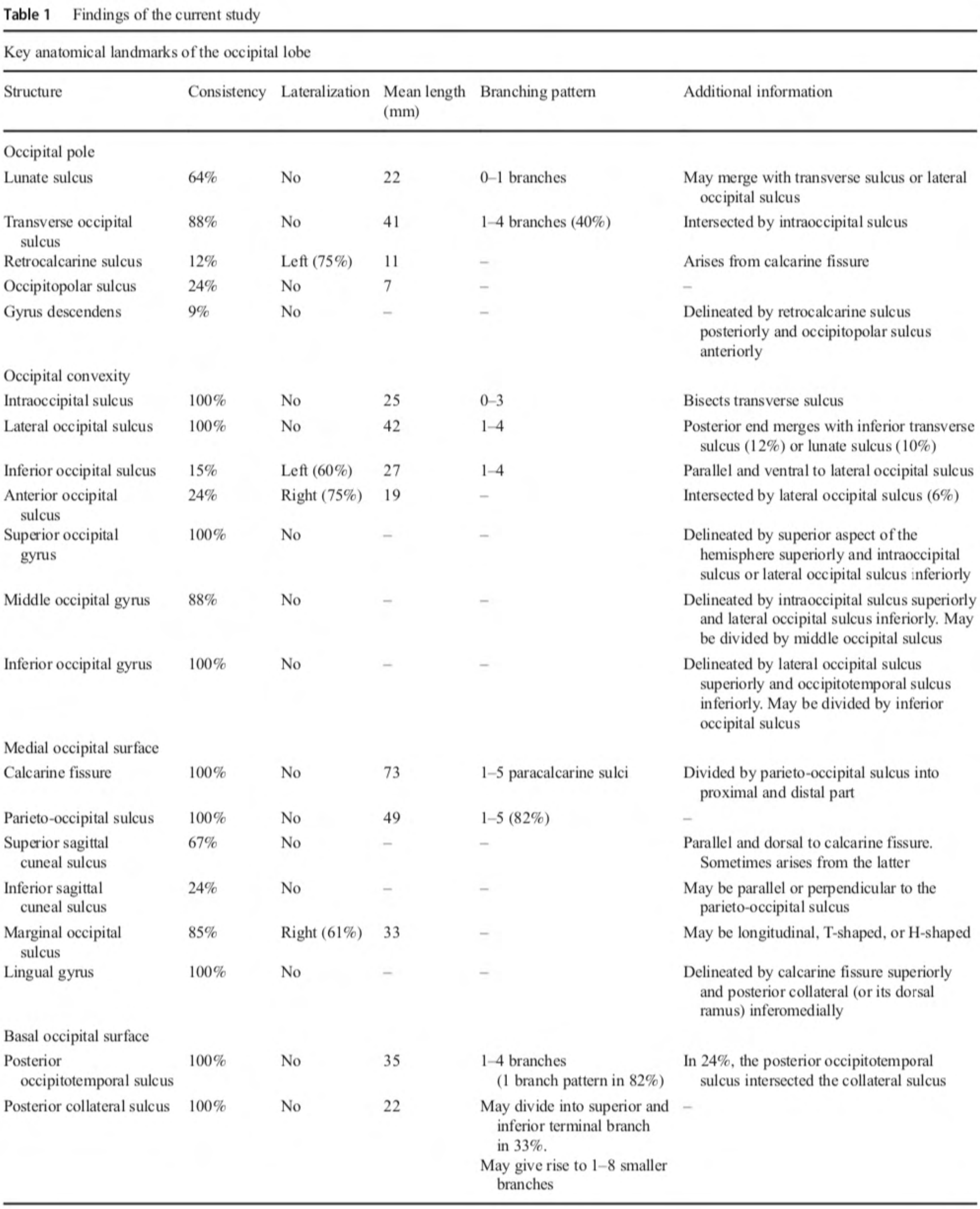


Table 1 Findings of the current study

Key anatomical landmarks of the occipital lobe

Structure	Consistency	Lateralization	Mean length (mm)	Branching pattern	Additional information
Occipital pole					
Lunate sulcus	64%	No	22	0–1 branches	May merge with transverse sulcus or lateral occipital sulcus
Transverse occipital sulcus	88%	No	41	1–4 branches (40%)	Intersected by intraoccipital sulcus
Retrocalcarine sulcus	12%	Left (75%)	11	–	Arises from calcarine fissure
Occipitopolar sulcus	24%	No	7	–	–
Gyrus descendens	9%	No	–	–	Delineated by retrocalcarine sulcus posteriorly and occipitopolar sulcus anteriorly
Occipital convexity					
Intraoccipital sulcus	100%	No	25	0–3	Bisects transverse sulcus
Lateral occipital sulcus	100%	No	42	1–4	Posterior end merges with inferior transverse sulcus (12%) or lunate sulcus (10%)
Inferior occipital sulcus	15%	Left (60%)	27	1–4	Parallel and ventral to lateral occipital sulcus
Anterior occipital sulcus	24%	Right (75%)	19	–	Intersected by lateral occipital sulcus (6%)
Superior occipital gyrus	100%	No	–	–	Delineated by superior aspect of the hemisphere superiorly and intraoccipital sulcus or lateral occipital sulcus inferiorly
Middle occipital gyrus	88%	No	–	–	Delineated by intraoccipital sulcus superiorly and lateral occipital sulcus inferiorly. May be divided by middle occipital sulcus
Inferior occipital gyrus	100%	No	–	–	Delineated by lateral occipital sulcus superiorly and occipitotemporal sulcus inferiorly. May be divided by inferior occipital sulcus
Medial occipital surface					
Calcarine fissure	100%	No	73	1–5 paracalcarine sulci	Divided by parieto-occipital sulcus into proximal and distal part
Parieto-occipital sulcus	100%	No	49	1–5 (82%)	–
Superior sagittal cuneal sulcus	67%	No	–	–	Parallel and dorsal to calcarine fissure. Sometimes arises from the latter
Inferior sagittal cuneal sulcus	24%	No	–	–	May be parallel or perpendicular to the parieto-occipital sulcus
Marginal occipital sulcus	85%	Right (61%)	33	–	May be longitudinal, T-shaped, or H-shaped
Lingual gyrus	100%	No	–	–	Delineated by calcarine fissure superiorly and posterior collateral (or its dorsal ramus) inferomedially
Basal occipital surface					
Posterior occipitotemporal sulcus	100%	No	35	1–4 branches (1 branch pattern in 82%)	In 24%, the posterior occipitotemporal sulcus intersected the collateral sulcus
Posterior collateral sulcus	100%	No	22	May divide into superior and inferior terminal branch in 33%. May give rise to 1–8 smaller branches	–

3.2 RESULTS: SLEDGERUNNER FASCICULUS

3.2.1 MICROANATOMIC DISSECTION

A medial to lateral microanatomic fiber dissection focused on the area of the cuneus, lingual gyrus, posterior half of precuneus, isthmus of the cingulate gyrus and posterior parahippocampal gyrus was employed in order to study and record the morphology, connectivity and correlative topographic anatomy of the sledge runner fasciculus (Fig. 1). Initially, peeling away the cortex of the aforementioned gyri exposes the arcuate or U fibers (Fig. 1). Progressive dissection of the regional U fibers reveals the Sledge Runner fasciculus along with fibers arching from the cingulum over the splenium of the corpus callosum (distal part of the superior arm and proximal part of the inferior arm of the cingulum). A distinct group of fibers exhibiting a vertical trajectory and encountered at the depth of the calcarine fissure correspond to the tract previously described by H.Sachs and known as “stratum calcarinum” (Fig. 2).

3.2.2 CONNECTIVITY AND MORPHOLOGY

The Sledge Runner fasciculus (SRF) was consistently identified as an oblique band of fibers travelling under the U-fibers of the medial surface of the occipital lobe, connecting the areas of the anterior cuneus, anterior half of the lingual gyrus, cingulate isthmus and posterior parahippocampal gyrus (Fig. 2). With respect to its trajectory and configuration, the SRF demonstrated a dorsomedial to ventrolateral direction with two medial curves - one at the level of the major forceps and the other at the inferior margin of the medial wall of the ventricular atrium- thus, creating its peculiar sled-like shape (Fig. 4). It was also consistently found to exhibit a superior narrow part, corresponding to the antero-superior part of the cuneus, which was seen to widen progressively as the tract descended towards the lingual gyrus (Fig. 4). The average length of the SRF was 4,9cm (range:4,7-5,2cm), while its average width was 1,7cm (range:1,3-2) at its narrowest and 2,1cm (range: 1,8-2,5) at its widest part.

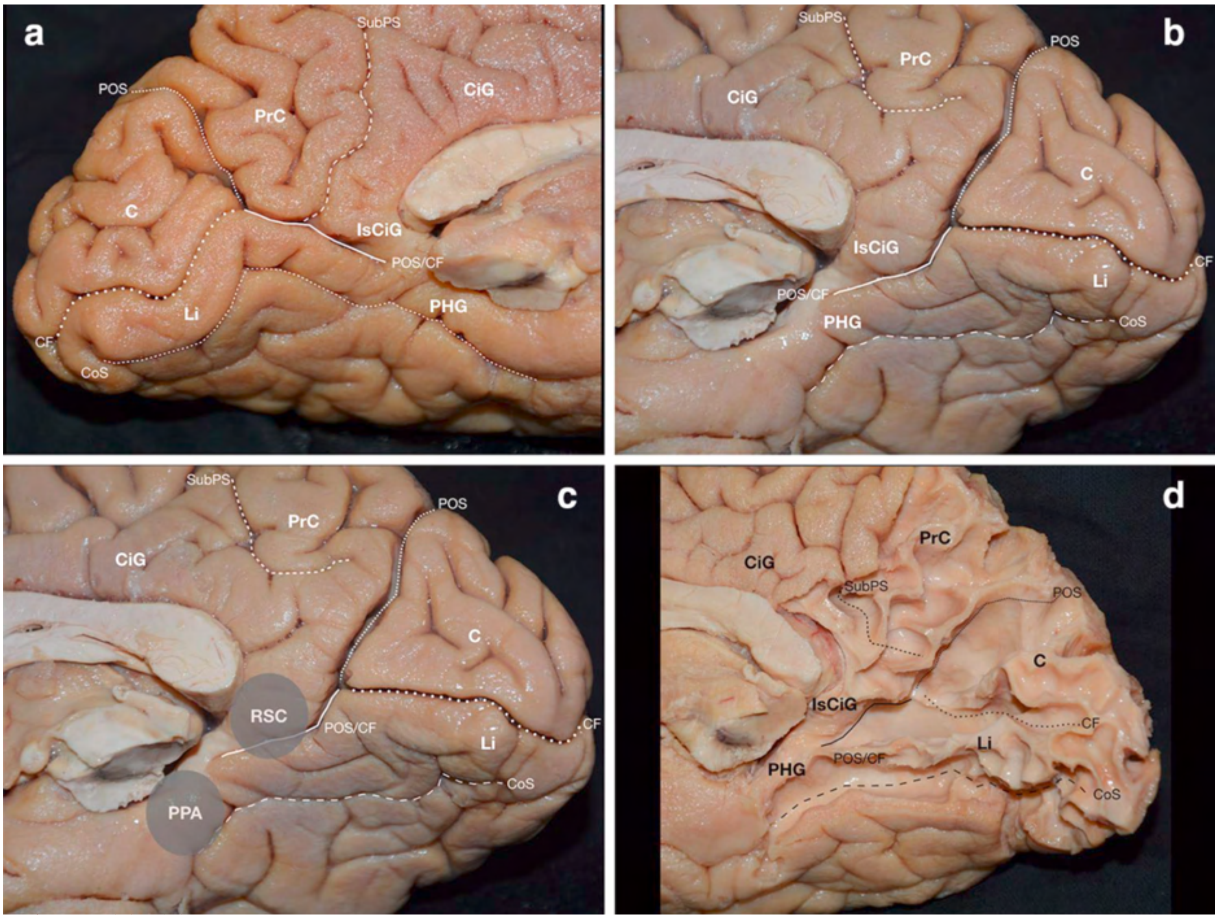


Fig. 3.7(a), (b). Sulcal and gyral anatomy of the medial and basal cerebral surface of a left (a) and right (b) hemisphere. The parieto-occipital sulcus (demarcating the precuneus, isthmus of the cingulate gyrus and cuneus), the calcarine fissure (demarcating the cuneus and the lingual gyrus), their common stem (demarcating the lingula posterior parahippocampal gyrus and the isthmus of the cingulate gyrus), the collateral sulcus (demarcating the parahippocampal and fusiform gyri) and sub-parietal sulcus (demarcating the isthmus of the cingulate gyrus and the precuneus) are illustrated

(c) The cerebral areas known as the Retrosplenial Cortex (RSC) and Parahippocampal Place Area are demarcated in the specimen shown in Figure 1b in order to correlate the anatomical landmarks to their functional equivalent

(d) The arcuate or U fibers of the medial surface of a right hemisphere are depicted. The plane of the parieto-occipital sulcus, calcarine fissure, their common stem and sub-parietal sulcus is marked for better orientation

C= Cuneus, CiG= Cingulate gyrus, CF= Calcarine fissure, CoS= Collateral sulcus, IsCiG= Isthmus of the Cingulate gyrus, Li= Lingual gyrus, PHG= Parahippocampal gurus, POS= Parieto-occipital sulcus, POS/CF= Parieto-occipital sulcus & Calcarine Fissure common stem, PPA= Parahippocampal Place Area, PrC= PreCuneus, RSC= Retrosplenial Cortex, SubPS= Sub-Parietal Sulcus. Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

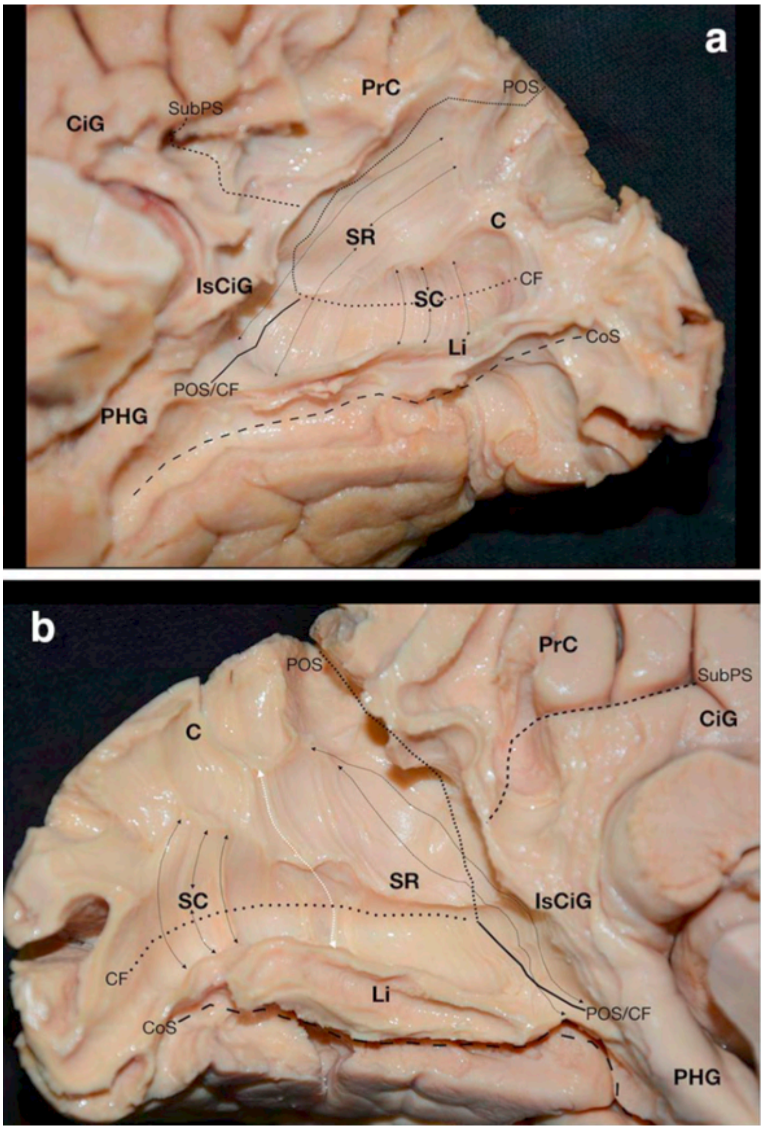


Fig. 3.8 Dissecting the U-fibers of a right (a) and a left (b) hemisphere reveals the fibers of the Sledge Runner fasciculus (SRF), the fibers of the cingulum arching over the splenium of the corpus callosum and a group of vertically oriented fibers located at the depth of the calcarine fissure, corresponding to the tract known as the “stratum calcarinum”

(a) Right hemisphere: the SRF is seen to course in an oblique direction- just under the U-fibers of the medial cerebral surface-connecting the cuneus, the anterior part of the lingual gyrus, the cingulate isthmus and the posterior part of the parahippocampal gyrus. Note the fibers of the stratum calcarinum connecting the superior and inferior banks of the calcarine fissure. The direction and trajectory of the SRF and stratum calcarinum (SC) are marked with curved arrows. This white matter morphology of both the SRF and SC was consistently encountered in all studied specimens

(b) Left hemisphere: The anatomical silhouette of the SRF and SC is delineated with curved arrows. Note how the most anterior fibers of the SRF cross the plane of the parieto-occipital sulcus as they travel ventrally towards the isthmus of the cingulum and posterior part of the parahippocampal gyrus. Note also the clear anatomical boundary between the fibers of the SRF and SC in this specimen (distance between the most anterior black curved arrows placed on th SC and the posteriorly placed white arrow on the SR)

C= Cuneus, CiG= Cingulate gyrus, CF= Calcarine fissure, CoS= Collateral sulcus, IsCiG= Isthmus of the Cingulate gyrus, Li= Lingual gyrus, PHG= Parahippocampal gurus, POS= Parieto-occipital sulcus, POS/CF= Parieto-occipital sulcus & Calcarine Fissure common stem, PrC= PreCuneus, SC= Stratum Calcarinum, SRF= Sledge Runner fasciculus, SubPS= Sub-Parietal Sulcus

3.2.3 CORRELATIVE ANATOMY WITH RESPECT TO THE MEDIAL SURFACE SULCI AND GYRI

The characteristic aforementioned silhouette of the sledge runner fasciculus places its superior fibers in a deep plane just posterior to the superior 2/3rds of the parieto-occipital sulcus. As the bundle travels anteriorly, in order to connect the area of the cuneus with the isthmus of the cingulate gyrus, its respective fibers are found deep at the level of the inferior 1/3rd of the parieto-occipital sulcus. There were no SRF fibers crossing the plane of the sub-parietal sulcus or entering the white matter of the precuneal lobule.

Deep to the calcarine fissure, the SRF fibers were seen to cross the distal part of the fissure in an almost vertical fashion, connecting the cuneus with the anterior half of the lingual gyrus. In relation to the common trunk formed by the proximal parts of the calcarine fissure and the parieto-occipital sulcus, the SRF fibers course in an almost parallel fashion deep to the trajectory of the sulcus, extending both superiorly and inferiorly in order to reach the level of the cingulate isthmus and posterior part of the parahippocampal gyrus, respectively (Fig. 2). With respect to the regional gyral anatomy, the SRF lies deep at the level of anterior half of cuneus, anterior half of the lingual gyrus, isthmus of cingulate gyrus and posterior part of parahippocampal gyrus.

3.2.4 SUBCORTICAL CORRELATIVE ANATOMY

We observed the fibers of the cingulum lying adjacent to the fibers of the SRF. This relation was particularly tight with regard to the most anteroinferior part of the SRF, which runs deep to the isthmus of the cingulate gyrus and posterior part of the parahippocampal gyrus. To clarify and illustrate more vividly the regional anatomy, we dissected this part of the sledge runner fasciculus and we further observed that it lies medial and posterior to the fibers of the cingulum, displaying a postero-supero-medial to antero-infero-lateral direction while the cingulum fibers travel antero-supero-medially to postero-infero-laterally. (Fig. 5).

Deep to the plane of the calcarine fissure, we consistently observed a distinct group of vertically oriented fibers known as the stratum calcarinum, running between the upper and lower banks of the fissure and connecting the upper and lower lips of the calcarine cortex. This elegant tract lies posterior to the SRF and in 60% of the studied specimens (12/20) it exhibits a clear demarcation from the SRF (Fig. 4).

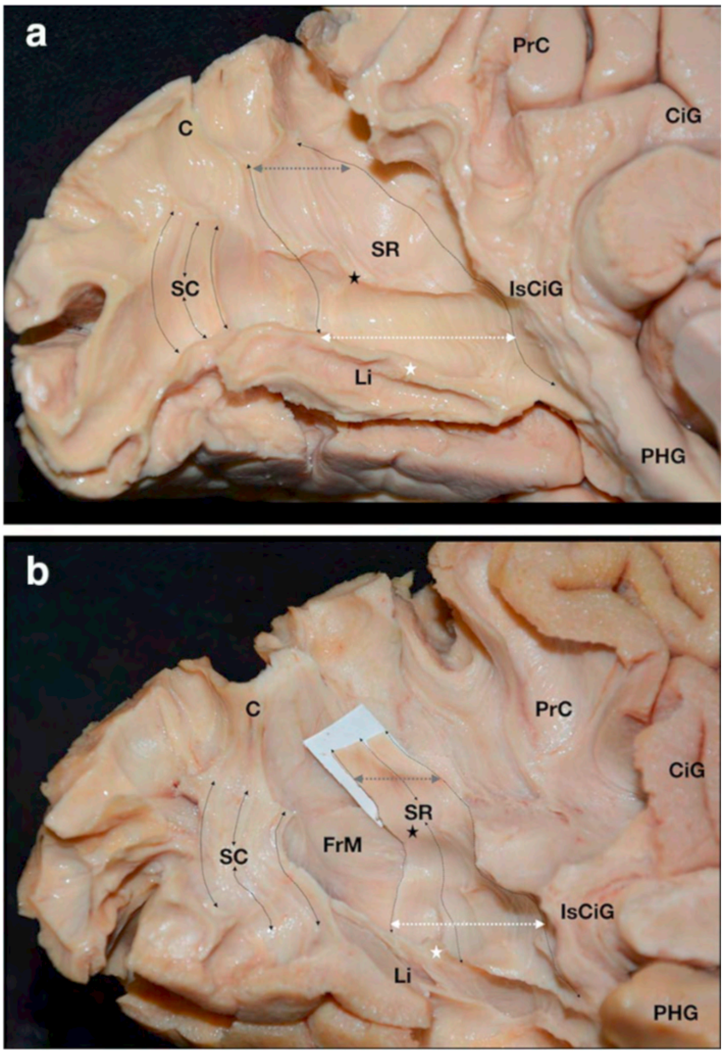


Fig. 3.9 (a, b) The morphology and configuration of the SRF is illustrated in two left hemispheres. The standard and consistent dorsomedial to ventrolateral direction of the SRF is depicted in both specimens. Note how the tract progressively widens from its dorsal narrow part, corresponding to the area of the cuneus (marked with the grey arrow), to its wider ventral part at the area of the cingulum and posterior parahippocampal gyrus (marked with the white arrow). During its course the SRF usually exhibits two medially directed curves, as seen and marked with black and white stars in these specimens

In the specimen included in fig 4b, we preserved the fibers of the SRF (marked with the white strap) while deepening the dissection plane posteriorly and exposing the more medially located fibers of the forceps major, thus illustrating the upper curve to lie at the level of the major forceps (marked in both specimens with the black star). The lower curve, marked with the white star, roughly corresponds to the level of the infero-medial wall of the ventricular atrium

C= Cuneus, CiG= Cingulate gyrus, FrM= Forceps Major, IsCiG= Isthmus of the Cingulate gyrus, Li= Lingual gyrus, PHG= Parahippocampal gurus, PrC= PreCuneus, SC= Stratum Calcarinum , SRF= Sledge Runner fasciculus Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

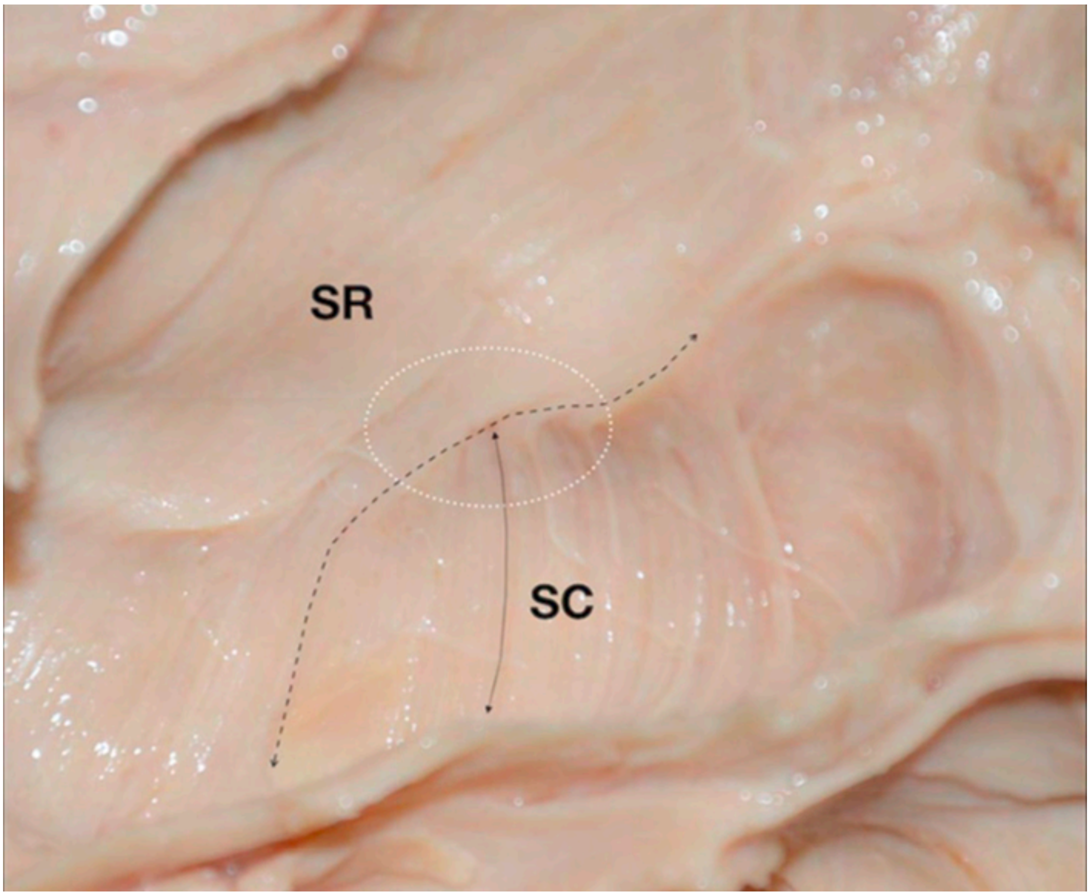


Fig. 3.10 High magnification of the regional anatomy of a right hemisphere at the level of the SRF and SC fasciculi i.e. just under the U fibers of the medial surface of the occipital lobe. Note the tight anatomical relationship between the fibers of the SR and SC illustrated with the white circle. Continuous and dashed arrows delineate the trajectory of the SR and SC respectively**.** SC= Stratum Calcarinum , SRF=Sledge Runner fasciculus. Reprinted from Koutsarnakis et al by permission of Springer Nature, Brain Structure & Function

In the remaining 40% of hemispheres (8/20) this tract was seen to intermingle with the fibers of the SRF anteriorly, displaying however a different orientation and trajectory (vertical for the SC vs. oblique for the

SRF) (Fig. 6).

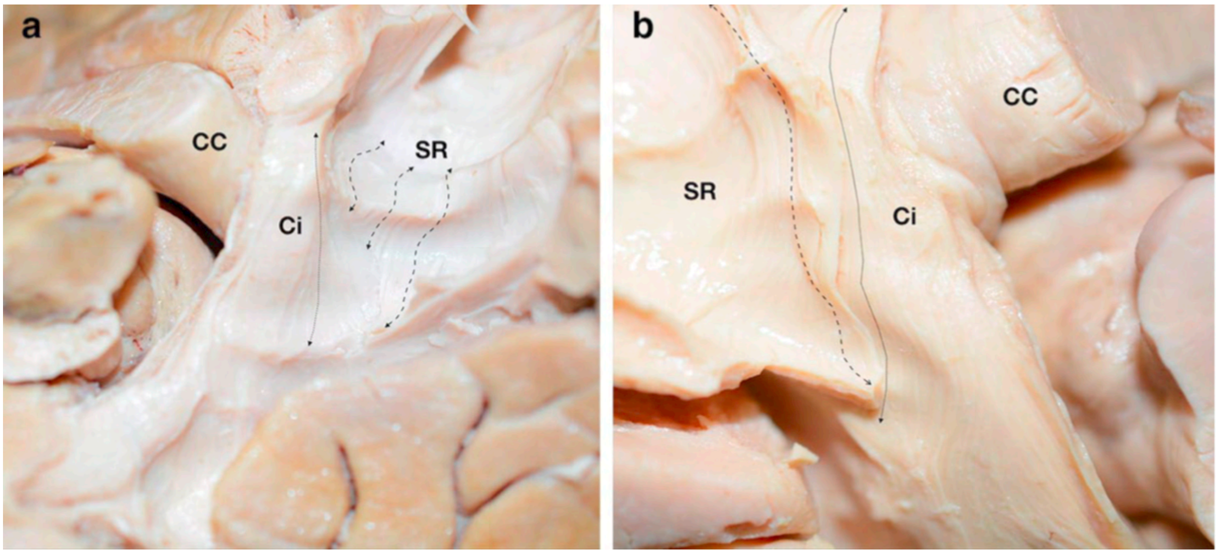


Fig. 3.11(a, b) Photos of a right (a) and left (b) cerebral hemisphere zooming in the correlative topography of the SRF with regard to the fibers of the cingulum. In both figures the anatomical vicinity between the most anteriorly descending fibers of the SRF and the fibers of the inferior arm of the cingulum is illustrated. The different trajectories of the aforementioned fibers are marked with arrows. Note that the SRF travels in a postero-supero-medial to antero-infero-lateral direction while the fibers of the cingulum take an antero-supero-medial to postero-infero-lateral course**.** CC= Corpus Callosum, Ci= Cingulum, SR=Sledge Runner fasciculus. Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

Gradual Dissection of the SRF reveals the fibers of the forceps major, running from the splenium of the corpus callosum towards the medial wall of the atrium and occipital horn (Fig. 7). By removing the forceps major and the subsequently encountered ventricular ependyma we finally enter the atrium and occipital horn. During this process we observed the superior part of the SRF lying medially and coursing almost vertically in relation to the location and trajectory of the forceps major while the inferior SRF part was always found to correspond to the medial wall of the atrium.

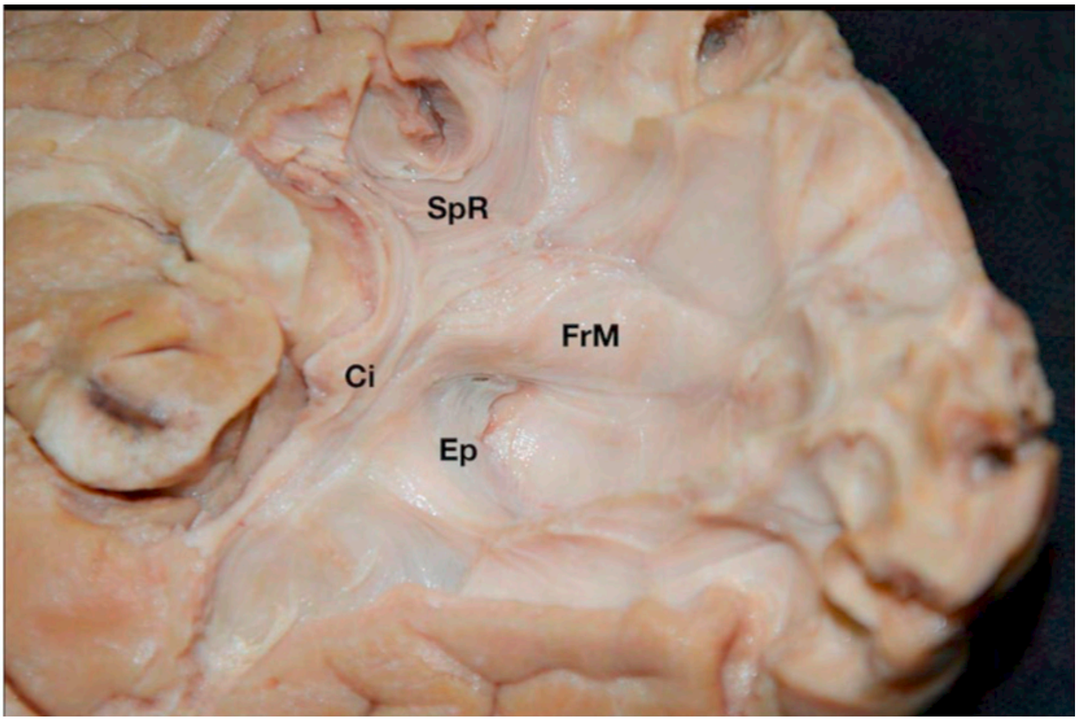


Fig. 3.12 Oblique view of a right hemisphere. Gradual white matter dissection exposes the fibers of the major forceps and the ventricular ependyma of the medial wall of the atrium**.** Ci=Cingulum, Ep=Ependyma, FrM= Forceps Major, SpR= Splenial Radiations. Reprinted from Koutsarnakis et al by permission of Springer Nature, Brain Structure & Function

3.3 RESULTS: MIDDLE LONGITUDINAL FASCICULUS

3.3.1 WHITE MATTER DISSECTIONS STEPS

Starting the dissection from the superior temporal sulcus (STS) and gyrus (STG), including the transverse gyri, we moved our plane posteriorly and superiorly towards the parieto-occipital area. Following the removal of cortical grey matter, the arcuate or U-fibers of the lateral aspect of

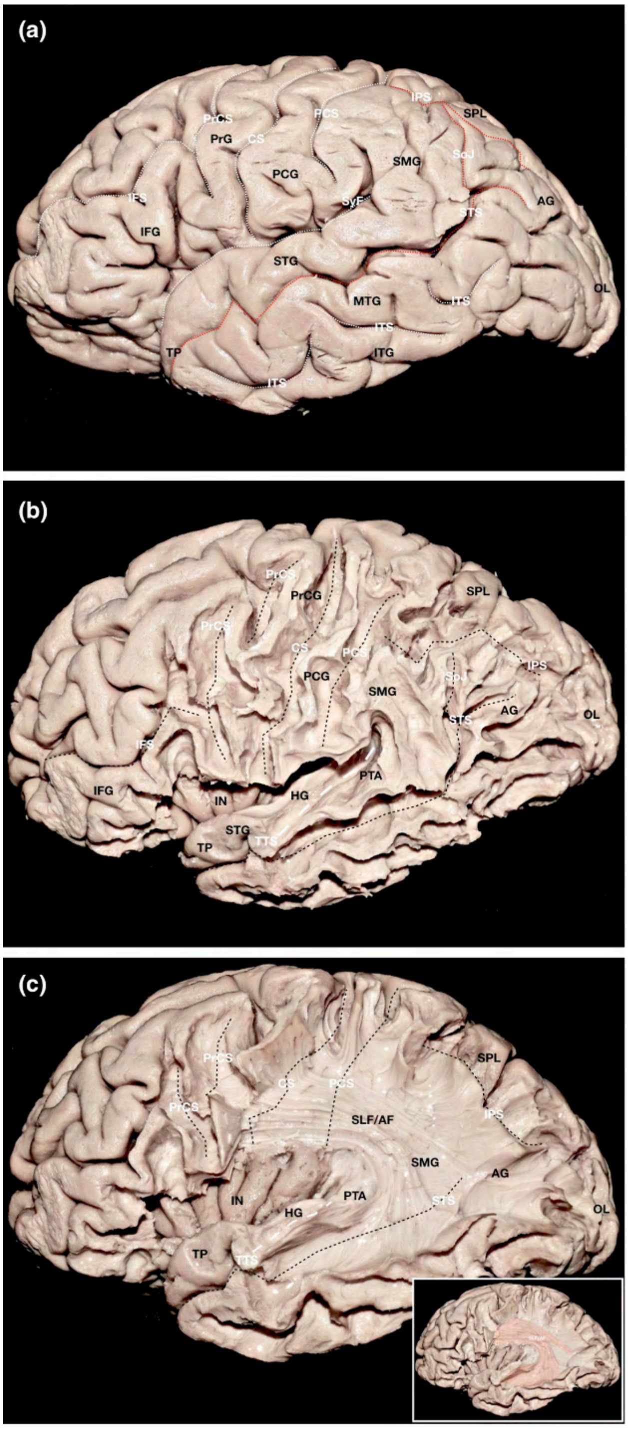


Fig. 3.13 Cortical and superficial subcortical anatomy.

(a) Sulcal and Gyral anatomy of the lateral surface of a left hemisphere. The STS (demarcating the STG and the MTG), IPS (demarcating the SPL and the IPL) and SoJ (demarcating the SMG and AG) are marked with red dotted lines. The illustrated sulci of the lateral surface are marked with white dotted lines.

(b) Same specimen with the U-fibers revealed (Step 1). The plane of the exposed sulci is outlined with black dashed lines for orientation purposes. Emphasis is placed on the anatomy of the STG and transverse gyri. The anterior transverse gyrus or Heschl's gyrus is demarcated from the posterior transverse area, which is defined as the remaining posteriorly placed transverse gyri (1-3), with the Tranvesre Temporal Sulcus (depicted using white bold dashed line).

(c) Same specimen illustrating the SLF/AF complex (Step 2). The U-fibers of the inferior central lobe, IPL and TPO junction have been dissected and the SLF/AF complex, connecting the IFG, MFG and central lobe with the IPL and temporal lobe is illustrated. The inner fibers of the "C" shaped part of the SLF/AF complex terminating at the STG and STS should be removed with caution in order to preserve the underlying MdLF fibers. The Transverse Temporal Sulcus plane is depicted using a white bold dashed line, while the rest of the sulci with black dashed lines. Inset: the SLF/AF complex highlighted in red. AG = Angular Gyrus, CS = Central Sulcus, HG = Heschl's Gyrus, IFG = Inferior Frontal Gyrus, IFS = Inferior Frontal Sulcus, IN = Insula, IPS = Intraparietal Sulcus, ITG = Inferior Temporal Gyrus, ITS = Inferior Temporal Sulcus, MTG = Middle Temporal Gyrus, OL = Occipital Lobe, PCG = Postcentral Gyrus, PCS = Postcentral Sulcus, PrCS = Precentral Sulcus, PrG = Precentral Gyrus, PTA = Posterior Transverse Area, SLF/AF = Superior Longitudinal Fasciculus/Arcuate Fasciculus Complex, SMG = Supramarginal Gyrus, SoJ = Sulcus of Jensen, SPL = Superior Parietal Lobule, STG = Superior Temporal Gyrus, STS = Superior Temporal Sulcus, SyF = Sylvian Fissure, TP = Temporal Pole, TTS = Transverse Temporal Sulcus. Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

the hemisphere are evident (Step 1) (Fig. 2). These fibers connect adjacent gyri and form the most superficial layer of white matter. Removing the U-fibers of the inferior central lobe, inferior parietal lobule (IPL) and temporo-parieto-occipital (TPO) junction, discloses the superior longitudinal fasciculus (SLF)/arcuate fasciculus (AF) complex, which essentially connects the IFG and middle frontal gyrus (MFG) with the IPL and temporal lobe (Step 2) (Fig. 2). Dissecting the U-fibers of the STG and STS unveils a distinct group of fibers that originate from the temporal pole (TP) and anterior segment of the STS/STG and exhibit a horizontal trajectory, corresponding to the anterior part of the MdLF (Step 3) (Fig. 3). The majority of the MdLF fibers were found to enter the transverse gyri and course upwards and posteriorly, just under the SLF/AF complex. Removing the SLF/AF complex helps to identify and record the parietal course of the MdLF. In this step, the insula and the most anterior part of the inferior frontal gyrus (IFG) were also included in the dissection with the aim to reveal the dorsal external capsule, the UF and IFOF and to differentiate them from the MdLF. More specifically, the U-fibers of the insula are dissected away

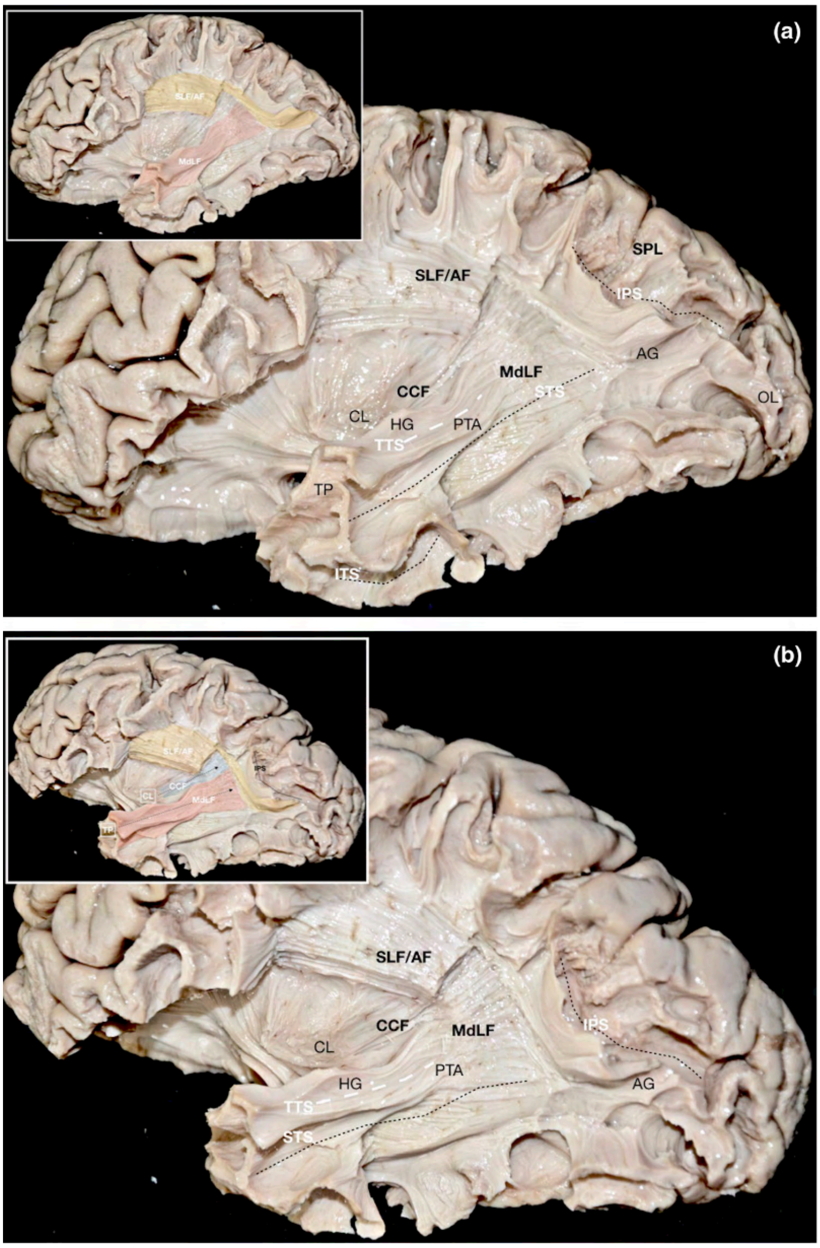


Fig. 3.14 Relationship between the MdLF and the IPL. Correlative anatomy with respect to the SLF and CCF (Step 3)

(a) Same specimen as in Fig. 2. The temporal part of the MdLF is found under the fibers of the SLF/AF complex. The majority of the MdLF fibers were seen to enter the transverse gyri and course upwards and posteriorly, just medial to the SLF/AF complex. The U-fibers of the insula are dissected in order to expose the claustrum, delineate the claustrocortical fibers of the dorsal external capsule and distinguish them from the MdLF. The U-fibers of the IPS and TPO junction are preserved to illustrate the MdLF relationship with the IPL. Inset: the MdLF is highlighted in red and the remaining SLF/AF complex fibers in yellow.

(b) Superolateral view of the same specimen. MdLF fibers and CCF fibers of the dorsal external capsule are illustrated. The MdLF lies postero-laterally with respect to the dorsal external capsule. The fibers of the MdLF can be tracked down to the TP while these of dorsal external capsule are followed up to the claustrum. The MdLF passes deep to the IPS and continues towards the SPL and occipital lobe. The transverse temporal sulcus plane is depicted using white bold dashed line while the rest of the exposed sulci using black dashed lines. Inset: The MdLF, SLF/AF complex and CCF are highlighted in red, yellow and blue, respectively. AG = Angular Gyrus, CCF

= Claustro-cortical Fibers, CL = Claustrum, HG = Heschl's Gyrus, IPS = Intraparietal Sulcus, ITS = Inferior Temporal Sulcus, MdLF = Middle Longitudinal Fasciculus, OL = Occipital Lobe, PTA = Posterior Transverse Area, SLF/AF = Superior Longitudinal Fasciculus/Arcuate Fasciculus Complex, SPL = Superior Parietal Lobule, STS = Superior Temporal Sulcus, TP = Temporal Pole, TTS = Transverse Temporal Sulcus. Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

in order to delineate the claustrocortical fibers of the dorsal external capsule and to distinguish them from the MdLF. The U-fibers of the intraparietal sulcus (IPS) and TPO junction were preserved to determine whether MdLF fibers change trajectory and terminate at the AG and SMG or instead head towards the SPL and occipital lobe. Not unexpectedly, MdLF fibers can be readily identified and differentiated from the dorsal external capsule fibers. Although these tracts exhibit the same direction (antero-inferior to postero-superior), the MdLF lies postero-laterally with respect to the dorsal external capsule, while their anterior origin is completely different i.e. claustrum for the dorsal external capsule and STG for the MdLF. None of the MdLF fibers was seen to change trajectory and terminate to the angular gyrus (AG) and supramarginal gyrus (SMG). On the contrary, we found this part of the MdLF to pass deep to the IPL and to continue towards the SPL and occipital lobe. Interestingly, fibers stemming from the SLF were seen travelling through the IPS and finally terminating at the AG. Dissecting away the U-fibers of the IPS, reveals fibers of the MdLF reaching the postero-superior part of the SPL and the parieto-occipital arcus (POA) (101) (106) (98). Removing the U-fibers of the TPO junction, unveils MdLF fibers continuing further posteriorly to enter the occipital lobe (Step 4) (Fig. 4). In this dissection step we recorded a discrete group of fibers, which were seen to run under the U-fibers of the occipital lobe and exhibit a vertical trajectory, corresponding to the Vertical Occipital Fasciculus (VOF). After removing the VOF, the stem of the MdLF was observed to course vertically and medially, in relation to the VOF, and was seen to reach the posterior border of the occipital lobe (Step 5) (Fig. 4). With regard to the anterior part of the MdLF, special attention was placed to the proper and careful dissection of the U-fibers of the anterior IFG and the anteriormost part of the temporal pole. Our aim was to disclose the UF, IFOF and ILF and to determine whether the most anterior part of the MdLF reaches the TP. Interestingly, the MdLF was consistently found to reach the anterior segment of the STG and the dorsal TP, while it was clearly demarcated and distinguished from the UF, IFOF and ILF. Following the complete exposure of the MdLF in the lateral cerebral aspect, we meticulously dissected, detached and retracted its fibers, starting from the TP and anterior STG, with the goal to record its connectivity and possibly identify a segmentation pattern (Step 6) (Fig. 5). Interestingly enough, the fibers originating at the dorsolateral TP were seen to travel through the transverse gyri to reach the SPL and the POA. More specifically, MdLF fibers entering the Heschl's gyrus, i.e. the first of the transverse temporal gyri in an anteroposterior direction, were documented to follow a superior trajectory and to terminate at the supero-posterior part of the SPL, while fibers travelling through the posterior transverse area, were found to course obliquely to reach the more medially and posteriorly placed POA. In addition, fibers originating at the most anterior part of the TP and STS were identified to travel ventrally in the depth of the STS, following a horizontal trajectory and fanning-out at the level of the posterior STS to reach through the AG the posterior border of the occipital lobe. In 70% of the studied hemispheres (14/20) the MdLF reached the superior third of the posterior border of the occipital lobe while in 30% we also observed termination fibers at the middle third. Following the posterior retraction of the 3 segments of the MdLF, the fibers of UF, IFOF and ILF can be identified (Step 7) (Fig. 6).

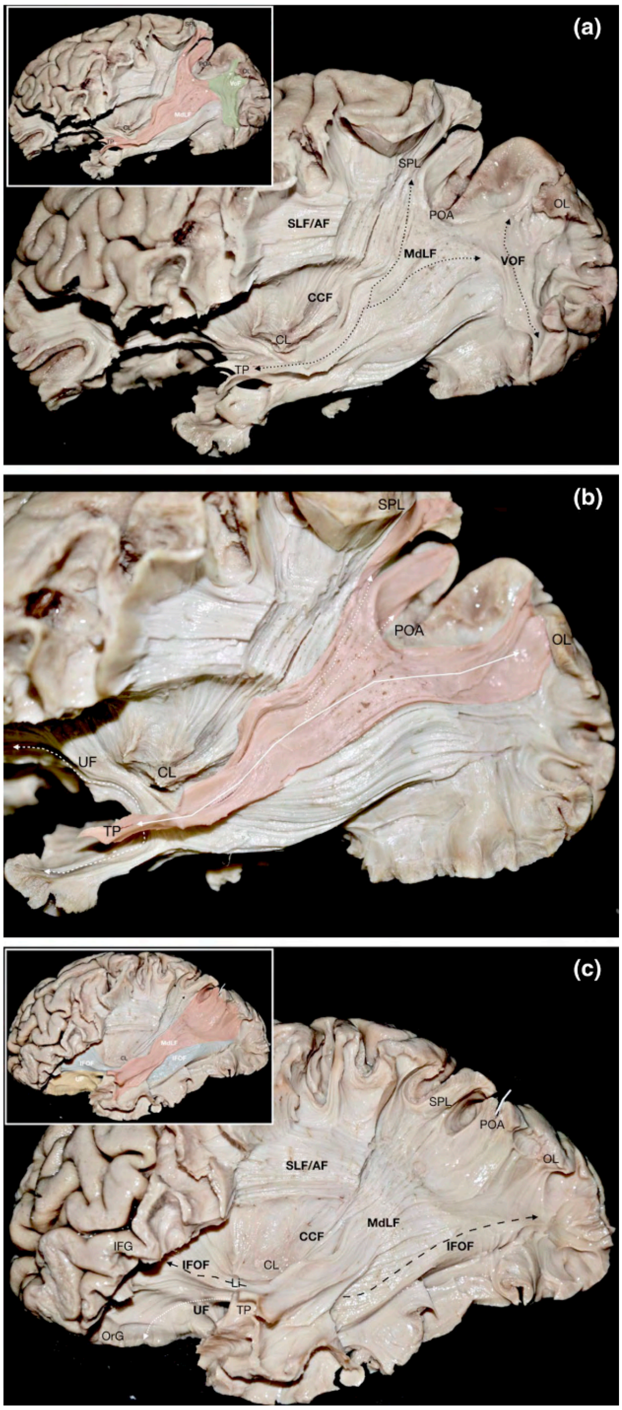


Fig. 3.15 Illustration of the temporo-parietal and temporo-occipital connections of the MdLF

(a) Different specimen. Left lateral side. The MdLF temporo-parietal connection is delineated (Step 4) extending up to the postero-superior part of the SPL/PrC and the parieto-occipital area. Dissecting away the U-fibers of the TPO junction exposes fibers of the MdLF continuing posteriorly to enter the occipital lobe. The VOF, running under the U-fibers of the occipital lobe and exhibiting a vertical trajectory can be also identified. Inset: the MdLF is highlighted in red and the VOF in Green. The trajectories of the MdLF and VOF are outlined with black dotted arrows.

(b) Same specimen as in Fig. 4a. Following dissection of the VOF, the MdLF temporo-occipital connection reaching the posterior border of the occipital lobe/cuneus is illustrated (Step 5). The silhouette of the MdLF is highlighted in red. The temporo-occipital connection is indicated with the white arrow and the temporo-parietal connection with the white dotted arrows. The UF is outlined with white dashed arrowed line. The UF lies medially to the MdLF at the anterior temporal lobe and terminates more anteriorly and inferiorly in the temporal pole.

(c) Same specimen as in Fig. 2. Relationship between the MdLF, IFOF and UF. The MdLF is seen to reach the anterior part of the STG and the TP. It is also clearly distinguished from the UF and IFOF, which travel in a deeper dissection plane as they form the ventral external capsule at the level of limen insula. The trajectory of the IFOF is demonstrated with the black dashed arrow as it courses ventromedial to the MdLF at the level of the temporal lobe and the sagittal stratum. The orbito-frontal part of the UF is depicted with the white dotted arrow. Inset: The MdLF, IFOF and UF are highlighted in red, blue and yellow, respectively. CCF = Claustro-cortical Fibers, CL = Claustrum, IFG = Inferior Frontal Gyrus, IFOF = Inferior Fronto-Occipital Fasciculus, Li = Limen Insula, MdLF = Middle Longitudinal Fasciculus, OL = Occipital Lobe, OrG = Orbital Gyri, POA = Parieto-Occipital Arcus, SLF/AF = Superior Longitudinal Fasciculus/Arcuate Fasciculus Complex, SPL = Superior Parietal Lobule, TP = Temporal Pole, UF = Uncinate Fasciculus, VOF = Vertical Occipital Fasciculus. Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

3.3.2 TRAJECTORY AND MORPHOLOGY

The MdLF was invariably identified and recorded as a white matter bundle travelling under the U-fibers of the anterior STG/STS area and medial to both the U-fibers and the SLF/AF complex at the posterior temporal lobe and IPL. It was documented to connect the STG to the SPL and parieto-occipital area, by passing through the transverse gyri, and the STG to the posterior border of the occipital lobe through the AG. Regarding its configuration, the MdLF exhibits an anterior narrow part that progressively fans-out at the posterior temporal lobe to reach the different parietal and occipital areas (SPL/PrC, POA and the occipital lobe/cuneus). With respect to its trajectory, the MdLF was observed to follow an anterolateral to posteromedial direction, as it moves from a more superficial layer anteriorly (medial to the U fibers) to a deeper dissection plane posteriorly (medial to the SLF/AF and VOF complex). Interestingly, as the MdLF runs through the transverse gyri it demonstrates a characteristic “S-shaped” configuration with two slight curves; a lateral curve facing posteriorly and a medial curve facing anteriorly. The fibers that do not enter the transverse gyri exhibit a horizontal configuration with a slightly inferior and medial trajectory.

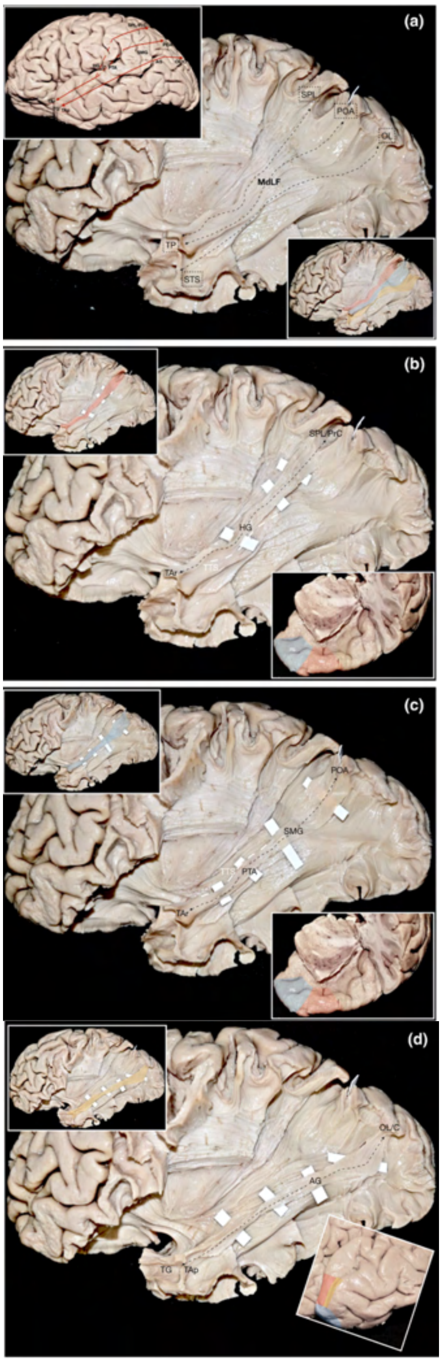


Fig. 3.16 Connectivity and segmentation pattern (Step 6)

(a) Left hemisphere - Same as in Fig. 2. The MdLF is consistently recorded to connect various segments of the TP and STG with the SPL/PrC, POA and occipital lobe/cuneus, by passing through the transverse gyri and the IPL (SMG and AG). The fibers originating at the dorsolateral TP were seen to travel through the transverse gyri to reach the SPL and the parieto-occipital arcus (MdLF-I &MdLF-II). The fibers originating at the anteriormost STS and TP, reach the occipital lobe/cuneus (MdLF-III) without travelling through the transverse gyri. Upper inset: Connectivity and terminations of the MdLF (red line and arrows) superimposed on the superficial anatomy, Lower inset: Trajectory and terminations of the three segments of the MdLF; MdLF-I, MdLF-II and MdLF-III highlighted in red, blue and yellow, respectively.

(b) Same specimen, Hyper-Selective dissection of the fibers of the MdLF-I. MdLF fibers that originate from the dorsolateral TP, corresponding to the area TAr, enter the Heschls's Gyrus (anterior to the plane of Transverse Temporal Sulcus) and follow a superior trajectory to terminate at the supero-posterior part of the SPL/PrC. The trajectory and connectivity of MdLF is marked with the black dashed arrow. Upper inset: The MdLF-I highlighted in red. Lower inset: a superolateral view of the exposed dorsal TP and superior STG on a left hemisphere, after cutting though the temporal stem and disconnecting the frontal lobe. The TG and TAr areas are highlighted in blue and red, respectively. Note the axial cut on the central core.

(c) Same specimen as above, Hyper-selective dissection of the MdLF-II. The MdLF-I has been carefully removed and the trajectory and connectivity of the MdLF-II is vividly illustrated. MdLF fibers originating from the dorsolateral TP, corresponding to the area TAr, are seen to travel through the posterior transverse area (posterior to the plane of transverse temporal sulcus) and to course obliquely in the depths of SMG, finally reaching the parieto-occipital arcus i.e the area folding around the parieto-occipital sulcus. Upper inset: The MdLF-II highlighted in blue. Lower inset: The TG and TAr areas highlighted in blue and red, respectively. **(d)** Same specimen, Hyper-selective dissection of the MdLF-III. The MdLF-I and MdLF-II have been removed and the fibers of the MdLF-III are revealed. The MdLF-III consists of fibers originating at the most anterior part of the TP and STS, which correspond to the areas TG and TAp, respectively. These fibers travel in the depth of the STS, pass under the AG and reach the posterior border of the occipital lobe/cuneus. Upper inset: The MdLF-III highlighted in yellow. Lower inset: an antero-inferior view of the TP of the same left hemisphere highlighting the areas TG, TAr and TAp in blue, red and yellow, respectively. AG = Angular Gyrus, C = Cuneus, HG = Heschl's Gyrus, MdLF = Middle Longitudinal Fasciculus, OL = Occipital Lobe, POA = Parieto-Occipital Arcus, PrC = Precuneus, PTA = Posterior Transverse Area, SMG = Supramarginal Gyrus, SPL = Superio Parietal Lobule, STS = Superior Temporal Sulcus, TP = Temporal Pole, TTS = Transverse Temporal Sulcus . Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

3.3.3 SUBCORTICAL CORRELATIVE ANATOMY

Before highlighting the spatial relationship of the MdLF with adjacent fiber pathways we have to stress that in almost all cases we were able to achieve a discrete cleavage plane of this tract. We could therefore properly dissect it away from neighboring white matter bundles, mark it with white stripes, follow and lift the fibers of the different subcomponents from their origin to their termination points (Figs. 5,6 and 7). The specific plane of latero-medial dissection and the distinct axonal connectivity of the discrete segments of the MdLF differentiate it from all the other fiber tracts that travel in the vicinity such as the SLF/AF complex, ILF, IFOF, UF, claustrocortical and external capsule radiations.

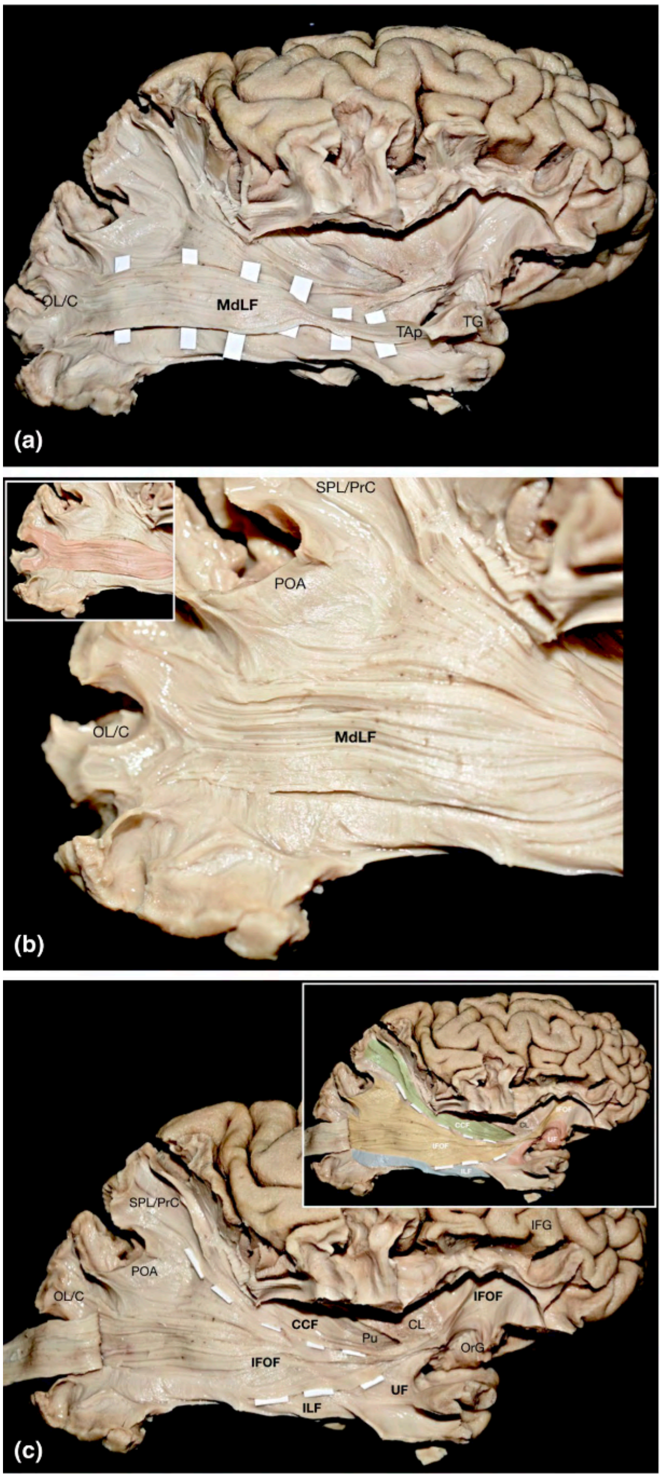


Fig. 3.17 MdLF Occipital terminations and relationship with deeper fiber tracts (Step 7) **(a)** Different specimen. Right lateral side. Hyper-selective dissection of the MdLF-III. **(b)** Focused view of the occipital area of the same specimen as in Fig. 6a. Fibers of the MdLF-III are seen to terminate at the superior and middle third of the occipital lobe/cuneus. In 70% of the hemispheres studied (14/20) the MdLF was recorded to reach the superior third of the posterior border of the occipital lobe while in the remaining 30% termination fibers at the middle third were also detected. Inset: the MdLF-III highlighted in red. **(c)** Same specimen as in Fig. 6a. Following the dissection and retraction of the MdLF-III (step 7) the fibers of UF, IFOF and ILF can be identified. The silhouette of the IFOF is depicted and demarcated from the CCF and UF with small white pads. The IFOF lies medial to the MdLF. The UF lies also medial to the MdLF at the anterior temporal lobe and terminates more anteriorly in the temporal pole as illustrated in the figure. In contrast to the MdLF, the fibers of the ILF are seen to originate from the ventral TP and to course in an inferior plane with respect to the MdLF, however sharing some cortical terminations. Inset: The MdLF, IFOF, UF, CCF and ILF highlighted in red, yellow, orange, green and blue, respectively. C= Cuneus, CCF= Claustro-cortical Fibers, CL= Claustrum, IFG= Inferior Frontal Gyrus, IFOF= Inferior Fronto-occipital Fasciculus, ILF= Inferior Longitudinal Fasciculus, MdLF= Middle Longitudinal

Fasciculus, OL= Occipital Lobe, OrB= Orbital Gyri, POA= Parieto-occipital Arcus, PrC= Precuneus, Pu= Putamen, SPL= Superior Parietal Lobule, UF= Uncinate Fasciculus. Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

MdLF and SLF/AF complex

We consistently identified the fibers of the MdLF to course just medial to the SLF/AF complex at the area of the parietal and occipital lobe. A tight anatomical proximity was observed between the fibers of the MdLF residing in the posterior transverse area and the most medial fibers of the "C" shaped AF at the level of the STG. We therefore focused our dissection at the temporo-parietal junction and consistently developed a cleavage plane between the arching fibers of the AF and the more medially located fibers of the MdLF, which were seen to course towards the SPL and POA (Fig. 2c, 3a,b).

MdLF and Dorsal External Capsule

Although the MdLF fibers that reside in Heschl's gyrus and the Dorsal External Capsule exhibit the same direction and trajectory there is nevertheless a clear cleavage plane between them. Indeed, the MdLF courses more superficially and posteriorly than the dorsal external capsule while their anterior terminations are completely different and distinct; the claustrum for the dorsal external capsule and the STG for the MdLF (Fig. 3b)

MdLF and UF

Deep to the anterior part of the STG, fibers of the UF and MdLF were found to course in proximity. However, we observed the UF to lie medially to the MdLF at the anterior temporal lobe and to terminate more anteriorly in the temporal pole (Fig. 4b,7d).

MdLF and IFOF

We consistently recorded the IFOF to course in a deeper dissection plane than the MdLF, as its fibers dive towards the limen insula to reach the frontal lobe, thus corresponding to the ventral external capsule, whereas the MdLF was seen to lie in a more superficial plane; medially to the U-fibers of the anterior STG-STS. Moreover, as the tracts travel posteriorly towards the occipital lobe, both the IFOF and MdLF merge with the sagittal stratum following however a distinct course; the MdLF runs dorsolaterally while the IFOF exhibits a medial trajectory (Fig. 4c, 6c).

MdLF and ILF

The ILF connects the TP to the occipital region, with its main stem travelling deep in the fusiform gyrus. Starting from the TP and focusing on their anterior correlative topography, the MdLF originates from the dorsal TP while the ILF from the ventral TP (Fig. 6c, 7a,b). More specifically, the most inferior fibers of the MdLF are apparent at the level of the STS (Fig. 7c) while the stem of the ILF is located below the level of the ITS with its most superior fibers at the level of the middle temporal gyrus but always terminating more anteriorly and caudally in the TP, when compared to the MdFL fibers (Fig. 7a,b). At a deeper subcortical level, we recorded the anterior terminations of the MdLF to lie superior and posterior to the Uncinate Fasciculus fibers while the ILF lying inferior to them (Fig. 7d,e). Again, the ILF fibers terminate distinctly more anteriorly in the temporal pole (Fig. 7d,e). Importantly, the ILF fibers turn towards the medial TP at the most anterior aspect of the tract (Fig. 7b,e). Tilting our dissection posteriorly, we consistently observed the fibers of the ILF to course and terminate in an inferior plane with respect to the MdLF (Fig. 7a,d,e). However, as they approach the posteriormost aspect of the occipital lobe and during their course in the sagittal stratum, the most superior ILF fibers seem to share occipital cortical terminations with the most inferior of the MdLF fibers in most of the cases (Fig. 7b).

3.3.3 SEGMENTATION & CONNECTIVITY

After dissecting, detaching and retracting posteriorly the fibers of the MdLF, we consistently identified and recorded a specific connectivity and segmentation pattern. More specifically, fibers that originate from the dorsolateral TP were seen to enter the transverse gyri and to reach the SPL/PrC and POA, while the fibers originating more anterior and inferior (anteriormost part of STS and TP) were never encountered to pass through the transverse gyri. Instead, they course in a more medial and inferior trajectory, exhibiting a horizontal configuration and finally reaching the occipital lobe (Fig. 5). Three segments and connectivity patterns were invariably recorded. In line with previous white matter anatomy studies where the subcomponents of a full bundle have been described [i.e. SLF; (107) (108) (109) (110)], we used a similar nomenclature and we defined the three MdLF segments as MdLF-I, MdLF-III and MdLF-III.

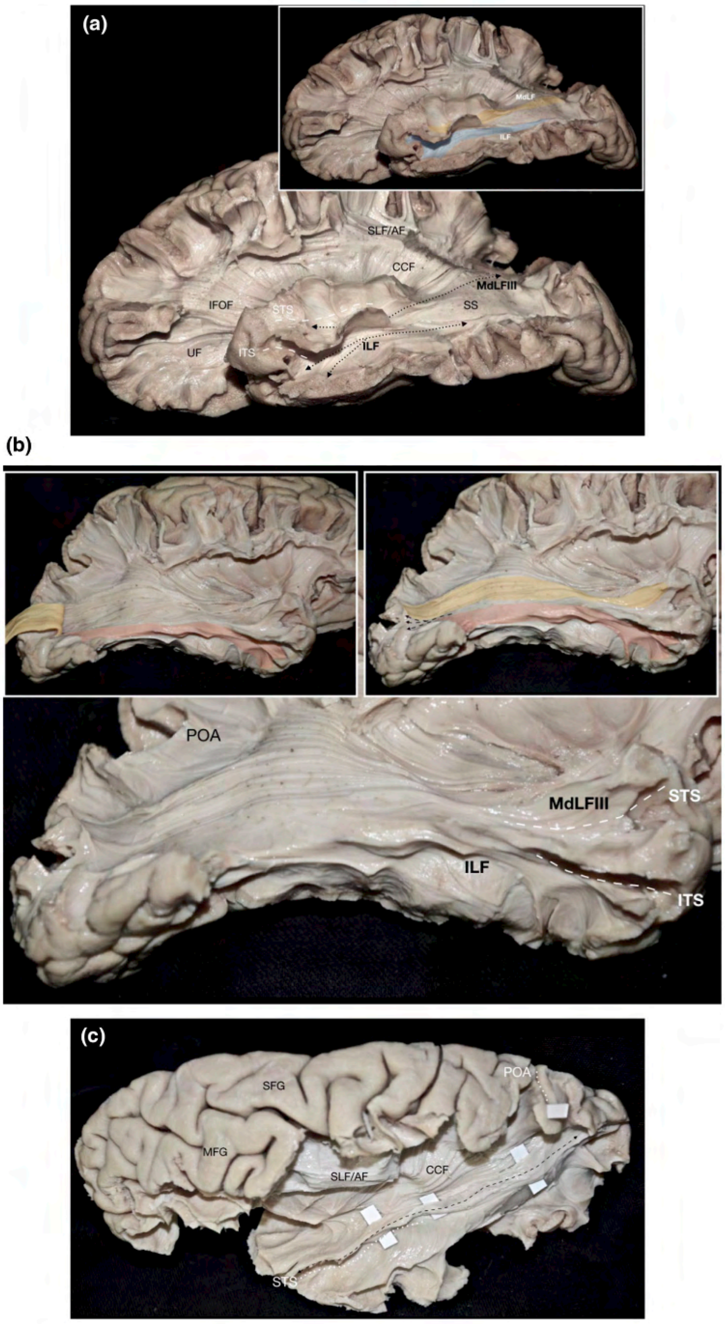
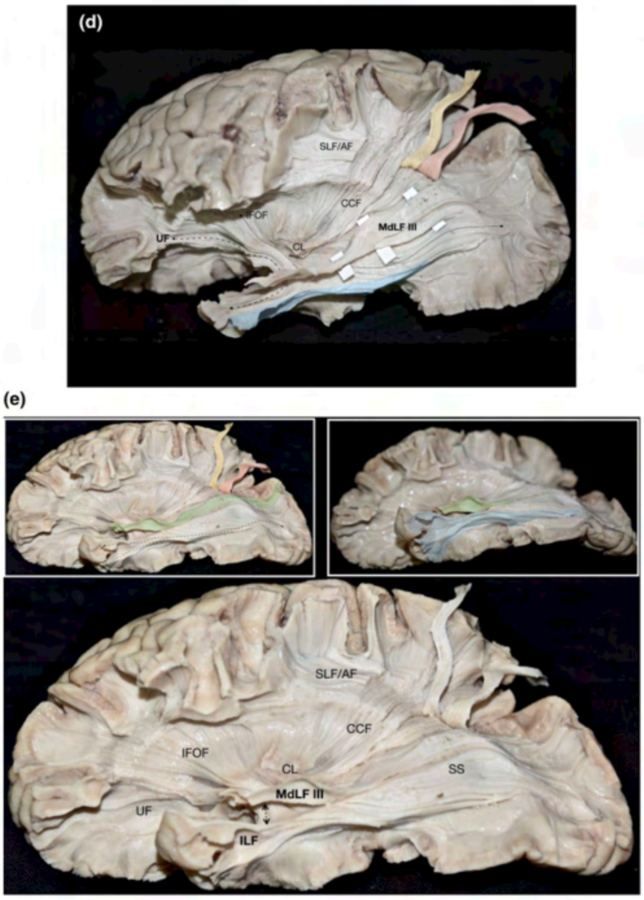


Fig. 3.18 MdLF III correlative anatomy with respect to ILF at the sulcal and deep subcortical levels.

(a) Different specimen. Left hemisphere. Inferolateral view. The levels of the STS and ITS are outlined with dashed white lines. The MdLF III is seen terminating anteriorly at the level of the STS and dorsal TP, while the ILF anterior terminations are being recorded at the level of ITS and ventral TP. Inset: The MdLF III and ILF highlighted in yellow and blue, respectively.

(b) Same specimen as in Fig. 6. Right hemisphere. Inferolateral view. Again, MdLF III and ILF anterior terminations at the level of the STS and ITS/ventral TP, respectively. ILF fibers are seen turning towards the medial TP at the most anterior aspect of the tract. Posteriorly both tracts merge with the sagittal stratum and share occipital cortical terminations. Insets: MdLF III and ILF are highlighted in yellow



and red respectively. In the right inset their shared occipital cortical terminations are outlined with black dashed arrowed lines. In the left inset the MdLF III has been retracted posteriorly.

(c) Different Specimen. Left hemisphere. Superior view. The STS and POA are outlined with white dotted lines. MdLF III is demarcated with small white pads and outlined with a black dashed arrowed line. The MdLF III is seen as a distinct white matter tract, coursing at the level of STS towards the occipital lobe. Residual U-fibers of the STS delineate MdLF III from other long white matter tracts in vicinity including ILF.

(d) Same specimen as in Figure 4a. Left hemisphere. Lateral view. MdLF III is dissected away from neighboring tracts and demarcated with small white pads. ILF is highlighted in blue. UF is outlined with black dashed arrowed line. The anterior terminations of the MdLF lie superior and posterior to the uncinate fasciculus fibers while the ILF lying inferior to them. The ILF fibers terminate distinctly more anteriorly in the temporal pole. IFOF is outlined with black dotted arrowed line. MdLF I & II have been retracted posteriorly and highlighted with yellow and red, respectively.

(e) Same specimen as in Figure 4a. Left Hemisphere. Inferolateral view. The distincty different anterior terminations of MdLF III and ILF are apparent. The space between them is outlined with black dotted arrowed line. Again, the ILF is seen turning towards the medial TP. Right inset: MdLF III and ILF are highlighted in green and blue respectively. Left inset: MdLF I, II (retracted posteriorly) and III are highlighted in yellow, red and green respectively while the ILF is outlined with dashed arrowed lines.

CCF= Claustro-cortical Fibers, CL= Claustrum, IFOF= Inferior Fronto-occipital Fasciculus, ILF= Inferior Longitudinal Fasciculus, ITS= Inferior Temporal Sulcus, MdLF= Middle Longitudinal Fasciculus, MFG=

Middle Frontal Gyrus, POA= Parieto-occipital Arcus, SFG= Superior Frontal Gyrus, SLF/AF= Superior Longitudinal Fasciculus/Arcuate Fasciculus Complex, SS= Sagittal stratum, STS= Superior Temporal Sulcus, UF= Uncinate Fasciculus. Reprinted from Koutsarrnakis et al by permission of Springer Nature, Brain Structure & Function

MdLF-I: Dorsolateral TP & STG -Heschl's Gyrus-SPL/Precuneus

The MdLF fibers that travel through the anterior transverse gyrus (Heschl's Gyrus), exhibit an "S-shaped" configuration and terminate at the postero-superior SPL (Fig. 5b). These fibers reside more anteriorly and superiorly than the MdLF fibers entering the Posterior Transverse Area and also exhibit a superior trajectory towards the SPL (Fig. 5a). This segment travels parallel and posterolateral in relation to the claustrocortical fibers of the dorsal external capsule (Fig. 3b).

MdLF-II: Dorsolateral TP & STG- Posterior transverse area- SMG - POA

The MdLF fibers that originate at the dorsolateral TP and travel through the Posterior Transverse Area were seen to course obliquely and deep to the SMG. More specifically, they were always seen to terminate in a "U-shaped" configuration as a subcortical loop of fibers folding around the parieto-occipital sulcus, namely the parieto-occipital arcus (POA) (Fig. 5a,c). The MdLF-II lies more posteriorly, inferiorly and medially when compared to the MdLF-I and in an oblique and posteriorly directed course (Fig. 5a).

MdLF-III: most anterior part of TP/STS & STG -AG – occipital lobe/cuneus

The MdLF fibers that stem from the most anterior part of the temporal pole and STS were consistently recorded to course in a relatively deep and inferior trajectory at the level of the STS. This segment exhibits a horizontal configuration and fans-out at the level of the posterior STS to reach the posterior border of the occipital lobe and cuneus by passing deep to the AG (Fig. 5a,d, 7). It joins the sagittal stratum as its most dorsolateral part. In 70% of the hemispheres this segment was seen to terminate at the superior third of the posterior lip of the occipital lobe, while in 30% we also observed termination fibers in the middle third (Fig. 6b).

CHAPTER 4: DISCUSSION

4.1 SURFACE ANATOMY OF THE OCCIPITAL LOBE

The area of the occipital lobe is characterized by a heterogeneous and highly variable superficial anatomy. Since the first focused descriptions of its sulco-gyral morphology (6, 7, 111), the nomenclature used to describe the most consistent structures of the occipital lobe has evolved through a number of studies. Nevertheless, to this day, many authors seem to use different and sometimes conflicting terms to describe the same structures. Thus, in the absence of universal anatomical definitions a non-standardized nomenclature exists in most of the modern neuroanatomical textbooks and publications. A brief review of the contemporary literature and terminology appears in table 2.

Our aim was therefore to explore the surface morphology of the occipital lobe and to compare our findings with the current literature, with the overarching goal to standardize a robust nomenclature for clinical and anatomical use.

LATERAL OCCIPITAL SURFACE AND OCCIPITAL POLE

The lateral occipital surface is a morphologically complex area and as such it is inconsistently described in the literature. It is bordered anteriorly by an arbitrary line that connects the lateral extension of the parieto-occipital sulcus to the pre-occipital notch. Many non-consistent sulci indent the lateral occipital surface in a non-standard fashion. Most of them, appear as shallow grooves running in different directions and have been described by Iaria and Petrides as the “lateral accessory occipital sulci”(112).

Three sulci travelling in a longitudinal trajectory on the lateral occipital surface i.e. the intraoccipital sulcus, lateral occipital sulcus and inferior occipital sulcus, are constantly observed and have been repeatedly described in the literature. However, the overlapping and inconsistent terminology used in previous studies adds anatomical perplexity and creates unnecessary confusion.

LATERAL OCCIPITAL SULCUS

The Lateral Occipital Sulcus is one of the most constant sulci on the lateral occipital surface. It is identified as a long sulcus running horizontally and parallel to the inferior border of the hemisphere in all studied hemispheres. Initially, Elliot Smith used the term “prelunate sulcus” to describe this structure in the early 20th century(7).In current literature the term “lateral occipital sulcus” is accepted, but not universally. Iaria and Petrides adopt this term, describing this structure as a horizontal sulcus located immediately anterior to the lunate sulcus.(112). Ribas and colleagues use the same name for this sulcus but additionally accept the term “Inferior Occipital Sulcus”.(102) Alves and colleagues describe this sulcus as the main horizontal sulcus of the lateral occipital surface dividing the occipital convexity into two parts but use the name “inferior occipital sulcus” (106). Again, the term “Inferior Occipital Sulcus” is used by Testut and Jacob and by Ono and colleagues in older studies(9, 113).Malikovic and colleagues further introduce the complex term “Inferior Lateral Occipital sulcus” for this structure(114).

In our view, the anatomical prefix “inferior” is improper due to the presence of a prominent sulcus that is readily identified in 15% of the studied specimens and is located inferior to the Lateral Occipital Sulcus. Therefore, the term “lateral” is more accurate than the term “inferior” with respect to the sulcal correlative topography of the occipital lobe.

TRANSVERSE OCCIPITAL SULCUS

In line with the current literature, we recorded the transverse occipital sulcus as fairly consistent sulcal landmark on the occipital convexity (88% of the studied hemispheres). In most of the cases it is identified as a vertical sulcus arising from the posterior end of the intraoccipital sulcus. The term "transverse occipital sulcus" appears in the literature in a conflicting way. Ono, Ribas and Alves use this term for this specific sulcus (9, 102, 106) while Iaria and Petrides use the same term to describe the intraoccipital sulcus (112). Nonetheless, since the intraoccipital sulcus exhibits a horizontal rather than a vertical configuration the term "transverse" seems inappropriate and adds confusion to the reader.

INTRAOCCIPITAL SULCUS

The intraoccipital sulcus always indents the supero-lateral aspect of the occipital convexity (100% of cases) and is, in essence, the posterior continuation of the intraparietal sulcus. In the classical studies of the early 20th century the terms "Paraoccipital sulcus" and "Sulcus Occipitalis Primus" have been used (7, 115). In modern literature, this structure has been interchangeably named as the "Superior Occipital Sulcus", "Paraoccipital Sulcus" or "Transverse Occipital Sulcus". Iaria and Petrides use the term «Transverse Occipital Sulcus" to describe this structure (112). This approach may however add unnecessary perplexity and confuse the reader since the term "Transverse Occipital Sulcus" is used in the majority of the recent studies to describe a vertically oriented sulcus located at the posterior end of the intraoccipital sulcus (see comment above). Most authors prefer the term “Superior Occipital Sulcus” while Alves and colleagues advocate the term “Intraoccipital Sulcus”(106). In our view both these options are proper. Nevertheless, this sulcus is usually recorded as the continuation of the intraparietal sulcus and therefore the name “Intraoccipital” seems more appropriate since it better conveys the concept of cerebral anatomical integrity.

LUNATE SULCUS

The lunate sulcus is defined as a crescent-shaped sulcus facing the apex of the occipital lobe. It has been a topic of extended research due to the fact that it is considered homologous to the “Affenspalte”, a sulcus that anatomically delineates the primary visual cortex in non-human primates. Connolly in 1950 and Allen in 2006 offered a solid description of the morphology of the lunate sulcus and its different morphological patterns.(8, 116) Allen proposed three different anatomical configurations for the lunate sulcus as opposed to the 5-tier pattern of Connolly. With regard to Allen’s categorization, the “typical lunate sulcus” consists of a continuous sulcus, while the “composite lunate sulcus” is formed by the convergence of 2 or more adjacent sulci. The third category refers to the absence of an obvious lunate sulcus. In the current study, the lunate sulcus was readily identified in 66% of the specimens. This percentage is significantly higher than that of previous reports (106, 112, 117, 118). Moreover, we recorded the lunate sulcus to merge with the transverse or the lateral occipital sulcus in less than 25% of cases. The term used to describe this sulcus remains constant and consistent throughout the literature and therefore no misinterpretations exist with regard to the anatomical nomenclature.

ANTERIOR OCCIPITAL SULCUS

The anterior occipital sulcus is defined as a vertical sulcus running parallel to the arbitrary line used to demarcate the anterior border of the occipital lobe. It has been described in previous studies (106, 114, 117, 119). Interestingly, the frequency of this sulcus is highly variable in the literature. Alves and colleagues recorded the anterior occipital sulcus in only 10% of the studied hemispheres (106) while Malikovich et al identified this sulcus in all specimens (114). In our study the anterior occipital sulcus was evident in 24% of the hemispheres, showing a predominance for the right side. The nomenclature used is consistent throughout the relevant literature.

RETROCALCARINE AND OCCIPITOPOLAR SULCI

The retrocalcarine and occipitopolar sulci are two crescent-shaped, vertical, short and non-constant sulci that have been scarcely described in the literature (112, 114). In the current study, we have recorded these sulci to appear concurrently in less than 10% of the cases. They were found to lie anterior to the apex of the occipital pole and when both present, they delineate the gyrus descendens.

MARGINAL OCCIPITAL SULCUS

In the current study we identified, documented and described for the first time in the literature a straight, “H” or “T” shaped sulcus, running at the level of the superior margin of the occipital lobe or slightly lateral to it, either separating the superior occipital gyrus from the cuneus or indenting the superior occipital gyrus(Fig7). Due to the topography of the sulcus, which lies close to the superior margin of the occipital convexity and between its medial and lateral aspects, we have coined the term “marginal occipital sulcus” since it reflects its main anatomical characteristic.

MEDIAL AND BASAL SURFACE OF THE OCCIPITAL LOBE

CALCARINE SULCUS

The Calcarine Sulcus originates at the retrosplenial area and travels in a postero-superior trajectory towards the area of the occipital pole. It meets with the inferior segment of the parieto-occipital sulcus in a point known as the Cuneal Point. This point divides the Calcarine Sulcus into two parts that have been described in the literature with variable terms. Early publications describe the part of the calcarine sulcus anterior to the cuneal point as the “sulcus calcarinus proprius”(7) or the “trunk of the parieto-occipital and calcarine sulci”(115). In current literature the terms “proximal calcarine sulcus”(102) or “anterior calcarine sulcus”(112) are more common. The part of the calcarine sulcus extending posterior the cuneal point is known as the “distal”(106) or “posterior calcarine sulcus”(112). In earlier studies, the name “retrocalcarine sulcus”(7) is also encountered, but currently this term stands for the bifid termination of the calcarine sulcus.

Malikovich and colleagues propose a 3-part segmentation of the calcarine sulcus: an anterior part (anterior to the CP), a middle part and a posterior part that corresponds to the termination of the sulcus in the area of the occipital pole and is known as the retrocalcarine sulcus. The same authors recorded the retrocalcarine sulcus in 79.9% of the specimens and found it running on the medial aspect of the hemisphere in the majority of cases(114). On the contrary, we identified the retrocalcarine sulcus in 12% of cases, most often seen to reach the apex of the occipital pole. In our view, the classical segmentation using the terminology “proximal” and “distal calcarine sulcus” is more appropriate and applicable in the majority of cases. With regard to the morphology of the calcarine sulcus we have observed an M-shaped (two-apex) pattern in 70% of specimens. Interestingly, in our cohort the anterior apex was always seen to point towards the cuneal point. On the contrary, Malikovich and colleagues recorded the single apex pattern to be the most frequent (60% of cases) (114).

PARIETO-OCCIPITAL SULCUS

The parieto-occipital sulcus represents a consistent landmark on the medial cerebral aspect. Along with the distal part of the calcarine sulcus it demarcates the cuneal lobule from the precuneal lobule. In our study, the parieto-occipital sulcus appears on the superior margin of the hemisphere, continuing as the external perpendicular fissure, in the majority of the cases. In line with the literature, a “Y-shaped” morphology was most frequently evident. The terminology regarding this sulcus is widely accepted.(120)

SUPERIOR AND INFERIOR SAGITTAL SULCI

The cuneus is frequently indented by a number of small sulci that may follow different trajectories. These sulci usually branch off the calcarine or the parieto-occipital sulci but may also stem individually. In the literature, the most typical morphological sulcal pattern of the cuneus comprises two sulci, namely the inferior sagittal sulcus and superior sagittal sulcus (112, 115). In our view the term “paracalcarine sulci” used by some authors (114) is not appropriate since these sulci do not always lie adjacent nor arise from the calcarine sulcus.

We identified two sulci in this area. One of them was present in 24% of cases and was recorded to travel either adjacent to the calcarine sulcus or to branch from its distal part. For classification purposes, we prefer the term “inferior sagittal sulcus” as it reflects more accurately the sulcal trajectory and topography. The second sulcus was recorded in 67% specimens and was encountered adjacent and parallel to the parieto-occipital sulcus. In some cases, this sulcus was also seen to branch off the parieto-occipital sulcus. Again, in our view the term “superior sagittal sulcus” is more characteristic and suitable for this structure.

INTRALINGUAL SULCI

Our results concerning the sulcal morphology of the lingual gyrus are in agreement with the literature. In 90% of cases we recorded 1 or 2 sulci indenting this area and dividing it into 2 or 3 parts. The terms “lingual” (114, 115) or “intralingual” sulci (9, 121) have been widely accepted in modern studies. In our view, the prefix “intralingual” is more precise since it reflects the exact location of these sulci.

COLLATERAL AND TEMPORO-OCCIPITAL SULCI

The basal temporo-occipital surface is traversed by two longitudinal sulci i.e. the posterior collateral sulcus and the posterior temporo-occipital sulcus. Chau and colleagues divide the collateral sulcus into a rhinal segment, a proper segment and a caudal (or occipital) segment, with the latter originating at the level of the temporo-occipital line.(121) The same author recorded a bifurcation pattern of the caudal collateral sulcus in 87% of the studied hemispheres. In the current study this pattern was identified in 33% of cases. Our findings with regard to the anatomy of the posterior temporo-occipital sulcus are generally in line with the literature. The frequency of the interrupted pattern of the temporo-occipital sulcus was in agreement with the study by Chau and colleagues (30 and 33% respectively). In our cohort the percentage of the temporo-occipital sulcus recorded to intersect with the collateral was lower than the percentage published by the same authors (24 and 40% respectively). The terminology used for this sulcus is consistent in modern literature.

SURGICAL UTILITY OF CEREBRAL SULCI.

The microsurgical concept of using cisterns, fissures and cerebral sulci as operative corridors to access deep seated lesions has been mainly proposed and popularized by the seminal anatomical and clinical work of Professor Yasargil(122-124) In this context, during the so called trans-sulcal approach, the surgeon has to open the arachnoid covering of the sulcus and carefully advance the intraoperative dissection up until the sulcal fundus is reached, while preserving the pial planes that invest the vessels that live inside the sulcus. Given the fact that most of the cerebral sulci point towards the respective part of the ventricular system(125) , this surgical maneuver offers a safe, straight and effective operative trajectory for managing para and intraventricular lesions. When compared to the standard transcortical approach, the trans-sulcal corridor minimizes normal brain transgression and provides a shorter working angle to attack deep seated lesions(34, 37-39, 126-131).However, the clinical applicability, feasibility and effectiveness of the trans-sulcal operative variant depends heavily on the unique anatomical characteristics of the sulcus that is intended to be used. Hence, the sulcal length, depth, trajectory and its surface morphology have to be meticulously studied on preoperative imaging(36, 38, 127-129, 131). A complex, non-continuous and shallow sulcus is a potential contraindication for performing the approach. In our previous anatomo-imaging studies 14,15 that refer to this topic we have shown that a straight, uninterrupted sulcal segment of 2, 5 - 3cm has to be dissected in real clinical settings in order to provide adequate access and optimal surgical maneuverability for intraventricular lesions. This length can be reduced down to 1, 5 -2cm with the use of small tubular retractors that can be gradually advanced under intraoperative navigation into the ventricular compartment(132). In addition, special attention has to be placed to the presence of gyri that reside within the sulcus – the so called “intrasulcal gyri”- which, when prominent and voluminous, can convert a transsulcal approach to a mixed transsulcal - transcortical as the surgeon tries to reach the sulcal fundus(37, 38).

Although using normal cerebral corridors like the sulci for approaching and resecting deep seated lesions is a time consuming process, it is nonetheless a very delicate and elegant endeavor that, under specific circumstances, respects cortical anatomy and minimizes normal parenchymal injury (122-126). Accurate knowledge of cortical and subcortical functional anatomy, meticulous preoperative planning and advanced microneurosurgical dissection skills affect surgical precision and ultimately patient's outcome.

4.2 SLEDGERUNNER FASCICULUS

Although many texts and atlases have previously investigated the anatomy and fiber tract morphology of the occipital lobe (10, 26, 133) (11, 12) (15) (17) (18) (23) (106) (134) (135) (136) (137) (138), it wasn't until the publication of the laboratory anatomical report by Vergani and colleagues entitled "Intralobar fibres of the occipital lobe: A post mortem dissection study" in which the authors identified a novel fiber bundle that wasn't previously described and named it "sledge runner fasciculus" after its peculiar shape (43). In this study the authors explored the white matter architecture of the occipital lobe in three (3) cadaveric hemispheres through the fiber dissection (Klingler's) technique and compared their results to the anatomic atlas written by H.Sachs "The hemispheric white matter of the human brain. Part I: The occipital lobe" (137). During their dissections they found a very close concordance between the histological preparations of Sachs and the Klingler's technique that they used, with the only difference being the identification of an unrecognized fiber pathway located in a plane deep to the calcarine fissure. However, Vergani and colleagues did not proceed to a more detailed description of this tract in terms of morphology, topography and connectivity since it was out of the scope of their manuscript. Since then, there have been only two published anatomo-tractographic studies entitled "The white matter tracts of the cerebrum in ventricular surgery and hydrocephalus" by Gungor and colleagues (42) and "Fiber Tracts of the Medial and Inferior Surfaces of the Cerebrum" by Baydin and colleagues (44) that refer to this fiber tract, but again the anatomic descriptions provided are not detailed due to the more generic objective of these laboratory investigations.

In this context, the present study attempts to address this gap and enhance anatomical knowledge regarding the sledge runner fasciculus (SRF) through cadaveric white matter dissections combined with a DTI protocol carried out in a public available dataset from the HCP. Additional available ROIs in individual space, descriptive measures and degree of variability for the most commonly used DTI metrics are also provided. DTI based tractography is a sophisticated neuroimaging technique widely used to reconstruct and noninvasively map the cerebral white matter architecture. It is however prone to anatomic inaccuracies and artifacts, particularly when applied to complex subcortical areas, related not only to the MR noise but also to the crossing, kissing and bending effect of the fiber tracts and thus it is deemed unfit to discover and describe new white matter pathways (139) (140) (141) (142) (143) (144) We therefore opted to combine DTI tractography with the fiber microdissection technique, which is considered the gold standard method for investigating novel fiber tracts and is used to validate evidence coming from DTI studies. More specifically, twenty (20) normal adult cadaveric hemispheres were dissected using the Klingler's technique and the microscope and 35 normal individuals with available DTI data from the HCP were analyzed using ROI-based DTI tractography, with the aim to describe in detail the topography, morphology and connectivity of this elegant fiber tract, establish the degree of correspondence between microanatomic dissection and in vivo tractography findings and provide descriptive DTI measures for the SRF. We therefore consistently identified the SRF as a distinct white matter pathway lying under the U fibers of the medial occipital lobe, exhibiting an oblique dorsomedial to ventrolateral direction and connecting the areas of the anterior cuneus, anterior lingula, isthmus of the cingulum and posterior parahippocampal gyrus. It originates as a relatively narrow tract, at the area of the cuneus, and during its course, it fans out and progressively widens as it descends towards the parahippocampal region, displaying two medial curves at the level of the forceps major and inferior part of the ventricular atrium respectively. With regard to its topography, the SRF was seen to cross the plane of the calcarine fissure and that of the common trunk formed by the calcarine fissure and parieto-occipital sulcus, thus connecting the cuneus to the lingula and posterior parahippocampal region, while it was observed to course deep to the proximal 1/3 of the parieto-occipital sulcus, connecting the cuneus to the isthmus of the cingulum. It was consistently found not to cross the plane of the sub-parietal sulcus or to enter the white matter of the precuneal lobule. The fibers of the SRF lie in the same plane and just anterior to the fibers of the stratum calcarinum, a vertically oriented white matter tract that connects the upper and lower lips of the calcarine cortex that has been previously described in the anatomic atlas of H. Sachs (137). The two tracts display a clear boundary in 60% of studied specimens, while in the remaining 40% they were observed to progressively intermingle in their ventral projection, exhibiting however a different trajectory, which aids in their proper identification and differentiation. Due to this elegant morphology, these fiber pathways should be carefully identified and dissected since anatomic misinterpretation can very easily occur. Topographically and in deeper dissection plane, the dorsal part of the SRF was found to correspond to the forceps major while its ventral part to the medial wall of the ventricular atrium.

A particularly tight anatomic relationship between the SRF and the cingulum bundle at the area of the cingulate isthmus, just posterior to the splenium of the corpus callosum was revealed in our dissections. The cingulum bundle is a white matter tract which encircles the corpus callosum and through its radiations supports the connection of the frontal, temporal and parietal lobes (145, 146) (147). In particular, the posterior projection of this bundle known as posterior cingulum (Ito et al. 2015) (148) or parahippocampal cingulum (145, 146) or Cingulum Bundle V (147) connects the parahippocampal gyrus with the precuneus (44). As such, in order to reach the precuneus, the cingulum travels in the depth of the parahippocampal gyrus and cingulate isthmus sharing a similar trajectory with the sledge runner at this level. In this context, we aimed to elucidate this relationship by heavily focusing our dissections on the specific areas. We observed that as the SRF courses deep to the cingulate isthmus it lies superficially (medially) to the cingulum fibers with a postero-supero-medial to antero-infero-lateral direction while the cingulum fibers course from antero-supero-medially to postero-infero-laterally before they arch over the splenium of the corpus callosum (Fig. 5). Moreover, the termination fibers of the SRF were encountered at the posterior part of the parahippocampal gyrus while the cingulum was observed to continue its course towards the anterior temporal lobe (Fig. 5).

Regarding the in vivo reconstruction of the SRF, we applied a multi-ROI protocol in publicly available data from the HCP, which is fully described for replication and yielded high intra- and inter-rater reliability for the examined DTI indices. We also used a robust DTI algorithm, which has been previously shown to be reliable for the reconstruction of white matter tracts including fibers (e.g. lateral cortical projections and crossing pontine fibers of the corticospinal tract) that cannot be reconstructed with previous deterministic algorithms (149). By qualitatively comparing dissection and tractography findings, our study provides evidence of similar findings concerning the anatomical trajectory of the SRF (i.e. connections between the anterior cuneus, anterior lingual, isthmus of the cingulate gyrus and posterior parahippocampal gyrus) and its topography in relation to adjacent white matter tracts (i.e. cingulum bundle, hippocampal-cingulate pathway, forceps major). However, using predefined thresholds, we failed to reconstruct the left SRF in one subject; by applying different thresholds by means of FA and angle degree, the resulted tract was considered erroneous and unreliable (e.g. false-positive). The tracking of the SRF is challenging because of the turning angle and the curving features along its course as well as fiber intercrossing. Elevated CV% of DTI metrics might indicate the complexity of the SRF reconstruction. System- (e.g. B0 inhomogeneity or gradient non-linearity) or radiographer- (e.g. subject positioning, slice tilt) related factors can contribute to the increased intersubject variation. However, in a well-designed study where system- and user-related errors had been minimized, there was increased variability in DTI indices using ROIs measures in different brain anatomical structures (150) which is in line with previous studies (151) (152) (153) (154). In our study, the calculated CV% values of FA, AD and RD metrics are in accordance with previous studies. The above-mentioned findings as well as the high complexity of SRF and the high intra- and inter-observer agreement strengthen the reliability of our findings. A multimodal task-related fMRI-DTI study is definitely warranted to fully describe the structural trajectory and the functional role of SRF.

From an anatomical-functional point of view, we reconstructed a white matter tract which was so far under-recognized as a distinct white matter tract, has a significant functional role and its anatomical trajectory includes regions that are often involved in neurosurgical procedures. The reconstruction of white matter tracts in everyday radiological practice is often hampered by low-resolution DWI sequences which were initially included in the clinical protocols to exclude and/or identify recently-onset vascular lesions and not to reconstruct specific white matter tracts and especially those that are highly-relied on non-low resolution DTI data. In our study, we applied a DTI reconstruction algorithm which has previously led us to reliably reconstruct not only common associative white matter tracts such as the uncinate fasciculus but also the hippocampal perforant pathway (149) and the ipsilateral/contralateral cortico-cerebellar connections (155), Tractography protocols are applied using manually-placed or atlas-based ROIs. Even though using atlas-based ROIs created in a standard space such as MNI can be easily used to compare between subjects or studies (156), this approach cannot be applied in misaligned data or in white matter tracts with significant anatomical variations (such as the one examined in our study). The main purpose of our study was to identify the SRF using a reconstruction protocol that can be further used by experienced or non-experienced DTI users in clinical and research practice using available DTI platforms provided either by the MRI scanner manufacturers or other companies. Thus, by providing a detailed description of the anatomical trajectory of SRF on DTI data with a public access (i.e. Human Connectome Project) and the identification of multiple ROIs which are publicly available in individual space, our protocol might be helpful for both experienced and non-experienced raters on the identification and reconstruction of SRF.

Given its subcortical architecture, the SRF was consistently recorded to connect the cortices of the anterior cuneus, anterior lingula, isthmus of the cingulate gyrus and posterior parahippocampal gyrus in all studied hemispheres. Growing body of evidence suggests that these cerebral areas are primarily involved in the perception of complex visual scenes and in the recovery of familiar spatial knowledge, thus subserving spatial memory, wayfinding and visuospatial imagery (46) (47-51, 157) (52) (53, 54) (57) (56) (55) (158) (159) (58) (59) (160), More specifically, the posterior part of the parahippocampal gyrus, widely known in neuropsychology as the parahippocampal place area (PPA), has been documented through functional imaging and stroke studies to activate strongly to complex landscapes and cityscapes, mainly by encoding the main spatial outline of the scene (48-51) (161). To this end, the PPA seems to respond to a large topographical entity by treating it in a unified manner i.e. as a single discrete object, in contrast to hippocampal activity, which primarily encodes information about specific objects and their respective spatial location within a certain landscape, thus supporting a concept of double dissociation between scene and object recognition (162) (163) (164) (165) (166). Interestingly, PPA activity is not exclusively dependent on visual stimuli but can also be triggered by scenes and landscapes brought in mind during mental navigation tasks (55) (57) (167) (168).

The cerebral territory, in turn, demarcated by the anterior lingula, anterior cuneus and cingulate isthmus, collectively referred as the retrosplenial cortex (RSC) in the field of neurocognitive research, has been documented to respond mainly to familiar topographical entities (52) (55) (49, 50), Indeed, RSC is involved in the recovery of familiar spatial knowledge thus participating in the neural circuit of long term spatial memory (49, 50) (158) (169). In addition, evidence from fMRI studies indicates that the retrosplenial cortex also activates when subjects imagine orienting and navigating themselves in familiar places, hence playing a significant role in integrating visuospatial imagery (46) (48, 51) (52, 55) (161) (168)As such, damage to this brain area results in wayfinding and orientation issues, whereas lesions confined to the PPA manifest with difficulties in encoding the topographical structure and layout of newly introduced landscapes (56, 58-

66).Whether these two distinct but functionally complementary cortical regions are directly connected through a subcortical network or act alternatively as key hubs that promote an indirect connectivity between distant cerebral areas, has been a topic of recent research (46) (51) (45) (170) (171) (29) . To this end, the implementation of methodological advances in diffusion MRI (dMRI), such as the high angular resolution diffusion imaging (HARDI) protocol (144) (172) (173), along with the use of fMRI – dMRI techniques (174) (175) (176) (141) have offered valuable insights into the structural connectivity of the neural correlates of spatial navigation and visuospatial imagery. Indeed, growing body of evidence points towards a common white matter pathway that directly links the cortical areas of interest i.e. the PPA and RSC (46) (45) (177). This fiber tract, allegedly conveying the core cognitive ability of spatial navigation and visuospatial imagery, has been described in a recent tractographic study and has been alternatively named as the medial occipital longitudinal tract (MOLT) (45). Here, we provide anatomic and imaging data on the morphology and axonal connectivity of the SRF through microanatomic dissections and DTI tractography thus raising awareness on the structural architecture of this recently identified WM tract believed to participate in the neural circuit of spatial navigation and visuospatial imagery.

4.3 MIDDLE LONGITUDINAL FASCICULUS

The first description of the MdLF in humans can be traced back to the recent past when Makris and colleagues provided novel radiological evidence on its existence and structure. The authors, by implementing a focused DTI protocol, supported the hypothesis that the MdLF represents a long cortico-cortical tract between the STG and AG (91). Subsequent anatomical and anatomo-tractographic studies however underpinned a wider and at times different connectivity pattern, by including various post-rolandic areas such as the SMG, SPL, PrC, occipital lobe, cuneus and have inevitably introduced ambiguity and controversy regarding the tract’s inherent architecture (Table 3) (92-99). In this vein, although the main body of DTI data converge on the robust connectivity between the STG and AG (87, 93-97), the two available anatomic reports suggest otherwise(98, 99). On a closer look, Maldonado and colleagues claim that the thus far prominent MdLF terminations to the AG and SMG were not identified while Wang and colleagues have demonstrated very few fibers terminating to the IPL. Further, Maldonado describes the MdLF largely as a temporo-occipital tract with no parietal connections while Wang on the contrary emphasizes on the tract's dissemination to the SPL and PrC (98, 99).

Hence, in order to clarify the MdLF connectivity pattern, we meticulously investigated all the previously described putative connections of the STG and TP through a focused anatomo-imaging protocol. Indeed, we identified and recorded a tight anatomical relationship with all the aforementioned areas. However, although we have consistently demonstrated the MdLF to pass deep to the IPL (AG and SMG), we did not isolate any significant cortical terminations to the SMG and AG, therefore agreeing with previous anatomical and anatomo-tractographic studies (98, 99). The theory that the SMG-AG complex is as a principal MdLF termination area, advocated by the majority of DTI studies, is in our view susceptible to the inherent limitations of this technique, which are mainly attributed to the crossing, kissing and bending effects of adjacent white matter fibers and which consequently decrease the anatomical accuracy of this method (139, 140, 142, 143, 178). In this regard, the presence of a sizable SLF/AF complex located in a superficial plane to the MdLF in the area of the IPL (23, 42) and exhibiting abundant fibers radiating towards the IPS and AG (179) lends support to the notion that the hypothetical MdLF fibers terminating to the AG and identified as such by DTI studies are in essence SLF/AF fibers (Fig. 3). On the contrary, the potential MdLF connections to the SPL, PrC, occipital lobe and cuneus can be readily and consistently identified thus proving that this bundle is both a temporo-parietal and temporo-occipital white matter pathway (Fig. 4, 5). Importantly, the qualitative comparison of our dissection and tractography results provides evidence of similar findings concerning the anatomical trajectory of the entire MdLF and its topography in relation to adjacent white matter tracts (i.e. ILF, IFOF, UF, SLF).

Finally, a lack of agreement on whether the MdLF reaches the TP or not can be traced through out the relevant literature. Although the majority of the available DTI evidence points positively towards this direction (93-97) the study by Conner and colleagues places the MdLF further posteriorly along the temporal lobe (92). Ambiguity remains even in the two published anatomical reports, with Maldonado and colleagues not reaching a safe conclusion on this issue while Wang and colleagues on the contrary advocate that only the deep and long subcomponent of the MdLF, which terminates at the occipital lobe, reaches the temporal pole (98, 99). In this study, we have vividly demonstrated and consistently recorded all three segments of the MdLF to terminate in different areas of the TP (Fig. 4, 5). Recently, Ding and colleagues parcellated the human temporo-polar cortex into specific sub-regions by using cytoarchitectonic and chemoarchitectonic methods as well as pathological markers (180). According to the authors, the area TAr is located at the dorsolateral TP, anterior to the typical TA area or parabelt auditory cortex, the area TAp is located at the dorsal bank of the anterior superior temporal sulcus, and the area TG is a dysgranular region of the most anterior part of the TP, occupying to some extend the dorsal aspect of the TP (Fig. 5). Our results therefore suggest that the anterior terminations of the MdLF-I and II reside at the TAr area (Fig. 5a,b,c), while these of the MdLF-III correspond to the areas TG and TAp (180) (Fig. 6a,d).

Functional Considerations and segmentation pattern of the MdLF

Early theories have hypothesized that the MdLF is a component of the language pathway (87, 91). This hypothesis was largely based on its connectivity pattern which involved language specific areas such as the STG and IPL; More specifically, on the basis of contemporary speech processing models (181, 182), it has been advocated that the STG-AG MdLF connection is implicated in translating phonemes into articulatory forms while the STG-SMG connection subserves phonetic processing (95). Regarding the nondominant hemisphere, the MdLF has been associated with visuospatial processing due to its parietal connections (183-185). Beyond language and visuospatial functions, the MdLF has been also linked to the integration of higher order auditory and audiovisual functions (93, 95, 99) with very recent findings strongly implicating this tract in speech perception and auditory processing ability in noise (97)(table 3).

In line with our results, evidence from previous anatomical (98) and anatomo-tractographic studies (99) have supported the lack of a rich connectivity between the STG and the IPL (Geschwind's area) through the MdLF. In addition, direct cortical stimulation of the dominant MdLF in 8 patients during awake craniotomies revealed no language interference during picture-naming tasks while the detailed postoperative language assessment following surgical resection of brain regions including the MdLF showed no permanent speech related deficits (186).

However, the intraoperative stimulation and the surgical resections included only the anterior part of the MdLF and therefore no insights were gathered with respect to the function of the posterior part of the tract. Furthermore, a statistically significant leftward lateralization of the MdLF was not disclosed, in terms of descriptive DTI measures such as volume and FA, by previous (87, 93, 94, 99) and the present study. Conversely, it has been well documented that tracts crucial for language, such as the AF (187) and SLF (188), exhibit considerable asymmetry in terms of volume and FA, according to language lateralization (189). All the above tend to shift the paradigm of the MdLF away from language functions.

In our study, a tight anatomical relationship between the MdLF and the transverse gyri i.e. the primary and secondary auditory cortices, has been invariably recorded both in white matter dissections and in vivo tractography (Fig. 3). We have thus demonstrated the MdLF-I to course always through the anterior transverse gyrus (Heschl's Gyrus) (Fig. 5b) and the MdLF-II to travel just under the cortex of the posterior transverse gyri/posterior transverse area (Fig. 5c). Further, the observation that the MdLF proves to be the most prominent white matter pathway of the transverse gyri provides a sound structural basis for its alleged functional implication in auditory processing (190-193). In that respect, although assumptions on the role of the MdLF in higher auditory processing have been previously made (99, 194), none of the published studies has provided anatomical evidence on the structural correlation of the MdLF and its segments with the auditory cortex. The potential auditory role of the MdLF is additionally supported by novel functional data regarding specific subregions of the temporal pole to which the tract is seen to terminate. More specifically, we have demonstrated that the MdLF terminates at the dorsolateral TP and the most anterior part of the STS and TP, areas which correspond to the TAr, TAp and TG subregions respectively (180) (Fig. 5). According to functional studies in non-human primates, the area TAr (Fig. 5) i.e. the equivalent of the dorsolateral TP, has been implicated in high order auditory processing (195-197) with remarkable neural activities being detected following specific vocal calls (198). Moreover, the area TAp, which equals the upper bank and fundus of the superior temporal sulcus, was documented to respond both to auditory and visual stimuli in non-human primates, and has thus been considered as a polysensory association cortex (199, 200).

Functional literature focusing on auditory pathways and perception of sounds supports the hypothesis that non-primary auditory cortex located posterior to the Heschl’s gyrus is involved in the spatial processing of sounds (201-206) while areas in or anterior to Heschl’s gyrus subserve the processing of phonetic stimuli (207, 208) and pitch characteristics (209). Further, similar to the well-established dorsal and ventral visual streams, the existence of respective parallel auditory pathways is also advocated by field researchers (210-213). More specifically, Ahveninen and colleagues, using functional MRI (fMRI) and magnetoencephalography (MEG) in humans, demonstrated that the “what” auditory pathway, which is responsible for processing auditory object identity characteristics, stems from the anterior auditory cortex (anterolateral Heschl’s gyrus, anterior STG and posterior Planum Polare) while the “where” auditory pathway, which is responsible for processing the location characteristics of sound, stems from the posterior auditory cortex (posterior Planum Temporale and STG). Most importantly, they prove that the ‘‘where’’ pathway is activated significantly earlier than the ‘‘what’’ pathway therefore aiding in auditory object appreciation through a top-down spatial information transmission (214). In other words, the activation of the "where" pathway precedes in order to shift and maintain the attention towards the identity characteristics of the pertinent auditory object (215).

Hence, in an effort to couple function to anatomy, it could well be argued that the MdLF-II, which is anatomically proved to connect the TAr area to the posterior auditory cortex and posterior parietal cortex, may resemble the posterior or "where" pathway, whereas the MdLF-I, which connects the parietal cortex to the anterior auditory cortex and TAr, could represent the anterior or "what" auditory pathway. Hypothetically, the MdLF-I and MdLF-II as parts of the parallel "what" and "where" pathways, could reciprocally convey information in order to assist in the perception of sounds, possibly through changes in attentional biases. From a hodotopical standpoint, their common termination areas in the TAr (180) and the supero-posterior parietal cortex, could possibly function as hubs for the relay of information through a feed-forward and feed-back interaction. The MdLF-III in turn, which was found to connect the Polysensory area named as TAp (180, 199, 200) to the AG and occipital lobe/cuneus, could potentially play a role in the integration of auditory and visual information (95).

Finally, studies in patients with Semantic Dementia (216-221) and herpes simplex virus encephalitis (HSVE) (221-223) as well as data from positron emission tomography (PET) (224, 225) and repetitive transcranial magnetic stimulation (rTMS) (226, 227) in normal participants point towards a potential role of the TP and anterior temporal lobe in semantic processing and auditory comprehension. More specifically, findings stemming from functional imaging implicate the anterior STG, near the anterior-lateral aspect of Heschl's gyrus, in sublexical processing and auditory word-form recognition (228, 229). In the same vein, intraoperative brain mapping in 90 patients suggests that stimulation of the left STG leads to impairment of auditory single-word comprehension (230). Keeping with the putative role of MdLF in auditory processing and the fact that it represents an important subcortical connection of the STG, we could further postulate that it might serve as an anatomo-functional interface between auditory representations and semantic/lexical access.

CHAPTER 5: COCLUSIONS

5.1 CONCLUSION: SUPERFICIAL ANATOMY OF THE OCCIPITAL AREA

The superficial anatomy of the occipital lobe has been implicated in a number of contemporary and classical studies. Nevertheless, a vague understanding of the sulco-gyral morphology and topography of this region remains and is conveyed mainly as a lack of solid anatomical definitions and as an absence of a universal nomenclature. By combining a review of the relevant current literature with a meticulous investigation of the surface topography and morphology of the occipital sulci and gyri in 33 formalin fixed cerebral hemispheres, we attempt to offer a more sophisticated anatomical perspective and propose a universal taxonomy of the occipital cortical anatomy for clinical and anatomical use. In addition, we identify, record and describe for the first time in the literature a sulcus that runs on the superolateral aspect of the occipital surface, which we name the marginal occipital sulcus after its specific topography.

5.2 CONCLUSIONS: SLEDGERUNNER FASCICULUS

Laboratory white matter dissections and DTI studies were employed with the aim to investigate and record the structural architecture of a fiber tract residing in the medial part of the occipital lobe known as the SRF. By combining the Klingler's dissection method and a reliable DTI protocol with public available ROIs on dataset from the HCP yielding high intra- and inter-rater agreement values and providing descriptive and variability measures for DTI indices, our results support the hypothesis that the SRF is consistently involved in the axonal connectivity of cerebral areas that are believed to be strongly implicated in the cognitive ability of spatial navigation and visuospatial imagery.

5.3 CONCLUSIONS: MIDDLE LONGITUDINAL FASCICULUS

Focused fiber micro-dissections augmented by a tailored DTI protocol on the publicly available dataset from the Human Connectome Project were employed to clarify the structural architecture of a recently identified tract known as the MdLF. The applied multi-ROI protocol yielded high intra- and inter-rater reliability for the examined DTI indices, while the dissection and tractographic findings showed a good correspondence regarding the MdLF topography, morphology and axonal connectivity. Our results draw on the robust anterior terminations of MdLF to specific subregions of the TP, the intrinsic anatomical relationship of the tract to the auditory cortex and the lack of significant connections with the IPL (SMG and AG). The lack of leftward asymmetry and rich connectivity with the IPL along with data from direct intraoperative stimulation tend to shift the paradigm away from language function. Conversely, in light of the theory of parallel “where” and “what” auditory pathways, the strong relationship of the MdLF with the auditory cortex and the functional role of the cortical areas that it interconnects tend to shift the paradigm towards auditory function. Allegedly, the MdLF-I and MdLF-II as parts of the parallel “what” and “where” pathways, respectively, may play a role in the perception of sounds whereas the MdLF-III could underpin the integration of auditory and visual information. Since recent data support the notion that the TP and anterior STG should be treated as “hubs” for semantic processing and auditory word-form recognition, the working hypothesis viewing the MdLF as an anatomo-functional interface between auditory representations and semantic/lexical access gains further ground.

THE KLINGLER'S WHITE MATTER FIBER MICRO-DISSECTION TECHNIQUE: STRENGTHS AND LIMITATIONS

The Klingler's preparation entails the fixation of cerebral hemispheres in a formalin solution followed by a freeze-thaw process. The ice crystals that form during the freezing process separate the white matter fibers apart and therefore one can subsequently identify and dissect them in the setting of a micro-neurosurgical laboratory. As recently documented by *Zemmoura* and colleagues this procedure preserves the structural integrity of the nerve axons, and therefore the direct anatomical evidence provided is of high sensitivity and accuracy. Furthermore, the three-dimensional architecture of the subcortical pathways and their spatial relationships are maintained and can be explored. For these reasons, the fiber dissection technique is one of the "gold standard" direct anatomical methods used to validate indirect structural data coming from DWI tractographic protocols.

The fiber micro-dissection method is however an expensive, time-consuming, operator dependent and in vitro technique. The spatial resolution of the data provided is lower in comparison to histology, optical coherence tomography and polarized light imaging while there are also limitations when simultaneously exploring fiber tracts with intermingling perpendicular trajectories because the proper dissection of the one can result in the destruction of the other.

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