NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS MEDICAL SCHOOL

DEPARTMENT OF ANATOMY

CORTICAL ANATOMY AND SUBCORTICAL CONNECTIVITY OF THE TEMPORAL POLE

PhD DOCTORAL THESIS

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ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ ΙΑΤΡΙΚΗ ΣΧΟΛΗ

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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).

Η έγκριση διδακτορικής διατριβής από Ιατρικής Σχολής του Εθνικού & Καποδιστριακού Πανεπιστημίου Αθηνών, δεν υποδηλώνει την αποδοχή των γνωμών του συγγραφέα (Νόμος 5343/1932, άρθρο 202, παράγραφος 2).

PROLOGUE AND ACKNOWLEDGEMENTS

Substantial scientific attention has been devoted to understanding the neural basis of social and emotional processing. The appeal of understanding these processes is driven partially by a need to understand an important part of our own essence – our "social self".

I was always intrigued by the greatness people achieve when they work together. After all, historically, it is not our pure reason that made us prevail over the other animals of the planet. It is our social nature(Harari 2014). Our ability to collaborate and choose social and emotional connections over lonely individual paths. These are the bridges that take us to the other side. These are bringing us closer to happiness and success by harmony and true connections. They take us to an enchanted place where we can flourish!

This is the "place" where I met my neurosurgical family, my friends, my mentors. The ones that I could pursue my surgical and scientific endeavors with. The ones who made the conduct of my investigations feasible and joyful. The ones that we could navigate the complex intrinsic anatomy of the brain together in the lab and the operating room, but at the same time being part-time philosophers, movie and food critics, sommeliers, political analysts, athletes, and music players: my mentor Professor George Stranjalis and my inimitable neurosurgical "gang", Dr Christos Koutsarnakis, Dr Spyros Komaitis, Dr Vangelis Drosos, and Dr George Skandalakis.

The same appeal about our social nature and our inner mind combined with my passion for neuroanatomy and brain connectivity led me to the subject of my PhD: Exploring the mysterious temporal pole! A potential seat of emotions, intuitions, and behaviors. Is this where the conscious and unconscious interact?

Is this where our characters grow? Recent evidence shows that we are not the product of our conscious thinking but of what we process without our awareness. Sounds, pictures, odors, and past experiences transformed into emotions and unconscious roadmaps of what we like or dislike, of what we believe is right or wrong, moral or immoral (Brooks 2012).

Is this where the seedbed of our success resides? Unconscious mind is not a sum of primitive imprints and inhibited sexual compulsions but an adaptive and sophisticated process where most of our decisions are taking place. After all, the human brain can process 11 million information at any moment – from which we are aware of only about 40 (Wilson 2004)! Emerging data suggest that success is not only a result of tips and tricks, professional skills, IQ, and conscious decision making. But also, a result of our inner mind and street-smart abilities that make us dynamic, genuine, honest, trustworthy, but also able to "read" minds, situations, and concepts and to remember names and faces (Brooks 2012).

Brain research rarely generates new philosophies, but it usually endorses and further develops old ones. But how the above reasoning contained in the cognitive neuroscience *sphere can be clarified and investigated through the anatomy of the brain? The recent revival of the white matter fiber dissection technique first described by Klingler has provided valuable insights on the intrinsic white matter anatomy and its 3D representation in unprecedented detail (Klingler and Ludwig 1956). The concept of brain hodotopy (deriving from the Greek words hodos meaning road, pathway and topos meaning place) perceives brain function not only as a cortical phenomenon but as an integrative network epiphenomenon (De Benedictis and Duffau 2011); thus, emphasizing the role of the white matter connectivity in brain function. Combining the understanding of the brain connectivity and anatomo-functional organization, one can draw tentative conclusions pertinent to cognitive neuroscience that could be solidified following investigations from different standpoints and disciplines.*

I hope and believe that the results and output of this PhD study are contributing to the revealing of the rich environment of temporopolar subcortical connections with wide brain networks and as such provide further evidence to support its integral role in the multimodal processing of many of the aforementioned qualities that make us unique!

I would like to thank the members of my advisory committee Associate Professor Maria Piagkou, Professor Emeritus Panagiotis Skandalakis, and Professor Theodoros Troupis for their continuous support throughout my PhD studies. My father and mother who nurtured all the affections and aversions that made me choose my pathways and my people so far, and for providing me the unconditional love that we all need to believe in our dreams. Finally, my wife Mantha for her extraordinary patience, support, and confidence in me, without which my academic and professional endeavors would be impossible.

To my son and wife

CONTENTS

CHAPTER 1: INTRODUCTION

CHAPTER 2: MATERIALS AND METHODS

CHAPTER 3: RESULTS

CHAPTER 4: DISCUSSION

CHAPTER 5: CONCLUSIONS

ΠΕΡΙΟΧΟΜΕΝΑ

ΚΕΦΑΛΑΙΟ 1: ΕΙΣΑΓΩΓΗ

ΚΕΦΑΛΑΙΟ 2: ΥΛΙΚΑ ΚΑΙ ΜΕΘΟΔΟΙ

ΚΕΦΑΛΑΙΟ 3: ΑΠΟΤΕΛΕΣΜΑΤΑ

ΚΕΦΑΛΑΙΟ 4: ΣΥΖΗΤΗΣΗ

ΚΕΦΑΛΑΙΟ 5: ΣΥΜΠΕΡΑΣΜΑΤΑ

CURRICULUM VITAE

PERSONAL INFORMATION

Name and Surname: **Aristotelis Kalyvas**

Profession: **Medical Doctor (Neurosurgeon)**
Current Post: **Clinical Fellow in Neuro-oncology and Skull Base Surgery, Toronto Western Hospital University of Toronto, Toronto, Canada**
Date of birth: 02-APR-1986
Nationality: Greek
Languages: Greek (native speaker); English (proficient)

ACADEMIC EDUCATION

07/2019-07/2020	**Clinical Fellow in Neuro-oncology and Skull Base Surgery,** Toronto Western Hospital/University Health Network, University of Toronto, Toronto, Canada Scientific Coordinators: Drs. Fred Gentili, Gelareh Zadeh, Mark Bernstein, Paul Kongkham
06/2018-present	**PhD Candidate in Anatomy,** Department of Anatomy, Medical School, National and Kapodistrian University of Athens, Athens, Greece. *PhD research topic: "Cortical Anatomy and Subcortical Connections of The Temporal Pole"* Scientific Coordinator: Prof. Panagiotis Skandalakis, Department of Anatomy, Medical School, National and Kapodistrian University of Athens, Athens, Greece.
06/2015-06/2019	**Research Fellow,** Athens Microneurosurgery Laboratory, Evangelismos Hospital, Department of Neurosurgery, National and Kapodistrian University of Athens, Athens, Greece Scientific Coordinator: Prof. George Stranjalis, Department of Neurosurgery, National and Kapodistrian University of Athens, Athens, Greece
07/2011-07/2014	"**MSc in surgical sciences**" with **Distinction (Highest Grade) (07/2014)**, The University of Edinburgh, The Royal College of Surgeons of Edinburgh, United Kingdom Scientific Coordinator: Prof. James O Garden, Dean International, Department of Clinical Surgery, University of Edinburgh, Edinburgh, United Kingdom. *MSc Thesis: Efficacy, Complications and Cost of Surgical Treatments for Idiopathic Intracranial Hypertension: A meta-analysis.* Supervisor: Mr Ioannis Fouyas, Consultant Neurosurgeon, Department of Clinical Neurosciences, Western General Hospital, Edinburgh, UK. "**Diploma in surgical sciences**" with **Distinction (Highest Grade) (07/2013)**, The University of Edinburgh, The Royal college of Surgeons of Edinburgh, United Kingdom. Following successful completion of written examinations. "**Certificate in surgical sciences**" with **Distinction (Highest Grade) (07/2012)**, The University of Edinburgh, The Royal college of Surgeons of Edinburgh, United Kingdom. Following successful completion of written examinations.
09/2004-10/2010	"**Medical Degree (MD)**", "Ptychio Iatrikes", Grade: **Very Good,** Medical school of the University of

	Ioannina, Ioannina, Greece.
07/2004	**“High School Diploma”,** Grade: **Excellent,** 1st General High School of Ioannina, Ioannina, greece.

EMPLOYMENT HISTORY

07/2020-Present	**Clinical Fellow and Clinical Research Fellow in Neuro-oncology and Skull Base Surgery, Toronto Western Hospital/University Health Network, University of Toronto,** Toronto, Canada Supervisor: Prof. Fred Gentili Scientific Coordinators: Drs. Fred Gentili, Gelareh Zadeh, Mark Bernstein, Paul Kongkham
09/2018-05/2019	**Clinical Fellow in Intra-axial Surgical Neuro-oncology, Neurosurgery Department, National and Kapodistrian University of Athens**, Evangelismos Hospital, Athens, Greece. Supervisor: Prof. George Stranjalis Chair: Prof. Damianos Sakas
09/2018	Successfully passed the **Neurosurgery Specialty Certification Exams**. Governing Body: The Regional Prefect of Attica, Hellenic Republic, Greece.
01/2018-09/2018	**Chief Resident in Neurosurgery**, **Neurosurgery Department, National and Kapodistrian University of Athens**, Evangelismos Hospital, Athens, Greece. Chair: Prof. Damianos Sakas
11/2013-01/2018	**Resident in Neurosurgery**, **Neurosurgery Department, National and Kapodistrian University of Athens**, Evangelismos Hospital, Athens, Greece. Chair: Prof. Damianos Sakas
04/2012-09/2013	**Surgical Resident (Core Surgical Training as part of Residency in Neurosurgery)**, **General Surgery Department, University of Ioannina,** Ioannina, Greece. Chair: Prof. Christos Katsios
02/2012-03/2012	**Rural General Doctor**, Delvinaki Health Center, Ioannina, Greece

CLINICAL EXPERIENCE

11/2017-12/2017	**Skull Base Visiting Fellow**/Observer, **Toronto Western Hospital**, Toronto, Canada Scientific Coordinator: Prof. Fred Gentili
09/2017-10/2017	**Cerebrovascular Visiting Fellow**, **King’s College Hospital**, London, United Kingdom. Scientific Coordinator: Mr. Christos Tolias
09/2011-12/2011	**Postgraduate Student/ Pre-Residency Clinical Fellow of Hygeia Hospital** (**Scholarship),** Neurosurgery Department, Hygeia Hospital, Athens, Greece. Scientific Coordinator: Dr. Panagiotis Nomikos
02/2011 - 09/2011	**Military Service as a Medical Doctor**, 8th army Division, Hellenic Army, Greece
11/2010 - 01/2011	**Horonary Clinical Fellow, Orthopaedics department of General Hospital of Ioannina “Chatzikosta”**, Ioannina, Greece. Scientific Coordinator: Dr. Nikolaos Skaltsogiannis

TEACHING EXPERIENCE

02/2021	Delivered the lecture “**White matter tracts anatomy: Practical aspects for glioma surgery”** in the context of Neurosurgery Residency academic half-day program. The Brain School (thebrainschool.net), Toronto Western Hospital, Division of Neurosurgery, University of Toronto.

February 5, 2021

10/2020-11/2020 **Clinical Skills Tutor** in Neurology for Year 2 Medical Students, University of Toronto Medical School, Toronto, ON, Canada.

Teaching of 3 sessions (Neurology I, II, III on the 15OCT, 22OCT and 5NOV, respectively)

10/2020 **Guest Faculty** in 60th **W. Lougheed Microsurgical Course**, University of Toronto, Surgical Skills Centre ,Mount Sinai Hospital, Toronto, ON, Canada.

Scientific Coordinator: Dr. Ivan Radovanovic

09/2020 **Instructor** in 59th **W. Lougheed Microsurgical Course**, University of Toronto, Surgical Skills Centre ,Mount Sinai Hospital, Toronto, ON, Canada.

Scientific Coordinator: Dr. Ivan Radovanovic

09/2019 Delivered the lecture “**Cerebral Surface anatomy, imaging correlation and surgical applications”** in the context of Neurosurgery Residency academic half-day program. The Brain School (thebrainschool.net), Toronto Western Hospital, Division of Neurosurgery, University of Toronto September 20, 2019

05/2019 & 04/2018 Co-Organizer in **international Hands-on Workshop in Neurosurgical Anatomy and White Matter Dissection for 2 consecutive years,** EANS, Hellenic (Greek) Neurosurgical Society & Athens Microneurosurgery laboratory, Evangelismos Hospital, Athens, Greece

Scientific Coordinator: Prof. George Stranjalis

05/2019 & 04/2018 & 06/2017 & 04/2016 & 04/2015 **Faculty** in **international Hands-on Workshop in Neurosurgical Anatomy and White Matter Dissection** for **5 consecutive years**, EANS, Greek Neurosurgical Society & Athens Microneurosurgery laboratory, Evangelismos Hospital, Athens, Greece

Scientific Coordinator: Prof. George Stranjalis

2018-2019 **Lecturer** in **MSc Program “Clinical and Experimental Neurosurgery”**, Medical School , National and Kapodistrian University of Athens, Athens Greece.

Scientific Coordinator: Prof. George Stranjalis

2017-2018 **Lecturer** in **MSc Program “Applied Neuroanatomy”**, Medical School , National and Kapodistrian University of Athens, Athens Greece.

Scientific Coordinator: Prof. George Stranjalis, Prof. Elizabeth Johnson

03/2016 Delivered **lectures** in the context of **MSc program “Clinical Neuropsychology-Cognitive Neurosciences”,** National and Kapodistrian University of Athens, Athens, Greece & McGill University, Montreal Neurological Institute, Montreal, Canada.

Scientific Coordinator: Prof. Konstantinos Potagas

09/2015 **Guest Faculty** in **Cerebral and Cranial Base Anatomy hands-on workshop**, Laboratory for Education and Research in Neurosciences (LERNs), National and Kapodistrian University of Athens, Athens, Greece. September 24-26, 2015.

Scientific Coordinator: Prof. Elizabeth Johnson

03/2013 **Instructor** in the **Basic principles of wound suturing course,** Hellenic Medical Students’ International Comitee, University of Ioannina, Ioannina, Greece.

GRANTS

01/2021 “Safety and Feasibility of Focused Ultrasound-enabled Liquid Biopsy in patients with Brain Tumors”

Funding Body: The Canadian Cancer Society (CCS), the Canadian Institutes of Health Research - Institute of Cancer Research (CIHR-ICR), and Brain Canada Foundation (CCS/CIHR/BC SPARK GRANTS)

Total funding: CAN$ 150.000

Role: Co-investigator

Funding Competitive: Yes

SCHOLARSHIPS/AWARDS

2021 **Fellowship Teaching Award, Graduation and Awards Ceremony, Division of Neurosurgery, University of Toronto,** Toronto, Canada, June 18, 2021.

2020 **Award for the Best Clinical Research (Tumors section) in the annual Congress of Neurological Surgeons (CNS) virtual meeting, 2020.**

International Tuberculum Sellae Meningioma authors**.** International tuberculum sellae study: surgical outcomes and management trends.

2019 **Award for the Best Poster of the 33rd Hellenic (Greek) Neurosurgical Society and 4rth South East Europe Neurosurgical Society Congress,** Thessaloniki, Greece, June 2019:

Drosos E., **Kalyvas A**., Dogruel Y., Koutsarnakis C., Stranjalis G. Surface anatomy of the temporal lobe with emphasis on the topographic architecture of the temporal pole.

2018 **Award for the top 5 submitted abstracts of the 32nd Hellenic (Greek) Neurosurgical Congress (Joint Meeting of the Hellenic Neurosurgical Society with The Society of British Neurological Surgeons & Cyprus Neurosurgical Society),** Chania, Greece, May 24-26, 2018:

Kalyvas A, Koutsarnakis C, Skandalakis G, Komaitis S, Stranjalis G. Sledge Runner Fasciculus: Microanatomic architecture and tractographic morphology of a fiber tract subserving spatial navigation and visuospatial imagery.

2017 **"Zaharias Kapsalakis" Award for the Best Clinical/Research Study of the 31st Hellenic (Greek) Neurosurgical Congress,** Ioannina, June 15-17, 2017:

Stavrinou P, **Kalyvas A**, Goldbrunner R, Stranjalis G. Is there a survival benefit from treatment of glioblastoma recurrence? Comparison of the effect of different treatment strategies on survival.

2015 **Award for the Best Oral Presentation of the 29th Hellenic (Greek) Neurosurgical Congress,** Athens, May 28-30, 2015:

Liakos F, Koutsarnakis C, Liouta E, **Kalyvas AV**, Stranjalis G. The cerebral Isthmus: Definition, White Matter anatomy, Function.

2011 **Scholarship of Hygeia Hospital** (private hospital) for duration of **3 months** of postgraduate studies in the field of Neurosurgery, Hygeia hospital, Athens, Greece.

2004-2010 **Christodoulou Scolarship (Ioannina Bishopric)** for duration of **6 years** of undergraduate studies in the Medical School of the University of Ioannnina. (1st among other canditates. Principal criterion: High School Diploma Degree.)

PEER REVIEWED PUBLICATIONS (54)

(Original research: 26, First or equally first author: 17)

Equal first authorship denoted by asterisk*

Kalyvas AV, Vlachos K, Abu-Amara M, S Sampalis J, Glantzounis G. Bariatric surgery as metabolic surgery for diabetic patients. Current pharmaceutical design. 2014 May 1;20(22):3631-46.

Kalyvas AV, Linos D, Moris D. Concerns about Evaluating the Effect of Noise and Music in the Operating Room. Journal of the American College of Surgeons. 2014 Nov 1;219(5):1097-8.

Koutsarnakis C, Liakos F, **Kalyvas AV**, Sakas DE, Stranjalis G. A laboratory manual for stepwise cerebral white matter fiber dissection. World neurosurgery. 2015 Aug 31;84(2):483-93.

Piper RJ, **Kalyvas AV**, Young AM, Hughes MA, Jamjoom AA, Fouyas IP. Interventions for idiopathic intracranial hypertension. The Cochrane database of systematic reviews. 2015 Aug 7;8:CD003434.

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Kalyvas AV, Kalamatianos T, Pantazi, M, Lianos GD, Stranjalis G, Alexiou GA. Maternal environmental risk factors for congenital hydrocephalus: a systematic review. Neurosurgical Focus, 2016, 41.5: E3.

Koutsarnakis C, Liakos F, **Kalyvas AV**, Liouta E, Emelifeonwu J, Kalamatianos T, Sakas DE, Johnson E, Stranjalis G. Approaching the atrium through the intraparietal sulcus: Mapping the sulcal morphology and correlating the surgical corridor to underlying fiber tracts. Oper Neurosurg (Hagerstown). 2017 Aug 1;13(4):503-516. doi: 10.1093/ons/opw037.

Kalyvas AV, Kalamatianos T, Stranjalis G. Time trends in neurosurgical research output in Greece: what is the impact of the economic crisis? Neurosurgery. 2017 Feb 10

Koutsarnakis C, **Kalyvas AV**, Stranjalis G. Letter to the Editor. Approaches to the ventricular atrium. Journal of Neurosurgery. 2017 Apr;126(4):1373-1374.

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Kalyvas AV, Hughes MA, Koutsarnakis C, Morris D, Liakos F, Sakas DE, Stranjalis G, Fouyas I. Efficacy, complications and cost of surgical interventions for idiopathic intracranial hypertension: a systematic review of the literature. Acta Neurochir (Wien). 2017 Jan;159(1):33-49. doi: 10.1007/s00701-016-3010-2.

Themistocleous M, Giakoumettis D, Mitsios A, Anagnostopoulos C, **Kalyvas AV**, Koutsarnakis C. Hereditary hemorrhagic teleangiectasia patient presenting with brain abscess due to silent pulmonary arteriovenous malformation. Pan Afr Med J. 2016 Nov 11;25:145.

Themistocleous MS, Antoniades E, Giakoumettis D, **Kalyvas AV**, Mitsios A, Sfakianos G. Herpes simplex virus Type 1 encephalitis in an adolescent presenting with acute hydrocephalus. Journal of Surgical Case Reports. 2017 Jan 1;2017(2).

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Stavrinou P, **Kalyvas A**, Grau S, Hamisch C, Galldiks N, Katsigiannis S, Kabbasch C, Timmer M, Goldbrunner R, Stranjalis G. Survival effects of a strategy favoring second-line multimodal treatment compared to supportive care in glioblastoma patients at first progression. Journal of Neurosurgery. 2018 Nov 1;1(aop):1-6.

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Skandalakis GP, Koutsarnakis C, Pantazis N, **Kalyvas A**, Komaitis S, Lani E, Drosos E, Kalamatianos T, Hadjipanayis CG, Natsis K, Stranjalis G. The carotico-clinoid bar: A systematic review and meta-analysis of its prevalence and potential implications in cerebrovascular and skull base surgery. World Neurosurgery. 2019 Jan 22.

Kalamatianos T, Mavridis IN, Karakosta E, Drosos E, Skandalakis GP, **Kalyvas A**, Piagkou M, Koutsarnakis C, Stranjalis G. The parieto-occipital artery revisited: a microsurgical anatomic study. World Neurosurgery. 2019 ePub ahead of print

Drosos E*, **Kalyvas A***, Komaitis S, Skandalakis GP, Kalamatianos T, Liouta E, Neromyliotis E, Alexiou GA, Stranjalis G, Koutsarnakis C. Angiosarcoma-related cerebral metastases: a systematic review of the literature. Neurosurgical review. 2019 Jun 4:1-20.

Neromyliotis E, **Kalyvas AV,** Drosos E, Komaitis S, Bartziotas D, Skandalakis GP, Stranjalis G, Koutsarnakis C. Spinal Atypical Rhabdoid Teratoid Tumor in an Adult Woman: Case Report and Review of the Literature. World neurosurgery. 2019 Aug 1;128:196-9.

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Komaitis S*, **Kalyvas AV***, Skandalakis GP, Drosos E, Lani E, Liouta E, Liakos F, Kalamatianos T, Piagkou M, Emelifeonwu JA, Stranjalis G. The frontal longitudinal system as revealed through the fiber microdissection technique: structural evidence underpinning the direct connectivity of the prefrontal-premotor circuitry. Journal of neurosurgery. 2019 Oct 4;1(aop):1-3.

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Stranjalis G, Komaitis S, **Kalyvas AV**, Drosos E, Stavrinou LC, Koutsarnakis C, Kalamatianos T. Recent trends (2010-2018) in traumatic brain injury in Greece: Results on 2042 patients. Injury. 2020 Sep;51(9):2033-2039. doi: 10.1016/j.injury.2020.05.045. Epub 2020 Jun 1. PMID: 32536530.
Kalyvas A, Almeida JP, Mohan N, O'Halloran PJ, Vescan A, Gentili F. Expanded Endoscopic Endonasal Approach for Removal of a Tuberculum Sella Meningioma. World Neurosurg. 2020 Oct;142:62. doi: 10.1016/j.wneu.2020.06.067. Epub 2020 Jun 17. PMID: 32561487.
Almeida JP, Tabasinejad R, **Kalyvas A**, Takami H, Mohan N, O'Halloran PJ, Sanchez MM, Velasquez C, Zadeh G, Gentili F. The Importance of Long Term Follow Up After Endoscopic Pituitary Surgery: Durability of Results and Tumor Recurrence. Neurol India. 2020 May-Jun;68(Supplement):S92-S100. doi: 10.4103/0028-3886.287675. PMID: 32611898.
Almeida JP, **Kalyvas A**, Mohan N, Oswari S, Takami H, Velasquez C, Asha M, Zadeh G, Gentili F. Current Results of Surgical Treatment of Craniopharyngiomas: The Impact of Endoscopic Endonasal Approaches. World Neurosurg. 2020 Oct;142:582-592. doi: 10.1016/j.wneu.2020.05.174. PMID: 32987614.
O'Halloran PJ, Gutierrez E, **Kalyvas A**, Mohan N, Atallah S, Kalia S, Millar BA, Laperriere N, Conrad T, Zadeh G, Bernstein M, Shultz DB, Kongkham P. Brain Metastases: A Modern Multidisciplinary Approach. Can J Neurol Sci. 2020 Oct 12:1-32. doi: 10.1017/cjn.2020.224. Epub ahead of print. PMID: 33040758.
Komaitis S, Koutsarnakis C, Lani E, Kalamatianos T, Drosos E, Skandalakis GP, Liakos F, Liouta E, **Kalyvas AV**, Stranjalis G. Deciphering the frontostriatal circuitry through the fiber dissection technique: direct structural evidence on the morphology and axonal connectivity of the fronto-caudate tract. J Neurosurg. 2021 Jan 1:1-13. doi: 10.3171/2020.7.JNS201287. Epub ahead of print. PMID: 33385993.
Komaitis S, Liakos F, **Kalyvas AV**, Drosos E, Skandalakis GP, Neromyliotis E, Gerogiannis A, Troupis T, Stranjalis G, Koutsarnakis C. The corticotegmental connectivity as an integral component of the descending extrapyramidal pathway: novel and direct structural evidence stemming from focused fiber dissections. Neurosurg Rev. 2021 Feb 10. doi: 10.1007/s10143-021-01489-2. Epub ahead of print. PMID: 33564983.
Vincent Y, Landry AP, Purzner T, **Kalyvas A**, Mohan N, O'Halloran PJ, Gao A, Zadeh G. Adult IDH-mutant brainstem glioma: illustrative case. Journal of Neurosurgery: Case Lessons JNSCL, 1(12), CASE2078.
Samuel N*, **Kalyvas A***, Bernstein M, Kongkham P. Surgical paradigms in low grade glioma: lessons from the management of insular glioma. Canadian Journal of Neurological Sciences / Journal Canadien Des Sciences Neurologiques, 1-5. doi:10.1017/cjn.2021.10
Kalyvas A, Millesi M, Gentili F. Endoscopic extra-capsular resection of a giant pituitary adenoma: how I do it. Acta Neurochir (Wien). 2021 Apr 16. doi: 10.1007/s00701-021-04833-z. Epub ahead of print. PMID: 33861377.
COVIDSurg Collaborative, GlobalSurg Collaborative. SARS-CoV-2 vaccination modelling for safe surgery to save lives: data from an international prospective cohort study. Br J Surg. 2021 Mar 24:znab101. doi: 10.1093/bjs/znab101. Epub ahead of print. PMID: 33761533; PMCID: PMC7995808.
COVIDSurg Collaborative; GlobalSurg Collaborative. Timing of surgery following SARS-CoV-2 infection: an international prospective cohort study. Anaesthesia. 2021 Jun;76(6):748-758. doi: 10.1111/anae.15458. Epub 2021 Mar 9. PMID: 33690889.

Papadiochos I, Sarivalasis SE, Chen M, Goutzanis L, **Kalyvas A**. Pneumomediastinum as a Complication of Oral and Maxillofacial Injuries: Report of 3 Cases and a 50-Year Systematic Review of Case Reports. Craniomaxillofacial Trauma & Reconstruction. March 2021. doi:10.1177/1943387521997236
Kalamatianos T, **Kalyvas AV**, Komaitis S, Stavridi K, Liouta E, Drosos E, Liakos F, Koutsarnakis C, Stranjalis G. Trends in hospital stay and outcome of CNS tumor patients in Greece during the socioeconomic crisis period (2010-2018): analysis of 1785 neurosurgical patients according to histopathological diagnosis and demographic characteristics. Surgical Neurology International. Accepted - Under Production.
Liakos F, Komaitis S, Stranjalis G, Drosos E, Liouta E, Neromyliotis E, Skandalakis GP, Gerogiannis A, **Kalyvas AV**, Piagkou M, Koutsarnakis C. The topography of the frontal terminations of the uncinate fasciculus revisited using focused fiber dissections: Shedding light on a current anatomo-functional controversy. World Neurosurgery. Accepted - Under Production.

Stavrinou P, Drosos E, Komaitis S, Liakos F, **Kalyvas AV**, Neromyliotis E, Troupis T, Goldbrunner R, Stranjalis G, Koutsarnakis C. Direct comparison between the Kawase's approach and the retrosigmoid intradural suprameatal (RISA) corridor to access the petroclival region using CT quantitative volumetric analysis. A cadaveric study. J Neurosurg. Under Review.

Kalyvas A, Almeida JP, Nassiri F, O'Halloran PJ, Mohan N, Ye VC, Tang DM, Soni P, Potter T, Ezzat S, Kshettry VR, Zadeh G, Recinos PF, Gentili F. Endoscopic Endonasal Surgery For Prolactinomas: Prognostic Factors For Disease Control. World Neurosurgery. Under Review.

Toyota E, Nassiri F, Wang J, Ye V, Ali MI, **Kalyvas A**, Gonen L, Klironomos G, Gentili F, Zadeh G. Outcomes After Exclusive Use of Endoscopy in the Surgical Management of Recurrent Pituitary Adenomas. World Neurosurgery. Under Review.

Liouta E, **Kalyvas A**, Komaitis S, Drosos E, Koutsarnakis C, García-Gómez JM , Juan-Albarracín J, Katsaros V, Kalamatianos T, Argirakos T, Stranjalis G. Association between preoperative neurocognitive status and IDH1 mutation status in high- grade gliomas. British Journal of Neurosurgery. Under Review.

Yang K, Gutierrez E, Landry AP, **Kalyvas A**, Millesi M, Leite M, Jablonska P, Weiss J, Millar BA, Conrad T, Laperriere N, Bernstein M, Zadeh G, Shultz D, Kongkham PN. Multiplicity does not affect outcomes in brain metastasis patients treated with surgery. Neuro-oncology. Under Review.

Kalyvas A, Gutierrez E, O'Halloran P, Mohan N, Wong C, Millar BA, Laperriere N, Conrad T, Zadeh G, Bernstein M, Shultz DB, Kongkham P. Pachymeningeal failure in resected brain metastases: Incidence, characteristics and predicting factors in patients receiving adjuvant stereotactic radiosurgery. In progress.

Kalyvas A, Drosos E, Komaitis S, Dogruel Y, Skandalakis G, Liouta E, Neromyliotis E, Zadeh G, Stranjalis, G, Koutsarnakis C. Segmenting the temporal pole through the fiber dissection technique: structural evidence underpinning a connectivity based segmentation. In progress.

Papatsoutsos E, **Kalyvas A**, Drosos E, Koutsarnakis C, Komaitis S, Stranjalis G, Georgalas C. The limits of the endoscopic surgical approach to the lateral frontal sinus based on the DRAF III procedure and its modifications: a cadaveric study. In progress.

Gutierrez E*, **Kalyvas A***, Villafuerte CJ, Millar BA, Laperriere N, Conrad T, Zadeh G, Bernstein M, Weiss J, Kongkham P, S
Preoperative Dural Contact Correlates to the risk of Nodular Leptomeningeal Failure Following Adjuvant Stereotactic Radiosu
progress.

Kalyvas A*, Milesi M*, Leite M, Ye V, Yang K, Jacques L, Mete O, Zadeh G, Gentili F. Rathke's cleft cysts: long term surgical outcomes and recurrences. In progress.

Milesi M*, **Kalyvas A***, Leite M, Yang K, Jacques L, Mete O, Zadeh G, Gentili F. Endoscopic Endonasal surgery for Intrasellar Arachoid Cysts: Long terms outcomes and complication profile. In progress.

The International Tuberculum Sellae Meningioma authors. International Tuberculum Sellae Meningioma Study: Surgical Outcomes and Management Trends. In progress (multicenter)

The International Tuberculum Sellae Meningioma authors. International Tuberculum Sellae Meningioma Study: Preoperative grading scale to predict outcomes and inform approach selection. In progress (multicenter)

PASTOR study authors. Pituitary Apoplexy Surgical Timing and Outcome Registry (PASTOR). In Progress (multicenter)

GlobalSurg-CovidSurg Week authors. A machine leaned risk score for surgery in SARS-CoV-2. In Progress (multicenter)

GlobalSurg-CovidSurg Week authors. VTE risk in SARS-CoV-2 patients. In Progress (multicenter)

The ZPS authors. Multicenter external validation of the Zurich Pituitary Score. In progress (multicenter).

Kalyvas A, Zadeh G, Gentili F, Margolin E. Predictors of Visual Outcomes after Pituitary Adenoma Surgery and observation. In progress (prospective study - recruiting patients)

BOOK CHAPTERS

Komaitis S, **Kalyvas AV,** Stranjalis G. Intracerebral Haemorrhage. In Hellenic Stroke Organization (2018), *Cerebrovascular Accidents, Athens: Litsas.*

Kalyvas AV, Komaitis S, Stranjalis G. Cerebral edema in stroke patients. In Hellenic Stroke Organization (2018), *Cerebrovascular Accidents, Athens: Litsas.*

Kalyvas A, Bernstein M, Baticulon RE, Broekman MLD, Robertson FC. The 2020 COVID-19 pandemic impact on Neurosurgery. In Neurosurgery and Global Health, Springer Nature 2021, Germano (Ed). In production.

ABSTRACTS PUBLISHED IN REFEREED JOURNALS

Kalyvas AV, Themistocleous M, Boutos N, Themistoklis K, Korfias S, Sakas DE. Efficacy, safety and complication profile of the Prometra programmable pump in providing intrathecal baclofen therapy for intractable spasticity. Stereotact Funct Neurosurg. 2014;92(2):1-262.

Themistoklis K, Boutos N, Themistocleous M, **Kalyvas AV**, Sakas DE. Infectious complications and treatment options in intrathecal baclofen delivery systems. Stereotact Funct Neurosurg. 2014;92(2):1-262.

Themistocleous M, Anagnostopoulos C, **Kalyvas A**, Themistoklis K, Korfias S, Sakas D. Infected implantable devices. Treatment without removal. Stereotact Funct Neurosurg. 2014;92(2):1-262.
Kalyvas A, Korfias S, Boutos N, Themistoklis K, Themistocleous M, Sakas D. Intrathecal baclofen therapy as a treatment option for painful spasms in Friedreich Ataxia: 10 June–080. Neuromodulation. 2015 Aug 1;18(6).
Boutos N, Korfias S, Themistoklis K, **Kalyvas A**, Themistocleous M, Sakas D. Efficacy of a new catheter for intrathecal baclofen therapy: 10 June–083. Neuromodulation. 2015 Aug 1;18(6).
Themistoklis K, Korfias S, Boutos N, **Kalyvas A**, Themistocleous M, Sakas D. Long term follow-up of a new programmable pump system in intrathecal therapy for intractable spasticity: 10 June–081. Neuromodulation. 2015 Aug 1;18(6).
Stavrinou P, **Kalyvas A**, Katsigiannis S, Hamisch C, Krischek B, Stranjalis G, Goldbrunner R. P09. 56 Comparison of the effect of different treatment strategies within discrepant health-care systems on survival of glioblastoma patients. Neuro-Oncology. 2017 May;19(Suppl 3):iii82.
Skandalakis GP, **Kalyvas A**, Lani E, Komaitis S, Chatzopoulou D, Manolakou D, Pantazis N, Zenonos GA, Hadjipanayis CG, Stranjalis GS, Koutsarnakis C. Comparative Effectiveness of Preventive and Treatment Interventions for Cerebral Hyperperfusion Syndrome Following Bypass Surgery. Neurosurgery. 2019 Sep 1;66(Supplement_1):nyz310_501.
Kalyvas A, Neromyliotis E, Skandalakis GS, Koutsarnakis C, Komaitis S, Zadeh G, Gentili F, Gobin PY, Stranjalis G, Patsalides A. A Systematic Review of Surgical Treatments of Idiopathic Intracranial Hypertension (IIH): Should VSS Be Regarded as the First Line Surgical Modality?. Neurosurgery. 2020 Dec;67(Supplement_1):nyaa447_315.

CONGRESS ABSTRACTS

A. Oral Presentations

Kalyvas AV, Themistocleous M, Boutos N, Themistoklis K, Korfias S, Sakas DE. Efficacy, safety and complication profile of the Prometra programable pump in providing intrathecal baclofen therapy for intractable spasticity. XXIst Congress of the European Society for Stereotactic and Functional Neurosurgery, Maastricht, The Netherlands. September 17–20, 2014.
Themistoklis K, Boutos N, Themistocleous M, **Kalyvas AV**, Sakas DE. Infectious complications and treatment options in intrathecal baclofen delivery systems. XXIst Congress of the European Society for Stereotactic and Functional Neurosurgery, Maastricht, The Netherlands. September 17–20, 2014.
Themistocleous M, Anagnostopoulos C, **Kalyvas AV**, Themistoklis K, Korfias S, Sakas DE. Infected implantable devices. Treatment without removal. XXIst Congress of the European Society for Stereotactic and Functional Neurosurgery, Maastricht, The Netherlands. September 17–20, 2014.
Liakos F, Koutsarnakis C, Liouta E, **Kalyvas AV**, Stranjalis G. The cerebral Isthmus: Definition, White Matter anatomy, Function. 29th Hellenic (Greek) Neurosurgical Congress. Athens, Greece. May 28-30, 2015 (**Award winning presentation - as the best oral presentation of the Congress**).
Kalyvas AV, Korfias S, Themistoklis K, Boviatsis K, Boutos N, Vlachakis E, Sakas DE. Hemifacial spasm treatment via drilling of the internal acoustic meatus. 41st Hellenic (Greek) Medical Congress. Athens, Greece, June 10-13, 2015.
Boviatsis K, Korfias S, **Kalyvas AV**, Themistoklis K, Vlachakis E, Boutos N, Sakas DE. Synovial Cysts of the cervical and lumbar spine. Neurosurgical management. 41st Hellenic (Greek) Medical Congress. Athens, Greece, June 10-13, 2015.
Themistoklis K, Korfias S, Boviatsis K, **Kalyvas AV**, Boutos N, Vlachakis E, Sakas DE. Surgical excision of intraosseous meningioma and simultaneous cranioplasty with a pre-designed bone flap. 41st Hellenic (Greek) Medical Congress. Athens, Greece, June 10-13, 2015.
Stavrinou P, **Kalyvas A**, Goldbrunner R, Stranjalis G. Is there a survival benefit from treatment of glioblastoma recurrence? Comparison of the effect of different treatment strategies on survival. 31st Hellenic (Greek) Neurosurgical Congress, Ioannina, Greece, June 15-17, 2017.
Kalyvas A, Komaitis S, Koutsarnakis C, Liakos F, Stranjalis G. The topographic anatomy of the optic radiations in relation to the roof and floor of the atrium of the lateral ventricle. 31st Hellenic (Greek) Neurosurgical Congress, Ioannina, Greece, June 15-17, 2017.
Anagnostopoulos C, **Kalyvas A**, Komaitis S, Giakoumettis D, Stranjalis G. Incidence of GBM-associated hydrocephalus: a case series. 31st Hellenic (Greek) Neurosurgical Congress, Ioannina, Greece, June 15-17, 2017.
Liouta E, **Kalyvas A**, Koutsarnakis C, Liakos F, Stranjalis G. Neurocognitive and neurological deficits in patients with newly diagnosed supratentorial gliomas: A retrospective study. 31st Hellenic (Greek) Neurosurgical Congress, Ioannina, Greece, June 15-17, 2017.
Kalyvas A, Koutsarnakis C, Skandalakis G, Komaitis S, Stranjalis G. Sledge Runner Fasciculus: Microanatomic architecture and tractographic morphology of a finer tract subserving spatial navigation and visuospatial imagery. 32nd Annual Congress of the Hellenic Neurosurgical Society (Joint Meeting with The Society of British Neurological Surgeons & Cyprus Neurosurgical Society), Chania, Greece, May 24-26, 2018
Anagnostopoulos C, Drosos E, **Kalyvas A,** Komaitis S, Stanjalis G. Brain lesions in patients with a known malignancy outside the CNS. Are the always metastatic? 32nd Annual Congress of the Hellenic Neurosurgical Society (Joint Meeting with The Society of British Neurological Surgeons & Cyprus Neurosurgical Society), Chania, Greece, May 24-26, 2018
Liouta E., **Kalyvas A.**, Drosos E., Koutsarnakis C., Stranjalis G. Neurocognitive status is influenced by IDH1 genetic mutation

in malignant glioma. 33rd Annual Hellenic (Greek) Neurosurgical Congress. Thessaloniki, Greece, June 2019.
Karavasilis E, Christidi F, Koutsarnakis C, **Kalyvas A**, Velonakis G, Efstathopoulos E, Kelekis N. Snow Is Not Always Necessary For Sledge Runner: A Diffusion Tensor Tractography Study Of The Sledge Runner Fasciculus. European Congress of Radiology 2019.
The International Tuberculum Sellae Meningioma authors. International Tuberculum Sellae Meningioma Study: Surgical Outcomes and Management Trends. Congress of Neurological Surgeons (CNS) annual meeting (Virtual), 2020.
Received the "Best Clinical Research Award - Tumor"
The International Tuberculum Sellae Meningioma authors. International Tuberculum Sellae Meningioma Study: Preoperative grading scale to predict outcomes and inform approach selection. Congress of Neurological Surgeons (CNS) annual meeting (Virtual), 2020.

B. Posters

Korfias S, **Kalyvas AV**, Vlachakis E, Themistoklis K, Sakas DE. interhemispheric Hygroma with encephalocoele precipitating post-traumatic Hydrocephalus in a patient with serious Traumatic Brain Injury and decompressive craniectomy. 28th Hellenic (Greek) Neurosurgical Congress. Kavala, Greece. June 19-22, 2014.
Korfias S, Themistoklis K, Vlachakis E, **Kalyvas AV**, Sakas DE. Neurosurgical Management of serious Central Nervous System infections. 28th Hellenic (Greek) Neurosurgical Congress. Kavala, Greece. June 19-22, 2014.
Koutsarnakis C, Liakos F, Themistoklis K, **Kalyvas AV**, Stranjalis G. the "over the wire" technique for ventricular catheter revision and a proposed access kit for this purpose. 29th Hellenic (Greek) Neurosurgical Congress. Athens, Greece. May 28-30, 2015.
Anagnostopoulos C, **Kalyvas AV**, Koutsarnakis C, Stranjalis G. Solitary Fibrous Tumours. Presentation of 4 cases. 29th Hellenic (Greek) Neurosurgical Congress. Athens, Greece. May 28-30, 2015.
Kalyvas AV, Korfias S, Boviatsis K, Themistoklis K, Sakas DE. Cerebral Arteriovenous Malformations. Acute clinical presentation, diagnostic imaging and management. 29th Hellenic (Greek) Neurosurgical Congress. Athens, Greece. May 28-30, 2015.
Boviatsis K, Korfias S, Themistoklis K, **Kalyvas AV**, Sakas DE. Syringomyelia of the cervical spine due to cervical degenerative disk disease. 29th Hellenic (Greek) Neurosurgical Congress. Athens, Greece. May 28-30, 2015.
Kalyvas AV, Korfias S, Boutos N, Themistoklis K, Themistocleous M, Sakas DE. Intrathecal baclofen therapy as a treatment option for painful spasms in Friedeich Ataxia. INS 12th World Congress. Montreal, Quebec, Canada. June 6-11, 2015.
Themistoklis K, Korfias S, Boutos N, **Kalyvas AV**, Themistocleous M, Sakas DE. Long term follow-up of a new programmable pump system in intrathecal therapy for intractable spasticity. INS 12th World Congress. Montreal, Quebec, Canada. June 6-11, 2015.
Boutos N, Korfias S, Themistoklis K, **Kalyvas AV**, Themistocleous M, Sakas DE. Efficacy of a new catheter for intrathecal baclofen therapy. INS 12th World Congress. Montreal, Quebec, Canada. June 6-11, 2015.
Kalyvas A, Komaitis S, Papadiochos I, Papadogeorgakis N, Stranjalis G. Giant malignant carcinoma of the paranasal sinuses with intracranial expansion: removal through extended transbasal approach and reconstruction of anterior cranial fossa. 30th Hellenic (Greek) Neurosurgical Congress. Volos, Greece. June 16-18, 2016.
Komaitis S, **Kalyvas A**, Mpanos S, Stranjalis G .Surgical treatment of anterior cranial fossa meningiomas: A 5 year retrospective study. 30th Hellenic (Greek) Neurosurgical Congress. Volos, Greece. June 16-18, 2016.
Kalyvas AV, Hughes M, Koutsarnakis C, Liakos F, Sakas DE, Stranjalis G, Fouyas I. Efficacy, complications and cost of surgical interventions for idiopathic intracranial hypertension: a systematic review of the literature. EANS2016: 16th European Congress of Neurosurgery, Athens, Greece. September 4-8, 2016
Kalyvas AV, Loufardaki A, Koutsarnakis C, Liouta E, Kalamatianos T, Stranjalis G. Greek neurosurgical publication productivity: not in crisis. EANS2016: 16th European Congress of Neurosurgery, Athens, Greece. September 4-8, 2016
Kalyvas AV, Korfias S, Anagnostopoulos C, Skandalakis G, Themistocleous M, Sakas DE. Surgical resection of a traumatic pseudoaneurysm of the occipital artery. A case report. EANS2016: 16th European Congress of Neurosurgery, Athens, Greece. September 4-8, 2016
Liouta E, Gatzonis S, **Kalyvas A**, Komaitis S, Liakos F, Koutsarnakis C, Anagnostopoulos C, Stranjalis G. Typical versus non-typical idiopathic normal pressure hydrocephalus: the importance of cognition and gait characteristics in predicting tap test and shunt outcomes. EANS2016: 16th European Congress of Neurosurgery, Athens, Greece. September 4-8, 2016
Liakos F, Koutsarnakis C, **Kalyvas A,** Liouta E, Emelifeownu J. Stranjalis G. Approaching the atrium through the intraparietal sulcus: Mapping the sulcal morphology and correlating the surgical corridor to underlying fiber tracts. EANS2016: 16th European Congress of Neurosurgery, Athens, Greece. September 4-8, 2016
Liakos F, Koutsarnakis C, **Kalyvas A**, Komaitis S, Stranjalis G. The Superior Frontal Transsulcal Corridor to the Anterior Ventricular System: Exploring the Sulcal and Subcortical Anatomy Using White Matter Dissections and Diffusion Tensor Imaging Tractography. EANS2016: 16th European Congress of Neurosurgery, Athens, Greece. September 4-8, 2016
Anagnostopoulos C, Komaitis S, **Kalyvas A**, Liouta E, Stranjalis G. Intracranial meningioma surgery in patients over 70 years old. One year morbidity and mortality. EANS2016: 16th European Congress of Neurosurgery, Athens, Greece. September 4-8,

2016

Themistoklis K, Korfias S, **Kalyvas A**, Boutos N, Boviatsis K, Giakoumettis D, Vlachakis E, Sakas DE. A new « hybrid » pump for intrathecal baclofen therapy. XXII Congress of the European Society for Stereotactic and Functional Neurosurgery, Madrid, Spain, September 28-October 1, 2016.

Kalyvas A, Komaitis S, Anagnostopoulos C, Drosos E, Stranjalis Metastatic cerebral angiosarcoma: Case report and review of the literature. 31st Hellenic (Greek) Neurosurgical Congress, Ioannina, Greece, June 15-17, 2017.

Anagnostopoulos C, **Kalyvas A**, Komaitis S, Giakoumettis G, Stanjalis G. Metastatic Anaplastic Oligodendroglioma. A case report and review of the literature. 31st Hellenic (Greek) Neurosurgical Congress, Ioannina, Greece, June 15-17, 2017.

Liouta E, **Kalyvas A**, Koutsarnakis C, Liakos F, Anagnostopoulos C, Komaitis S, Giakoumettis D, Stranjalis G. Frequency of neurocognitive vs neurological deficits in a large series of newly diagnosed supratentorial gliomas. EANS2017: 17th European Congress of Neurosurgery, Venice, Italy. October 1-5, 2017

Drosos E, **Kalyvas A**, Anagnostopoulos C, Komaitis S, Stranjalis G. Multilevel spondylodiscitis with focal epidural abscess. 32nd Annual Congress of the Hellenic Neurosurgical Society (Joint Meeting with The Society of British Neurological Surgeons & Cyprus Neurosurgical Society), Chania, Greece, May 24-26, 2018

Anagnostopoulos C, Drosos E, **Kalyvas A**, Gogas C, Stranjalis G. Subacute thrombosis after stent assisted coil embolization of an MCA aneurysm, a case report. 32nd Annual Congress of the Hellenic Neurosurgical Society (Joint Meeting with The Society of British Neurological Surgeons & Cyprus Neurosurgical Society), Chania, Greece, May 24-26, 2018

Drosos E, **Kalyvas A**, Dogruel Y, Koutsarnakis C, Stranjalis G. Surface anatomy of the temporal lobe with emphasis on the topographic architecture of the temporal pole. (Award of the best poster). 33rd Annual Hellenic (Greek) Neurosurgical Congress. Thessaloniki, Greece, June 2019.

Drosos E, **Kalyvas A**, Komaitis S, Koutsarnakis C, Stranjalis G. Angiosarcoma related cerebral metastases: An illustrative case and systematic review of the literature. 33rd Annual Hellenic (Greek) Neurosurgical Congress. Thessaloniki, Greece, June 2019.

Kalyvas A, Neromyliotis E, Skandalakis GS, Koutsarnakis C, Komaitis S, Zadeh G, Gentili F, Gobin PY, Stranjalis G, Patsalides A. A Systematic Review of Surgical Treatments of Idiopathic Intracranial Hypertension (IIH): Should VSS Be Regarded as the First Line Surgical Modality? 2020 CNS meeting. Online.

INVITED LECTURES/PRESENTATIONS

05/2021	**Approaches to the ventricular atrium: Avoiding injury to the optic radiations and beyond.** Neurosurgery Rounds. Toronto Western Hospital, Division of Neurosurgery, University of Toronto. May 26, 2021.
02/2021	**White matter tracts anatomy: Practical aspects for glioma surgery.** Neurosurgery Residency academic half-day program. The Brain School (thebrainschool.net), Toronto Western Hospital, Division of Neurosurgery, University of Toronto. February 5, 2021
10/2020	**Endoscopic Transclival approach and lateral extensions.** 60th W. Lougheed Microsurgical Course, Mount Sinai Surgical Skills Center, University of Toronto
01/2020	**White Matter Tracts of the Lateral Surface of the Brain and their Clinical Significance**. Neurosurgery Rounds. Toronto Western Hospital, Division of Neurosurgery, University of Toronto. January 29, 2020.
09/2019	**Cerebral Surface anatomy, imaging correlation and surgical applications.** The Brain School (thebrainschool.net), Toronto Western Hospital, Division of Neurosurgery, University of Toronto. September 20, 2019
08/2019	**Cerebral Sulci and Gyri.** Neurosurgery Rounds. Toronto Western Hospital, Division of Neurosurgery, University of Toronto.
04/2019	**The cranial nerves**. In the context of MSc Program "Clinical and Experimental Neurosurgery", Medical School, National and Kapodistrian University of Athens, Athens, Greece.
03/2019	**White Matter Surgery and Brain Mapping**. In the context of MSc Program "Clinical and Experimental Neurosurgery", Medical School, National and Kapodistrian University of Athens, Athens, Greece.
12/2018	**Complications in Neurosurgery: Diagnosis, Management and prevention.** Hellenic (Greek) Neurosurgical Society educational meetings. Athens, Greece.
11/2018	**Cerebral Sulci and Gyri**. In the context of MSc Program "Applied Neuroanatomy", Medical School , National and Kapodistrian University of Athens, Athens Greece
09/2018	**Diagnosis and Management of Idiopathic Intracranial Hypertension**. Clinical Neuroscience multidisciplinary team meeting. Evangelismos Hospital, Athens, Greece.
06/2018	**Landmark Studies in Intracranial Aneurysms Management**. Clinical Neuroscience multidisciplinary team meeting. Evangelismos Hospital, Athens, Greece.
05/2018	**Brain mapping through clinical cases.** In the context of international Hands-on Workshop in Neurosurgical Anatomy and White Matter Dissection, Hellenic (Greek) Neurosurgical Society &

	Athens Microneurosurgery laboratory, Evangelismos Hospital, Athens, Greece [under the auspices of the **EANS**].
05/2018	**White Matter Dissection: The medial to lateral technique.** In the context of international Hands-on Workshop in Neurosurgical Anatomy and White Matter Dissection, Hellenic (Greek) Neurosurgical Society & Athens Microneurosurgery laboratory, Evangelismos Hospital, Athens, Greece [under the auspices of the **EANS**].
02/2018	**History and Technical Nuances of the Microscopic Transphenoidal Approach**. Clinical Neuroscience multidisciplinary team meeting. Evangelismos Hospital, Athens, Greece.
06/2017 & 05/2018	**White Matter Dissection: The lateral to medial technique.** In the context of international Hands-on Workshop in Neurosurgical Anatomy and White Matter Dissection, Hellenic (Greek) Neurosurgical Society & Athens Microneurosurgery laboratory, Evangelismos Hospital, Athens, Greece [under the auspices of the **EANS**].
02/2017	**Traumatic Brain Injury: Neurosurgical Management.** 22nd seminar (for CME) of Evangelismos Hospital, Evangelismos Hospital, Athens, Greece.
10/2016	**Pseudoaneurysms of the occipital artery: Diagnosis and management.** Neurosurgery rounds. Evangelismos Hospital, Athens, Greece.
03/2016	**Diffuse Low Grade Gliomas: Contemporary Management**. Hellenic (Greek) Neurosurgical Society Monthly Educational Meetings. Athens, Greece.
03/2016	**Diagnosis and management of CNS Lymphomas.** Local presentation. Neuro-oncology multidisciplinary team meeting. Evangelismos Hospital, Athens, Greece.
02/2015	**Anatomy of the orbit.** Local presentation. Clinical Neuroscience multidisciplinary team meeting. Evangelismos Hospital, Athens, Greece.
12/2011	**Neurosurgical management of GH secreting adenomas**. Local Presentation. Hygeia hospital, Athens, Greece.

REFEREEING/REVIEWING

Reviewer in *Neurosurgical Review*
Reviewer in World Neurosurgery
Reviewer in PLOS one
Reviewer in *Metabolic Brain Disease*
Reviewer in BMJ Open
Reviewer in *World Journal of Surgical Oncology*
Reviewer in *Scientometrics*
Reviewer in Life

OPINIONS IN THE PRESS

Kalyvas AV, Stranjalis G. Evolution of Neurosurgery in Greece. Inside Neurosurgeon, AANS International, AANS Neurosurgeon: Volume 26, Number 3, 2017. https://goo.gl/1rDjx3

TRAINING AND COURSES

02/2021	**Comprehensive World Brain Mapping Course**, Online Brain Mapping Course, AANS.
11/2018	**5th Endoscopic Skull Base Masterclass & Symposium 2018,** Leiden University Medical Center, Leiden, The Netherlands
05/2018	**The European Training Courses in Neurosurgery: Functional Neurosurgery & Head Injury**, The European Association of Neurosurgical Societies, Belgrade, Serbia
05/2017	**The European Training Courses in Neurosurgery: Spine & Peripheral Nerves**, The European Association of Neurosurgical Societies, Prague, Czech Republic
04/2017	**Intracranial glioma Workshop: From A to Z,** The European Association of Neurosurgical Societies, University of Thessaly, Larissa, Greece (Theoretical course)
11/2016	**Neurosurgical Approaches to the Cranial Compartments,** Royal College of Surgeons of Edinburgh, The stewart Skills Laboratory of The Royal College of Surgeons of Edinburgh, Edinburgh, United Kingdom (Hand-on Course)
06/2016	**5th Annual World Course in Advanced Techniques in Neurosurgical Oncology,** London, United Kingdom
06/2016	**The 16th Helsinki Live Demonstration Course in Operative Microneurosurgery,** Helsinki, Finland
12/2014	**Comprehensive Clinical Neurosurgery Review course,** Krakow, Poland (Theoretical course)
11/2014	**Neurosurgical Approaches to the Cranial Compartments,** Royal College of Surgeons of Edinburgh, The stewart Skills Laboratory of The Royal College of Surgeons of Edinburgh, Edinburgh, United Kingdom (Hand-on Course)
11/2013	**Neurosurgical Approaches to the Cranial Compartments,** Royal College of Surgeons of

	Edinburgh, The stewart Skills Laboratory of The Royal College of Surgeons of Edinburgh, Edinburgh, United Kingdom (Hand-on Course)
11/2013	**SPSS statistics course: Linear and logistic regression analysis,** medical statistics and Biometry Laboratory of The University of Thessaly, Technological Educational Institute of Epirus, Ioannina, Greece. (Theoretical course)
10/2013	**Basic SPSS statistics course,** medical statistics and Biometry Laboratory of The University of Thessaly, Technological Educational Institute of Epirus, Ioannina, Greece. (Theoretical course)
10/2013	**Advanced Trauma Life Support course (ATLS)**, American College of Surgeons, University Hospital of Ioannina, Ioannina, Greece.
09/2013	**Advanced Cardiac Life Support course (ACLS)**, American College of Emergency Physicians, National and Kapodistrian University of Athens Medical school, Hellenic Society of Cardiopulmonary Resuscitation, Athens, Greece.
02/2013	**24th Hands-on course in microsurgery**, Orthopaedics Department of The University of Ioannina , Hellenic Society for Reconstructive Microsurgery, Ioannina, Greece. (Hand-on Course)
10/2012	**Basic Surgical Skills (Intercollegiate BSS)** Course, The Royal college of Surgeons of England, University of Thessaly Medical school, Larisa, Greece. (Hand-on Course)
05/2009	**Basic Life Support (BLS/AED)** course, European Resuscitation Council, University of Ioannina, Ioannina, Greece.
10/2007-12/2007	**“First Aid” course**, Hellenic Res Cross, Ioannina, Greece.

PROFESSIONAL MEMBERSHIPS

2004-2010	**Hellenic Medical students’ international Committee (HELMSIC)** Member
2004-2010	**Scientific community of Hellenic (Greek) Medical Students (EEFIE)** Member
2010-2013	**Medical Association of Ioannina (Greece)** Member
2013-present	**Medical Association of Athens (Greece)** Member
2014-present	**Hellenic (Greek) Neurosurgical Society** Member
2016-present	**European Association of Neurosurgical Societies (EANS)** Member
2019-present	**General Medical Council (GMC), GMC Ref: 7716268** Fully registered medical practitioner with specialist registration (Neurosurgery)
2019-present	**Canadian Medical Association** Member
2019-present	**College of Physicians and Surgeons of Ontario (CPSO),** CPSO #: 119334
2020-present	**American Association of Neurological Surgeons (AANS)** Candidate (in Fellowship training)
2020-present	**International Stereotactic Radiosurgery Society** Member
2021-present	**Society for Neuro-Oncology (SNO)**, Member (trainee) #751898

PERSONAL INTERESTS/OTHER DISTINCTIONS

Co-Author of the Theatrical Play **“The man with the spotted tie”, ISBN: 978-960-99990-3-8**.
http://www.openbook.gr/2012/03/poua-gravata.html (2012)
Vice-President of the medical students’ association of the University of Ioannina, Ioannina, Greece (2007-2009)
Member of the administrative council of medical school of the University of Ioannina, Ioannina, Greece (2007-2009)
President of the high school students’ association (elected for 2 consecutive years), 1st General High school of Ioannina, Ioannina, Greece (2002-2003 & 2003-2004)

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ΤΡΙΜΕΛΗΣ ΣΥΜΒΟΥΛΕΥΤΙΚΗ ΕΠΙΤΡΟΠΗ

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ΕΠΙΠΛΕΟΝ ΜΕΛΗ ΤΗΣ 7ΜΕΛΟΥΣ ΕΠΙΤΡΟΠΗΣ

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THESIS PUBLICATIONS

Kalyvas A, Koutsarnakis C, Komaitis S, Karavasilis E, Christidi F, Skandalakis GP, Liouta E, Papakonstantinou O, Kelekis N, Duffau H, Stranjalis G. "**Mapping the human middle longitudinal fasciculus through a focused anatomo-imaging study: shifting the paradigm of its segmentation and connectivity pattern.**" Brain Struct Funct. 2020 Jan;225(1):85-119. doi: 10.1007/s00429-019-01987-6. Epub 2019 Nov 26. PMID: 31773331.

Skandalakis GP, Komaitis S, **Kalyvas A**, Lani E, Kontrafouri C, Drosos E, Liakos F, Piagkou M, Placantonakis DG, Golfinos JG, Fountas KN, Kapsalaki EZ, Hadjipanayis CG, Stranjalis G, Koutsarnakis C. "**Dissecting the default mode network: direct structural evidence on the morphology and axonal connectivity of the fifth component of the cingulum bundle.**" J Neurosurg. 2020 Apr 24:1-12. doi: 10.3171/2020.2.JNS193177. Epub ahead of print. PMID: 32330886.

Liakos F, Komaitis S, Drosos E, Neromyliotis E, Skandalakis GP, Gerogiannis AI, **Kalyvas AV**, Troupis T, Stranjalis G, Koutsarnakis C. "**The topography of the frontal terminations of the uncinate fasciculus revisited through focused fiber dissections: Shedding light on a current controversy and introducing the insular apex as a key anatomo-clinical area.**" World Neurosurg. 2021 Jun 15:S1878-8750(21)00837-8. doi: 10.1016/j.wneu.2021.06.012. Epub ahead of print. PMID: 34144169.

PRESENTATIONS

“Surface anatomy of the temporal lobe with emphasis on the topographic architecture of the temporal pole”

Drosos E., **Kalyvas A**., Dogruel Y., Koutsarnakis C., Stranjalis G. 33rd annual congress of the Hellenic (Greek) Neurosurgical Society and 4rth South East Europe Neurosurgical Society Congress, Thessaloniki, Greece, June 2019 (**Award for the Best Poster).**

“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, Skandalakis GP, Drosos E, Karavasilis E, Christidi F, Zadeh G, Gentili F, Duffau H, Stranjalis G. AANS Annual Scientific Meeting, (e-poster) 2020.

“Insights on the Connectivity of the Precuneus: Introducing the Retrosplenial Aslant Tract (RAT).”

Skandalakis GP, Koutsarnakis C, **Kalyvas A**, Placantonakis DG, Golfinos JG, Hadjipanayis CG, Kostas N. Fountas KN, Kapsalaki EZ and George Stranjalis G, CNS Annual meeting, Houston, TX, October 6-8, 2018.

“The Cingulum Bundle-V as Revealed Through the Fiber Microdissection Technique: Structural Data Demonstrating the Direct Connectivity of the medial Temporo-Parietal Circuitry”.

Skandalakis GP, Komaitis S, **Kalyvas A**, Lani E, Kontrafouri C, Drosos E, Liakos F, Piagkou M, Placantonakis DG, Golfinos JG, Fountas KN, Kapsalaki EZ, Stranjalis G, AANS Annual Scientific Meeting, (e-poster) 2020.

“Approaches to the ventricular atrium: Avoiding injury to the optic radiations and beyond.”

Kalyvas A. Neurosurgery Rounds. Toronto Western Hospital, Division of Neurosurgery, University of Toronto. May 26, 2021.

“White matter tracts anatomy: Practical aspects for glioma surgery.”

Kalyvas A. Neurosurgery Residency academic half-day program. The Brain School (thebrainschool.net), Toronto Western Hospital, Division of Neurosurgery, University of Toronto. February 5, 2021

“White Matter Tracts of the Lateral Surface of the Brain and their Clinical Significance.”

Kalyvas A. Neurosurgery Rounds. Toronto Western Hospital, Division of Neurosurgery, University of Toronto. January 29, 2020.

“Cerebral Surface anatomy, imaging correlation and surgical applications.”

Kalyvas A. The Brain School (thebrainschool.net), Toronto Western Hospital, Division of Neurosurgery, University of Toronto. September 20, 2019

“Cerebral Sulci and Gyri.”

Kalyvas A. Neurosurgery Rounds. Toronto Western Hospital, Division of Neurosurgery, University of Toronto. August 2019.

“White Matter Surgery and Brain Mapping.”

Kalyvas A. In the context of MSc Program “Clinical and Experimental Neurosurgery”, Medical School, National and Kapodistrian University of Athens, Athens, Greece. March 2019.

ABSTRACT

OBJECTIVE

To elucidate the anatomy of the white matter fiber tracts implicated in the connectivity of the temporal pole (TP).

METHODS

Thirty normal, adult, formalin-fixed cerebral hemispheres were investigated via the white matter dissection technique. Lateral to medial and medial to lateral dissections were performed in tandem using the surgical microscope.

RESULTS

The trajectory, morphology and connectivity of all fiber tracts terminating to/arising from the temporal pole was revealed and disclosed. Their temporopolar terminations were delineated. The middle longitudinal fasciculus (MdLF) was consistently recorded to connect the dorsolateral TP to the Parietal and occipital lobes, through the auditory cortex. Within the inferior arm of the cingulum, the Cingulum bundle V (CB-V) was recorded to link the medial TP to the precuneus. The Uncinate fasciculus (UF) was seen to connect the dorsal TP to the posterior orbital gyrus and pars orbitalis, posterior two thirds of the gyrus rectus and posterior one third of the paraolfactory gyrus.

CONCLUSIONS

Our results support the hypothesis that distinct subregions of the TP are subcortically connected to different cortical areas subserving various cognitive networks. The essential relationship of the MdLF with the auditory cortex and the functional role of the temporopolar area implicated in its connectivity tend to shift the paradigm of its function towards high-order auditory function. In view of its subcortical architecture, the CB-V allegedly participates as a major subcortical stream within the default mode network, possibly subserving the transfer of multimodal cues relevant to visuospatial and mnemonic information. The UF is involved in the connectivity of temporopolar areas implicated in encoding and storing mnemonic and emotionally colored representations to areas of the orbitofrontal cortex that underlie executive functions and behavioral shaping, in a way that memory-based representations alter our behavior.

ΠΕΡΙΛΗΨΗ

ΣΚΟΠΟΣ

Η περιγραφή της ανατομίας των δεματίων της λευκής ουσίας που συμμετέχουν στην συνδεσιμότητα του κροταφικού πόλου (ΚΠ).

ΜΕΘΟΔΟΣ

Τριάντα (30) ημισφαίρια υγειών ενηλίκων μονιμοποιημένα σε φορμόλη μελετήθηκαν με χρήση της μεθόδου παρασκευής της λευκής ουσίας κατά Klingler. Οι εν λόγω βήμα προς βήμα παρασκευές ολοκληρώθηκαν με κατεύθυνση από έξω προς τα έσω και από έσω προς τα έξω.

ΑΠΟΤΕΛΕΣΜΑΤΑ

Η πορεία, η μορφολογία και η συνδεσιμότητα των δεματίων του ΚΠ περιεγράφηκε λεπτομερώς. Η τοπογραφία των καταλήξεων τους σε συγκεκριμένες περιοχές του ΚΠ αποσαφηνίστηκε. Το μέσο επίμηκες δεμάτιο (ΜΕΔ) ανευρέθηκε να συνδέει το πλαγιο-ραχιαίο τμήμα του ΚΠ με τον βρεγματικό και ινιακό λοβό μέσω του ακουστικού φλοιού. Παρατηρήθηκε πως το τμήμα V του προσαγώγειου (Π-V) συνδέει τον έσω κροταφικό πόλο με το προσφηνοειδές λόβιο. Το αγκιστρωτό δεμάτιο (ΑΔ) ανευρέθηκε να συνδέει τον ραχιαίο κροταφικό πόλο με την οπίσθια κογχική έλικα και την κογχική καλύπτρα, τα οπίσθια 2/3 της ευθείας έλικας και το οπίσθιο 1/3 της παρα-οσφρητικής έλικας.

ΣΥΜΠΕΡΑΣΜΑΤΑ

Τα αποτελέσματα μας υποστηρίζουν πως συγκεκριμένες περιοχές του ΚΠ συνδέονται υποφλοιωδώς σε διάφορα φλοιϊκά δίκτυα υπεύθυνα για συγκεκριμένες ανώτερες λειτουργίες. Η ανώτερη επεξεργασία ακουστικών ερεθισμάτων θα μπορούσε να ευοδώνεται μέσω του ΜΕΔ, λαμβάνοντας υπόψη την ουσιώδη σύνδεση του ΜΕΔ με τον ακουστικό φλοιό αλλά και με συγκεκριμένες περιοχές του ΚΠ. Το Π-V, θεωρητικά θα μπορούσε να λειτουργεί ως η κύρια υποφλοιώδης οδός του «δικτύου αυτόματης λειτουργίας» ευοδώνοντας την μεταφορά οπτικοχωρικών και μνημονικών πληροφοριών. Το ΑΔ συνδέει περιοχές του ΚΠ υπεύθυνες για την συναισθηματική μνήμη με περιοχές του μετωπο-κογχικού φλοιού υπεύθυνες για επιτελικές λειτουργίες και συμπεριφορική διάπλαση και ως εκ τούτου θα μπορούσε να διαμορφώνει την συμπεριφορά μας μέσω προηγούμενων αποθηκευμένων στην μνήμη μας αναπαραστάσεων.

ABBREVIATIONS

AC=anterior commissure

AF=arcuate fasciculus

AG=angular gyrus

AP=ansa peduncularis

ATL=anterior temporal lobe

ATTF=anterior temporal transitional fold

BA=Brodman area

CB-V=cingulum bundle V

CC=corpus callosum

CITP=contralateral interhemispheric transfalcine transprecuneus approach

CG=cingulate gyrus

Col=collateral sulcus

DLOC=dorso-Lateral Occipital cortex

DTI=diffusion tensor Imaging

DWI=diffusion weighted imaging

FFA=fusiform Face Area

FM=forceps Major

fMRI=functional magnetic resonance

Fu=fusiform gyrus

IFG=inferior frontal gyrus

IFOF=inferior fronto-occipital fasciculus

ILF=inferior longitudinal fasciculus

IPL=inferior parietal lobule

IPS=intraparietal sulcus

IOG=inferior occipital gyrus

ITG=inferior temporal gyrus

ITS=inferior Temporal Sulcus

Li=lingual gyrus

MCA=middle cerebral artery

MdLF=middle longitudinal fasciculus

MEG=magnetoencephalography

MFG=middle frontal gyrus

MOG= middle occipital gyrus

MTG=middle temporal gyrus

MTS= middle Temporal Sulcus

PCC=posterior cingulate cortex

PET=positron emission tomography

PhG=parahippocampal gyrus

POA=parieto-occipital arcus

POS=parieto-occipital sulcus

PPA=parahippocampal place area

PrC=precuneus

Rhi=rhinal sulcus

RSA=representational similarity analysis

RSC=retrosplenial complex area

RSFC=resting-state functional connectivity

rTMS=repetitive transcranial magnetic stimulation

SD=semantic dementia

SLF=superior longitudinal fasciculus

SMG=supramarginal gyrus

SOG=superior occipital gyri

SPL=superior parietal lobule

SRF=sledge-runner fasciculus

SS=sagittal stratum

STG=superior temporal gyrus

STS=superior temporal sulcus

STTS=supracerebellar transtentorial transcollateral sulcus

TP=temporal pole

TPO=temporo-parieto-occipital

UF=uncinate fasciculus

VOF=vertical occipital fasciculus

CHAPTER 1: INTRODUCTION

1.1 INTRODUCTION TO THE SURFACE ANATOMY AND FUNCTION OF THE TEMPORAL POLE

Temporal pole surface anatomy

The temporal pole (TP) is a unique anatomical area of non-human primates, great apes, and humans, probably representing a part of higher-order function networks of the brain. Overall, the temporal lobe and its anatomy have been thoroughly studied and described since the Hippocratic ages. However, its functional significance, with special attention to the polar region was popularized after the studies of Bucy and Kluver, describing the homonymous syndrome in primates and humans (Insausti, Juottonen et al. 1998, Insausti 2013)

In its early descriptions the term “polar area” was attributed to the rostral-most part of the temporal lobe. However, cytoarchitectonic descriptions revealed the presence of a distinct pattern of cortical regions in a larger area posteriorly to the tip of the lobe, leading to Broadmann initially labelling the anterior temporal lobe as a homogenous area 38. Later, von Economo and Koskinas described additional subdivisions of the temporal pole cortex, extending its boundaries further caudally, unable however to clearly define them (Insausti 2013, Herlin, Navarro et al. 2021). Modern approaches to the region’s anatomy involve extended cytoarchitectonic (Ding, Van Hoesen et al. 2009, Olson, McCoy et al. 2013, Herlin, Navarro et al. 2021) and connectivity parcellations (Fan, Wang et al. 2014, Pascual, Masdeu et al. 2015). It is evident that the growing knowledge of the connectivity patterns and functional implications of the TP, furthers the need for reevaluating the anatomical terminology attributed to this region of the brain.

In gross anatomical terms, the limits of what is considered temporal pole region and which gyri contribute to its formation, is a matter of some controversy. The anterior limit is universally accepted as the tip of the temporal lobe, encased in the curvature of the greater wing of the sphenoid. The posterior limit, however, has been given different definitions. Chabardes et al in their review, used the termination of the sulci to demarcate the TP. On the lateral surface they set the limit at the termination of the Superior and Middle Temporal Sulci (STS and MTS respectively), based on the observation of Dejerine that the STS terminates 1cm posterior to the tip of the temporal lobe. Moreover, they reported a medial curvature of the STS, the Anterior Temporal Transitional fold (ATTF), placing the termination of the MTS at the level of the imaginary line that crosses ATTF's anterior edge. On the basal surface, they report the Inferior Temporal Sulcus (ITS) terminating posterior to the TP, whereas the Collateral sulcus (Col) terminates as Rhinal sulcus (Rhi) at the TP region, serving as the medial limit of TP. Overall, the Temporal Pole is defined as the convergence of the Superior, Middle and Inferior Temporal Gyri (STG, MTG and ITG respectively) with the Fusiform gyrus (Fu), anterior to these sulcal limits (Chabardès, Kahane et al. 2002)

In one of the most cited Neuroanatomical studies in Neurosurgery, Gulielme Ribas reported that the TP is formed by the STG and the ITG, with the MTG being shorter than the other two gyri. These gyri are delineated by the STS and ITS, the only two sulci of the lateral surface described in this study, with their starting point at the proximal limit of the TP. On the basal surface, the Fu terminates at the level of the lateral edge of the cerebral peduncle, posterior to the TP, hence it is not considered part of the pole, regardless of the taxonomy system. On the dorsal surface of the TP, the area anterior to the transverse gyrus of Heschl is described as the polar plane, presenting gyri in oblique angles (Ribas 2010), as described by Schwalbe (Insausti 2013). No clear boundaries for the TP area were described in the study (Ribas 2010).

Synchronous as well as subsequent studies altered some aspects of this description. Ding et al, as well as Blaizot et al, popularized the use of the limen insulae as the posterior border. Ding defined the temporopolar area as the part of the temporal lobe anterior to limen insula (Ding, Van Hoesen et al. 2009, Blaizot, Mansilla et al. 2010). Dorsally, 2 gyri of Schwalbe were described as the commonest variation, while the STS is often reported to extend to the tip of the pole. On the lateral surface the MTS is reported to end posterior to the TP cortex, whereas short irregular sulci are described within the limits of the pole. On the vetromedial surface, the posterior limit of the TP was set at the anterior edge of the uncus, with the collateral and ITS extending beyond that line into the pole.

Finally, the Rhinal sulcus, is described to extend towards the dorsal TP surface (Ding, Van Hoesen et al. 2009). On the other hand, Blaizot introduced some alterations in the terminology, describing TP as continuous with the parahippocampal gyrus ventrally with the end of the Col serving as a posterior and the Gyrus Semilunaris as a ventromedial border. The gyrus semilunaris, lying caudal to the limen insula, in the coronal level, emphasized the latter’s role as an anatomical barrier. On the lateral surface, the TP was described as continuous with the superior temporal gyrus

(STG) laterally, as also reported by Ono et al, whereas dorsally the gyri of Schwalbe extend up to the level of the insula (Blaizot, Mansilla et al. 2010).

In the following years, most descriptions retained the terminology with small modifications. Fan et al excluded the middle temporal gyrus (MTG) from the TP seeds, as a gyrus not participating in the formation of the pole. Insausti et al, described the morphology and limits of the TP area, following the paradigm of Ding and Blaizot, whilst emphasizing the observation that the STG often reaches the lateral aspect of the TP, limited medially by the temporopolar sulci of the dorsal surface (Insausti 2013). Chau et al defined the border of the Collateral-Rhinal sulci at the antero-lateral level of the peduncle, posterior to the uncus and thus the TP area. Also, they added the observation that the Fu consistently enters the TP (Chau, Stewart et al. 2014). Cikla et al studied the morphology of the temporooccipital sulci on the basal surface and reported that the extension of the Occipito-temporal and Collateral sulci to the TP was not the commonest variation (Cikla, Menekse et al. 2016). Olson et al repeated the notion that the TP is formed by the STG, MTG, ITG and Fu (Olson, McCoy et al. 2013). Finally, The most recent description of the Temporal pole summarizing the suggestions regarding the TP anatomy, demarcate the region posteriorly by the limen insula, laterally by the most lateral temporoparietal sulcus and ventrally by the extension of the ITS (Herlin, Navarro et al. 2021).

It is evident that, due to the lack of clear anatomical and functional limits, defining the Temporal pole and its constituents is a challenge. For this reason, the study of the superficial anatomy of the anteriormost region of the Temporal lobe, with the overarching goal to clarify the anatomy based on modern taxonomy systems is essential.

Temporal pole function

Klüver and Bucy in 1938 were the first ones to point out the functional significance of the temporal pole. They described anomalous sexual and social behavior as well as visual agnosia in non-human primates following bilateral anterior temporal lobectomy, including the amygdala and the hippocampal formation (Klüver and Bucy 1938). Later, bilateral anterior and medial temporal lobectomy surgery for epilepsy led to the identification of this syndrome in humans.

The first indications that the temporal pole contributes significantly in socioemotional processing derived from Animal studies (Kling and Steklis 1976, Kling, Tachiki et al. 1993) demonstrating that female monkeys with temporal pole lesions, showed deviating social behavior, and at times were even rejected from their social group; a behavior for which later Olson et al coined the term “social withdrawal” (Olson, Plotzker et al. 2007).

Semantic processing and semantic memory are additional functions that have been attributed to the temporal pole. Semantic memory or conceptual knowledge denotes the memory for meanings, including knowledge about meaning of sentences, objects, words, concepts, facts, events and people (Tulving 1972). A cohort of patients with bilateral temporopolar atrophy and a distinct type of dementia was identified and named Semantic Dementia (SD) by Snowden et al. (Snowden, Goulding et al. 1989). While autobiographical and episodic memory were intact, semantic knowledge and memory were significantly affected in SD, while the anomia seen in these patients was not aided by cueing emphasizing the semantic nature of the disorder (Jefferies, Patterson et al. 2008). In the same context, the hub-and-spoke model, introduced by Rogers el al. (Rogers, Lambon Ralph et al. 2004), Suggests that the temporal pole functions as a principal semantic hub synthesizing information from different modalities to form transmodal, domain-general concepts. In more detail, Patterson and Lambon Ralph (Patterson and Ralph 2016) argue that a broadly dispersed network reflect semantic knowledge. Within this network, modality-specific regions reciprocally send to and receive back information from the TP which acts as the trans-modal semantic hub. The information stored and reflected in these modality specific areas can represent color, shape, structure, visual movement, and others while the TP generates and defines concepts and meanings by synthesizing or analyzing the different information.

Semantic cognition is another function attributed to the TP and refers to the neurocognitive mechanisms that support semantically instilled verbal and non-verbal behaviours (Ralph, Jefferies et al. 2017). The temporal pole has been associated with semantic tasks in positron emission tomography (PET) studies, namely semantic priming (Mummery, Shallice et al. 1999) (where response to a word is facilitated when preceded by a semantically related word), semantic processes during reading (Price, Moore et al. 1997), semantic categorization tasks using pictures and words (Bright, Moss et al. 2004) , as well as during semantic decisions about auditory or visually presented words (Noppeney and Price 2002).

Socio–emotional cognition (Olson, Plotzker et al. 2007), knowledge relating to people (Giovanello, Alexander et al. 2003) , and specifically the Theory of Mind (Olson, Plotzker et al. 2007) referring to the ability to interpret and speculate other people's behavior by “reading” their beliefs and desires as well as to take a third-person perspective, have been also ascribed to the TP. Spreng and Mar showed bilateral TP activation while participants recalled episodes of their own past and inferred thoughts and feelings of other individuals. The study suggests that the TP aids in the process of using our past experiences to reason about others (Spreng and Mar 2012).

Last, Sugiura and colleagues have shown that TP is activated when recognizing famous and personally familiar faces, suggesting that the TP may be fundamental for face recognition (Sugiura, Kawashima et al. 2001) .Subsequent study by the same group demonstrated significant left TP activation for recognizing famous and personally familiar faces compared to the participants own face (Sugiura, Watanabe et al. 2005). Subsequently, the authors compared famous versus familiar names and demonstrated bilateral anterior temporal lobe (ATL) activation for both types of names compared to unfamiliar names (Sugiura, Sassa et al. 2006).

Parcellation of the temporal pole and subcortical connectivity

Whether specific subregions of the TP can be correlated with specific TP functions is a matter of ongoing controversy and many researchers have tried to approach this question from different standpoints.

The right dorsal TP has been implicated in social cognition by allegedly providing abstract conceptual knowledge of social behaviors (Zahn, Moll et al. 2009), the left dorsal TP in the correlations between person-related semantics and names, while bilateral ventral TP in the correlations between person-related semantics and faces (Tsukiura, Mano et al. 2010).

From a language standpoint, a parcellation of the left TP into a dorsal region processing both syntactic and prosodic information of speech and a more inferior one that is more selective for syntax was suggested in a functional magnetic resonance (fMRI) study (Humphries, Love et al. 2005). From a semantic memory point of view the right ventral ATL was activated equally for faces and spoken names, while the left was more selective for the spoken names (Shimotake, Matsumoto et al. 2015).

Pascual and colleagues, using resting state functional connectivity MRI parcellated the TP into 4 main subdivisions; a dorsal one, with primary connectivity to auditory/somatosensory and language networks; a ventromedial, mainly associated with visual networks; a medial, linked to paralimbic structures; and a lateral, connected to the default-semantic network (Pascual, Masdeu et al. 2015).

Visser and Lambon Ralph demonstrated that the left dorsal TP is mainly implicated in high-order auditory processing (Visser and Lambon Ralph 2011). Similarly, Skipper and colleagues showed that auditory stimuli activated superior regions to a greater degree, while visual stimuli activated inferior regions (Skipper, Ross et al. 2011). In the same vein, Jackson and colleagues conducted a resting-state and active-task fMRI study and divided the TP to ventrolateral areas that are bilaterally related to modality-general processes whilst ventral regions to visual processes and dorsal regions to high-order auditory processing (Jackson, Bajada et al. 2018).

Fan and colleagues using Diffusion tensor Imaging (DTI) studies with resting state functional connectivity MRI, parcellated the TP according to their connectivity pattern. first they divided the human TP into 3 subregions based on their connectivity.

These were the dorsally located TAr, and 2 ventral subregions; the medially located TGm and the laterally located TGl. The authors argued that a dorsoventral partitioning of the auditory and visual information processing exists in the TP, with dorsal TP associated with auditory while ventral TP with visual processing. The medial TP was related to olfactory information processing. Then, using probabilistic fiber tracking and resting-state functional connectivity (RSFC) analysis, they tried to elaborate on larger network and functional connectivity patterns of each subregion They demonstrated that TGm was connected with the orbitofrontal areas and other emotion-related regions, the TGl with the medial prefrontal cortex and major default mode network regions, and the TAr with the perisylvian language areas (Fan, Wang et al. 2014)

1.2 INTRODUCING THE MIDDLE LONGITUDINAL FASCICULUS (MDLF)

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 (Schmahmann and Pandya 2007). 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 (Klingler 1935, Klingler and Ludwig 1956). 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 (Basser, Mattiello et al. 1994, Le Bihan, Mangin et al. 2001, Catani, Howard et al. 2002, Mori and Zhang 2006, Schmahmann, Pandya et al. 2007, Catani and De Schotten 2008).

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 (Filley 1998, Filley 2005). Keeping with this, functional neuroimaging (Price 2000, Logothetis, Pauls et al. 2001, Maldjian, Laurienti et al. 2003, Yang, Qiu et al. 2016) and human brain mapping studies (Mazziotta, Toga et al. 2001, Sporns, Tononi et al. 2005, Raichle 2009, Duffau and Duffau 2010, Duffau 2011, Sarubbo, De Benedictis et al. 2015) reflect the concept of a cortico-subcortical correlation and integration, thus emphasizing on a hodotopical network approach to understand higher cerebral processing (Catani and Catani 2007, De Benedictis and Duffau 2011). 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 (Dejerine and Dejerine-Klumpke 1895, Makris, Meyer et al. 1999) or alternatively be compared to relevant studies on non-human primates (Makris, Papadimitriou et al. 2009). However, especially regarding novel tracts, neither of the two approaches seems to be accurate (Rilling, Glasser et al. 2008, Koutsarnakis, Kalyvas et al. 2019). Hence, the Klingler's technique is currently considered the gold standard method through which DTI results can be verified (Mandonnet, Sarubbo et al. 2018).

We therefore opted to study through a white matter anatomic dissection technique 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 (Seltzer and

Pandya 1984), it was not until 2009 that Makris et al provided preliminary supporting DTI evidence of its existence and connectivity in the human brain (Makris, Papadimitriou et al. 2009). 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 (Makris, Preti et al. 2013, Makris, Preti et al. 2013, Menjot de Champfleur, Lima Maldonado et al. 2013, Makris, Zhu et al. 2017, Conner, Briggs et al. 2018, Tremblay, Perron et al. 2019). 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 (Maldonado, de Champfleur et al. 2013, Wang, Fernandez-Miranda et al. 2013).

Our objective was therefore to clarify the debatable anatomical characteristics of the MdLF through focused dissections. 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.

1.3 INTRODUCING THE FIFTH COMPONENT OF THE CINGULUM BUNDLE (CB-V)

During the last decade a growing body of evidence has advocated the functional connectivity of the precuneus with areas of the temporal lobe.(Mancini, Mastropasqua et al. 2017, Hebscher, Levine et al. 2018) This synergy is a basic component of our default mode network, which is activated when the brain is in the condition of “resting consciousness”, and allegedly subserves high order functions such as planning, volition, episodic memory, attention, spatial updating, error detection, social intelligence, intelligence comparison and verbal creativity.(Marchette, Vass et al. 2014, Utevsky, Smith et al. 2014, Raichle 2015, Tosoni, Pitzalis et al. 2015, Sheldon, Farb et al. 2016, Burles, Slone et al. 2017, Epstein, Patai et al. 2017, Sun, Liu et al. 2019) Stronger connectivity of these regions is positively correlated with higher cognitive performance,(Zhang, Andreano et al. 2019) while in neurological and psychiatric conditions the activation of this circuitry is markedly altered.(Zhu, Tang et al. 2017, Liu, Zhang et al. 2018, Wang, Williams et al. 2019) Although the functional connectivity of the aforementioned cerebral regions and its significance have been repeatedly reported, the anatomical constraints of underlying structural circuits need to be further elucidated.

To this end, we focus on a long association fiber tract, previously described as the Cingulum bundle V (CB-V), which is believed to interconnect areas of the temporal lobe and the precuneus.(Wu, Sun et al. 2016) By employing the fiber micro-dissection technique in formalin fixed brains, we provide direct anatomical evidence on the tract’s invariable existence, morphological silhouette, termination pattern and spatial relationship with adjacent fiber tracts namely the inferior arm of the cingulum (Cing), the Sledge-runner fasciculus (SRF), the inferior longitudinal fasciculus (ILF) and the Forceps Major (FM). Our results aim to document and refine current knowledge on structural brain connectivity and organization in terms of cortical and subcortical axonal interactions. Moreover, useful insights are provided allowing the study of high-level functioning circuits residing in the posteromedial cortices in greater detail; thus, paving the way towards a more comprehensive understanding of these networks both in normal and pathological brain conditions. Lastly, surgical comments and functional considerations on the involvement of the fifth subcomponent of the cingulum bundle in operative trajectories designed to access lesions in and around the ventricular trigone are pointed out.

1.4 INTRODUCING THE UNCINATE FASCICULUS

The uncinate fasciculus has attracted increasing scientific interest due to its potential involvement in the pathophysiology of various psychiatric and neurological diseases(Kubicki, Westin et al. 2002, Burns, Job et al. 2003, Rodrigo, Oppenheim et al. 2007, Diehl, Busch et al. 2008, Matsuo, Mizuno et al. 2008, McDonald, Ahmadi et al. 2008, McIntosh, Munoz Maniega et al. 2008, Price, Cercignani et al. 2008, Craig, Catani et al. 2009, Sussmann, Lymer et al. 2009, Whitwell, Avula et al. 2010, Acosta-Cabronero, Patterson et al. 2011, Motzkin, Newman et al. 2011, Riva-Posse, Choi et al. 2014, Bhatia, Henderson et al. 2018). In addition, the propagation of elegant microneurosurgical approaches in awake conditions for the treatment of lesions residing in or extending to the temporal stem and insular region have further stressed the need for a more accurate understanding of the tract's anatomical architecture and functional significance (Duffau, Capelle et al. 2000, Lang, Olansen et al. 2001, Duffau, Capelle et al. 2003, Duffau 2009, Sanai, Polley et al. 2010, Kim and Kim 2012, Hameed, Qiu et al. 2018). To this end, fiber dissection and tractographic studies focusing on the structural silhouette of the uncinate fasciculus have converged towards a hook-like morphology, with the tract's main stem travelling through the extreme and external capsules - in proximity to the inferior occipitofrontal fasciculus- and its terminations radiating towards the orbitofrontal area and antero-medial temporal lobe respectively (Ebeling and von Cramon 1992, Ture, Yasargil et al. 2000, Catani, Howard et al. 2002, Kier, Staib et al. 2004, Peuskens, van Loon et al. 2004, Schmahmann, Pandya et al. 2007, Fernandez-Miranda, Rhoton et al. 2008, Wang, Sun et al. 2008, Peltier, Verclytte et al. 2010, Martino, De Witt Hamer et al. 2011, Thiebaut de Schotten, Dell'Acqua et al. 2012, Martino and De Lucas 2014, Bhatia, Henderson et al. 2017, Gungor, Baydin et al. 2017).

Even though the main anatomical characteristics of this elegant tract have been outlined, ambiguity has recently emerged with regards to the exact topographical and morphological pattern of its frontal terminations. According to the classical description, the uncinate fasciculus connects the medial and lateral orbitofrontal cortices to the anterior segment of the three temporal gyri, the temporal pole and uncus(Ebeling and von Cramon 1992). However, recent data stemming from modern, sophisticated anatomo-imaging studies support the presence of an additional dorsal segment, which projects to the dorsolateral and ventrolateral prefrontal cortices of the inferior, middle and superior frontal gyri, thus adding perplexity and obscurity to the structural architecture and putative functional role of the tract (Hau, Sarubbo et al. 2016, Leng, Han et al. 2016, Baydin, Gungor et al. 2017, Hau, Sarubbo et al. 2017).

To shed light on this current controversy, we carried out a fiber dissection study focusing on the morphology and topography of the frontal extensions of the uncinate fasciculus. We implemented the white matter dissection technique as the stand alone method of investigation since the anatomic results obtained are of high accuracy and because it is currently employed as the gold standard procedure for validating DWI tractographic data (Catani, Jones et al. 2005, Koutsarnakis, Liakos et al. 2015, Koutsarnakis, Liakos et al. 2016, Liakos and Koutsarnakis 2016, Koutsarnakis, Liakos et al. 2017, Koutsarnakis, Kalyvas et al. 2018, Komaitis, Kalyvas et al. 2019, Komaitis, Skandalakis et al. 2019, Koutsarnakis, Kalyvas et al. 2019).

1.5 INTRODUCING OTHER WHITE MATTER TRACTS ARISING/TERMINATING FROM/TO TEMPORAL POLE

The inferior longitudinal fasciculus (ILF) is a long association white matter tract that travels from the temporal pole to the occipital and temporal-occipital areas. It is a multilayered, bidirectional tract implicated in visually directed decisions and behaviors through processing and regulating visual information by subserving the ventral visual stream (Milner and Goodale 2006, Herbet, Zemmoura et al. 2018).

The anterior commissure (AC) is a commissural white matter fiber tract of the brain, located ventro-caudally with respect to the globus pallidus, superior and anterior to the temporal horn within the Gratiolet's canal, bordering on the posterior component of the uncinate fasciculus and reaching the temporal pole (Pescatori, Tropeano et al. 2017). It crosses the midline travelling just anteriorly to the anterior columns of the fornix, and inferiorly to the ventromedial part of the anterior limb of the internal capsule (Schmahmann, Smith et al. 2008). It comprises two separate components; the anterior and posterior crus. The anterior crus, the so-called olfactory commissure, connects the olfactory systems of both hemispheres. The superior fibers of the posterior crus travel to the temporal lobe with some of them reaching the uncinate fasciculus and the temporal pole, while its inferior fibers join the sagittal stratum and terminate to the occipital lobe (Pescatori, Tropeano et al. 2017).

The ansa peduncularis (AP) is more of a concept and less of a discrete white matter fiber bundle. It lies between the anterior perforated substance inferiorly and anterior commissure superiorly and posteriorly and consists of various fiber tracts that travel around the cerebral peduncle. Klingler and Gloor in their landmark study describe 4 subcomponents of AP; the amygdaloseptal, amygdalohypothalamic, amygdalothalamic pathways and the ansa lenticularis (Klingler and Gloor 1960).The ventral amygdalofugal fiber system comprises the amygdaloseptal and the amygdalohypothalamic pathways. The amygdaloseptal pathway, the so-called diagonal band of Broca, links the amygdala to the septal region, and the amygdalohypothalamic pathway links the amygdala to the hypothalamus (Klingler and Gloor 1960, Baydin, Yagmurlu et al. 2015). The amygdalothalamic pathway, or alternatively inferior thalamic peduncle or extracapsular thalamic peduncle (its fibers are lateral to the internal capsule), is of particular interest as it links the medial thalamus with the TP and the amygdala (Klingler and Gloor 1960, Ribas, Yağmurlu et al. 2018).

CHAPTER 2:
MATERIALS & METHODS

2.1 MATERIALS AND METHODS: GENERAL CONSIDERATIONS

Thirty (30) healthy adult hemispheres belonging to the Department of Anatomy of the Medical School of the University of Athens have been used for the purposes of this study. 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.

All specimens had been previously fixed in a 10–15% formalin solution for a minimum period of 8 weeks according to the Klingler’s technique. Careful microsurgical removal of the arachnoid membrane and vessels, under microscope (Carl Zeiss OPMIR Plus, Carl Zeiss AG, Oberkochen, Germany) was performed, thus providing an unobstructed view of the gyral and sulcal patterns. Subsequently, freezing in -15 C for a period of at least 15 days was performed followed by thawing under running water for a period of several hours (freeze-thaw) procedure (Klingler 1935, Klingler and Ludwig 1956, Ture, Yasargil et al. 2000, Martino, De Witt Hamer et al. 2011, Koutsarnakis, Liakos et al. 2015). Due to the freezing procedure, the formaldehyde crystals naturally expands in the space between the white matter tracts and thus allow for a feasible dissection process under the surgical microscope.

2.2 MATERIALS AND METHODS: SURFACE ANATOMY OF THE TEMPORAL POLE

All hemispheres were photographed from various angles, emphasizing the TP region, for documentation purposes. Then, the superficial anatomy was recorded using predetermined forms. The anatomy of the Superior, Middle and Inferior Temporal gyri (STG, MTG, ITG respectively) in the lateral surface, as well as the Fusiform (Fu) and Parahippocampal (PhG) gyri in the medio-ventral surface, were studied and thoroughly documented, focusing on their termination pattern at the temporo-polar region. On the dorsal surface the vertical gyrus of Schwalbe and the variations of its oblique sulci were recorded. Finally, the sulci delineating the temporal gyri, namely the Superior and Inferior Temporal Sulcus (STS, ITS respectively, the occipitotemporal sulcus and the Collateral (Col) and Rhinal (Rhi) sulci, along with their extension towards the polar region were studied and recorded.

The limits of the Temporal pole area were defined according to the information available in current literature. On the dorsal surface, the imaginary line crossing the frontotemporal junction at the level of the limen insula, delineated the temporal pole area posteriorly. On the basal surface, the uncus defined the limit, with the imaginary horizontal line running at its anterior limit, being the posterior limit of the polar region. On the lateral, surface the posterior limit was defined as the imaginary line that occurs from the convergence of the aforementioned lines, extending laterally.

2.3 DISSECTION TECHNIQUE: TEMPORAL TERMINATION PATTERNS OF ALL TRACTS REACHING THE TEMPORAL POLE.

The frontal lobe, anterior to the level of the central sulcus, as well as the insular lobe were removed prior to dissection in 4 hemispheres, retaining part of the temporal stem, for optimum exposure of the TP surface anatomy. (Ding, Van Hoesen et al. 2009) We employed the cortex sparing technique at the temporal pole region in order to properly accord each fiber tract terminating to the TP. (Martino, De Witt Hamer et al. 2011)

Our primary goal was to identify the white matter tracts that terminate to the cortex of the temporal pole. Through a stepwise approach, all surfaces of the anterior temporal lobe were dissected, retaining the cortex of the TP area. Every white matter tract that was observed to terminate at the TP, was recorded and subsequently dissected along its course posteriorly to be properly identified. Following their dissection, each tract was removed – along with its TP cortical terminations – revealing any underlying fasciculus. The relative anatomy of these tracts at their course through the temporal polar region as well as the relationship between their cortical terminations were then recorded in detail. Finally, each tract termination was allocated to the relevant region according to Ding's parcellation, to a realistic extent, creating a map of white matter tract terminations along the TP cortex.

The TP region was defined posteriorly, in each surface, by certain anatomical markers. On the dorsal surface, the posterior limit of the TP cortex was defined as the imaginary line crossing the limen insula or fronto-temporal junction towards the lateral surface (Ding, Van Hoesen et al. 2009, Blaizot, Mansilla et al. 2010, Fan, Wang et al. 2014). Anterior to this line the extension of the Superior Temporal gurus (STG) formed the dorsal surface of the pole. It was divided by 1-3 small vertical sulci delineating the short gyri of Schwalbe. On the basal surface, the TP cortex was defined as extending anterior to the imaginary horizontal line running lateral at the anterior limit of the uncus (Ding, Van Hoesen et al. 2009, Blaizot, Mansilla et al. 2010, Fan, Wang et al. 2014) and was formed by the anterior extension of the Inferior Temporal gyrus (ITG) and the Parahippocampal gyrus (PhG). Finally, on the lateral surface the TP was formed by the convergence of the STG, the ITG and the Middle Temporal gyrus (MTG), in most cases. Its posterior limit was defined as the imaginary line that occurs from the lateral extension of the aforementioned imaginary lines. It is important to note that Ding's map is a detailed anatomo-histological parcellation, therefore certain regions were anatomically ill-defined.

The cortex covering the tip and medio-dorsal surface of the TP was defined as the TG area. On the dorsal surface, posteriorly and dorso-medially to the TG area, the TI area was defined extending up to the insular cortex, however, it is a region without a clear anatomical limit in Ding's map. Dorso-lateral to the TG area, the anterior extension of the STG to the pole, was identified as the TAr area. Once more, no distinct anatomical landmark has been described to separate the two regions (Blaizot, Mansilla et al. 2010, Fan, Wang et al. 2014). Located directly infero-lateral to the TAr area, within the superior bank of the STS, the TAp area lies. Caudal to these, the TE area was defined consisting of the TEd and TEv areas as the temporo-polar extensions of the MTG and ITG respectively.

The extension of the ITG towards the ventral TP area was defined as the TEv area. In 8 hemispheres a relatively deep sulcus was evident at this level, demarcating an anterior and posterior part of the TEv area. Medially, along the medial bank and the depth of the collateral sulcus the area 35 was defined extending until the TI area superiorly. Finally, along the lateral bank of the collateral sulcus, the area 36 was defined extending medial to the TEv area and anterior to area 35, following the Rhinal sulcus when present, terminating between the TG and TI regions.

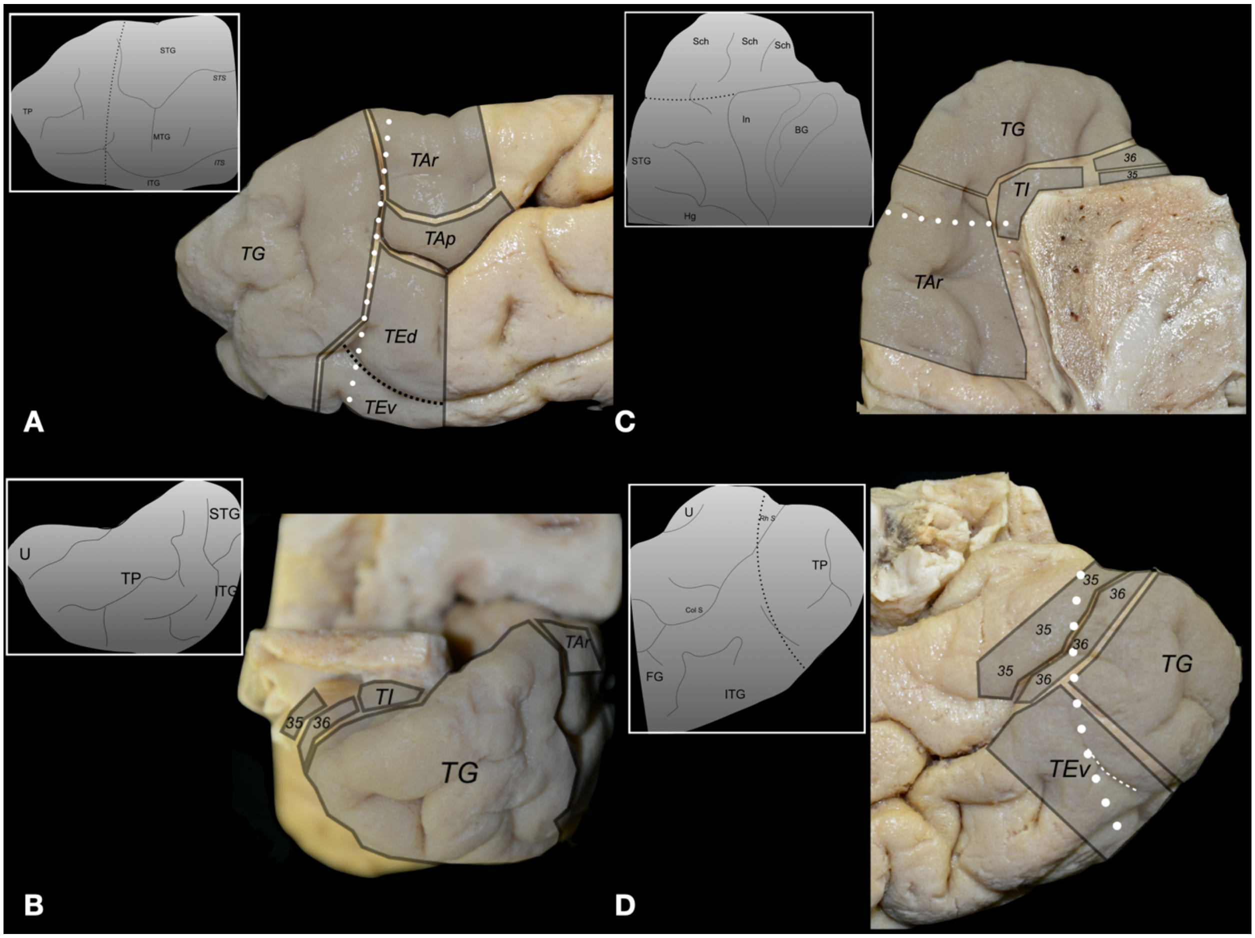


Fig 1: Parcellation of the temporal pole according to Ding and colleagues' map, as described in the main text. The traditional anatomical nomenclature of the sulci and gyri is described in the insets for correlation purposes. **A:** Lateral view, **B:** Anterior view, **C:** Superior view, **D:** Inferomedial view; The white dotted line indicates the limits of the temporal pole region. BG: Basal Ganglia, Col s: Collateral sulcus, FG: Fusiform gyrus, Hg: Heschl's gyrus, In: Insula, ITG: Inferior Temporal gyrus, ITS: Inferior Temporal sulcus, MTG: Middle Temporal gyrus, Rh s: Rhinal sulcus, Sch: Schwalbe's gyrus, STG: Superior Temporal gyrus, STS: Superior Temporal sulcus, TP: Temporal pole, U: Uncus

2.4 DISSECTION TECHNIQUE: MIDDLE LONGITUDINAL FASCICULUS

After 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 (Makris, Papadimitriou et al. 2009, Makris, Preti et al. 2013, Makris, Preti et al. 2013, Maldonado, de Champfleur et al. 2013, Menjot de Champfleur, Lima Maldonado et al. 2013, Wang, Fernandez-Miranda et al. 2013, Makris, Zhu et al. 2017, Conner, Briggs et al. 2018). We therefore performed lateral to medial anatomic dissections with special emphasis on the aforementioned area. 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.

2.5 DISSECTION TECHNIQUE: FIFTH COMPONENT OF THE CINGULUM BUNDLE

Upon meticulous dissection of the arachnoid membrane and vessels, all specimens were treated with the Klingler's method and investigated through the fiber micro-dissection technique. The operating microscope (Carl Zeiss OPMIR Plus, Carl Zeiss AG, Oberkochen, Germany) and micro-surgical instruments such as fine metallic periosteal elevators, various sized anatomical forceps, and micro-scissors were used as previously described.(Koutsarnakis, Liakos et al. 2017, Koutsarnakis, Kalyvas et al. 2018, Komaitis, Kalyvas et al. 2019, Koutsarnakis, Kalyvas et al. 2019) Because the area of interest is located deep to the parieto-occipital sulcus (POS), distal calcarine fissure and medial temporal lobe, we focused all dissections on this cerebral territory. Prior to dissection, the regional sulcal anatomy consisting of the parieto-occipital sulcus, proximal calcarine fissure, distal calcarine fissure, collateral sulcus, occipitotemporal sulcus and sub-parietal sulcus was studied in all cases.

We then started the dissection process by meticulously peeling away the cortex and underlying short association fibers - known as arcuate or "U" fibers - at the level of the parieto-occipital sulcus and up until the distal end of the calcarine sulcus. Cortical and white matter fiber dissections gradually proceeded to include the cuneus, precuneus, posterior cingulate cortex, retrosplenial area, ventral and medial temporal lobe and basal temporo-occipital area in an effort to map and record the topography, morphology, termination pattern and correlative anatomy of the CB-V.

Digital photographs were obtained in a stepwise fashion in different dissection stages and angles to illustrate more vividly the topographical architecture and spatial relationship of the regional white matter tracts. All figures included in this study are un-enhanced to closely resemble the white matter fiber tract anatomy encountered in standard laboratory settings.

2.6 DISSECTION TECHNIQUE: UNCINATE FASCICULUS

All specimens underwent the freeze-thaw process and were explored through the white matter fiber microdissection technique(J 1935, Klingler J 1956, Koutsarnakis, Liakos et al. 2015).

According to the classical description, the uncinate fasciculus connects the antero-medial temporal lobe to orbitofrontal and ventromedial prefrontal cortices, by travelling through the extreme and external capsules in the limen insula. New evidence however supports that fibers of the uncinate fasciculus are distributed to the dorsolateral and ventrolateral prefrontal areas. We, thus, focused our dissections on the orbitofrontal cortex, inferior frontal gyrus, middle frontal gyrus, anterior insula, limen insula and anterior temporal lobe. We were obliged to remove the temporal operculum and the temporal pole to gain better access to the orbitofrontal surface and to the region of the insula. To study and record the tract's fiber terminations to the ventromedial frontal area, we subsequently performed confined medial to lateral white matter dissections, focusing on the area of the gyrus rectus, paraterminal gyrus, paraolfactory gyrus and ventral cingulate gyrus. Hemispheric asymmetries or objective measurements of the tract's dimensions were not examined as it was out of the study's scope.

We used thin metallic periosteal elevators, micro-scissors, and fine anatomical forceps as our main dissection tools. All dissections were performed under the operating microscope and were documented with digital unenhanced photographs.

CHAPTER 3: RESULTS

3.1 RESULTS: SURFACE ANATOMY OF THE TEMPORAL POLE

Gyral Morphology

On the dorsal surface the pattern of the gyri of Schwalbe was documented. The commonest pattern was that of 2 gyri, divided by a straight sulcus between them and a lateral short sulcus, separating them from the rostral extension of the STG. This pattern was recorded in 66.6%, whereas the 3-gyri pattern was recorded in 24.3% and the 1-gyrus pattern in 9.1% of hemispheres.

On the lateral surface the TP cortex was formed by the convergence of all 3 gyri, namely the STG, MTG and ITG, in 75.8% of the hemispheres with the MTG terminating posterior to the pole in the remaining 24.2% of hemispheres.

On the ventral surface the ITG was the main constituent of the TP in all hemispheres. In the ventromedial surface the gyrus was continuous with the PhG in 51.5%, mainly when the Rhinal sulcus was absent, whereas in the remaining hemispheres the two gyri were divided by the Rhinal sulcus. The Fusiform gyrus extended anterior in the polar region in 18.2% of hemispheres.

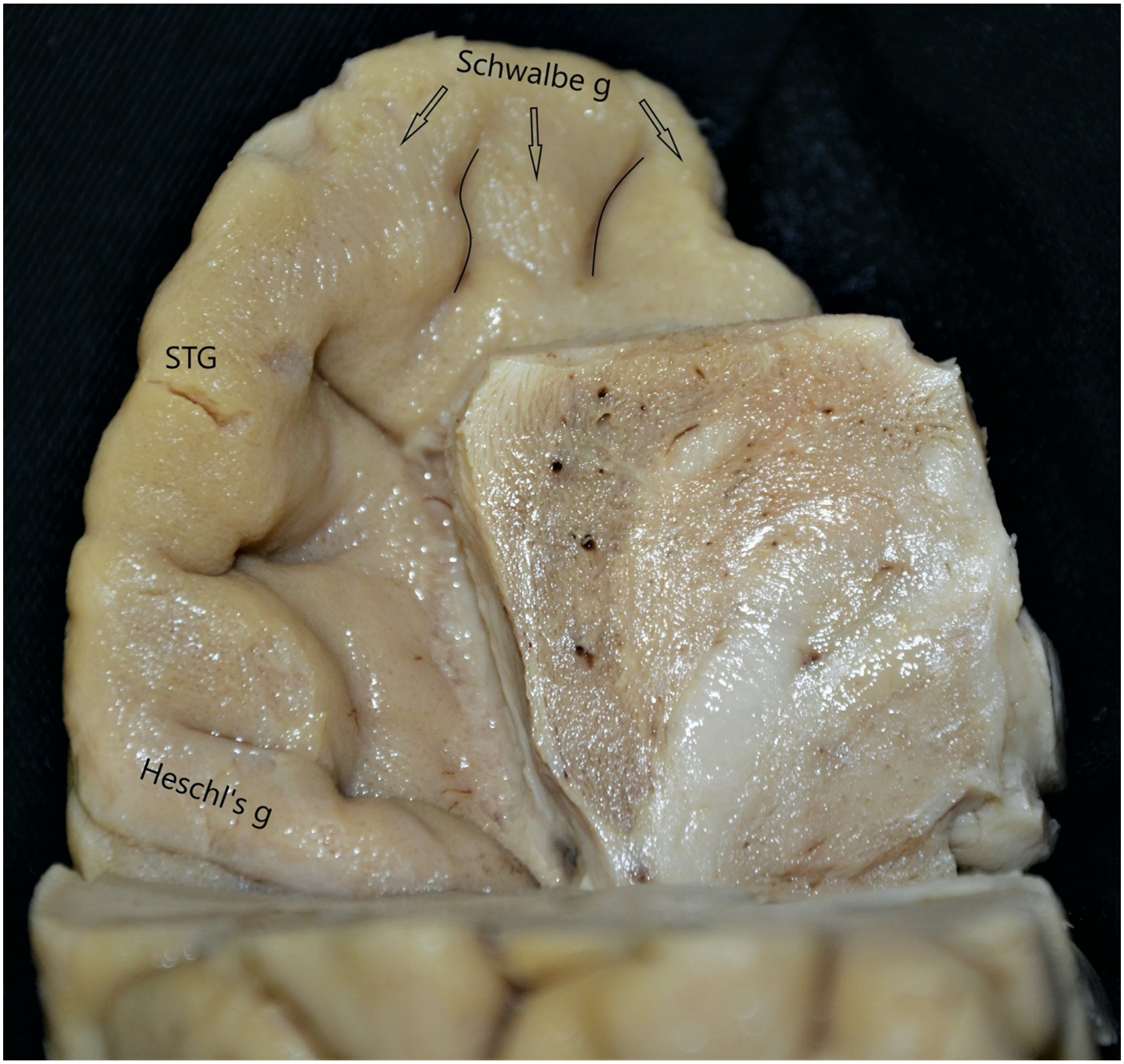


Fig 2: The pattern of the gyri of Schwalbe and the oblique sulci was documented. Here, the 3-gyri pattern with 2 oblique sulci dividing them, which was recorded in approximately 1/4 of the hemispheres, is demonstrated.

Sulcal morphology

On the dorsal surface the pattern of the oblique sulci followed the morphology of the gyrus of Schwalbe. The Rhinal sulcus, when present (66.6%), was recorded to extend to the dorsomedial surface in only in 6% of hemispheres.

On the lateral surface, the STS was recorded to extend in the TP area in 66.6% of hemispheres. Proximal to the posterior border of the TP, as was defined for this study, the sulcus displayed an oblique curvature at its endpoint, in 84.8% of hemispheres. The recorded trajectory was either medial, towards the lateral temporopolar sulcus, or lateral towards the ITS. The latter extended in the temporal pole region more often (84.8%), displaying a straight morphology.

On the basal surface the Occipitotemporal sulcus was rarely observed to extend beyond the posterior border of the TP (18.2%), as the ITG is the main gyrus forming the pole along this surface. The Collateral sulcus, depending on its relationship with the Rhinal sulcus, displayed variable patterns of polar extension. In 51.5% of hemispheres the Collateral sulcus was continuous with the Rhinal, thus it entered the pole as the latter. In 18.2% of hemispheres, the Collateral sulcus extended as a single sulcus in the TP area.

Finally, in 90% of hemispheres, a sulcus on the tip of the Temporal pole was recorded. This sulcus displayed irregular patterns in terms of morphology and no clear relationship with any of the aforementioned sulci.

3.2 RESULTS: TEMPORAL TERMINATION PATTERNS OF ALL TRACTS REACHING THE TEMPORAL POLE

White Matter Dissection Steps

We initiated our dissection from the basal surface, retaining the cortex of the anterior part of area TEv and areas 35 and 36 as well as area TG of the temporal pole. The horizontal sulcus at the TEv region demarcating this region's posterior and anterior parts, was used as the posterior limit of the cortex sparing area. The ITG and the FG were dissected first, followed by more medial cortical areas, through the collateral sulcus, to the PhG and postero-superiorly to the Lingual gyrus (Li), Cingulate gyrus (CG) and Precuneus (PrC. To fully expose all occipito-temporal connections, at this point, we extended our dissection plane to the lateral occipital cortex, in a lateral to medial fashion. This part of the dissection started at the lower parts of the posterior temporal lobe, specifically the ITG and extended posteriorly towards the Angular (Ang) gyrus and the gyri of the lateral occipital lobe, namely the Superior, Middle (when present) and Inferior Occipital gyri (SOG, MOG and IOG respectively).

On the lateral surface, our dissection started at the anterior parts of the MTG and STG, while preserving the superior surface of the STG cortex and the temporal planum. The superior part of the STG was dissected in a superior to inferior fashion to preserve and recognize the more superficial fibers of the MdLF. The frontal and insular lobes were dissected in order to reveal the temporal stem and UF. The parietal and occipital lobes, as well as the posterior part of the temporal lobe were dissected in subsequent stages to reveal the MdLF and the Sagittal Stratum (SS) and differentiate them from the ILF segment originating from the Dorso-Lateral Occipital cortex (DLOC). Finally, the lentiform nucleus was removed revealing the AC and the deeper fibers of the AP.

Starting from the basal surface removal of the gray matter of the Fu and the ITS revealed their u fiber system. Directly beneath the u-fibers of the Fu and the ITS, the main stem of the ILF was unveiled receiving fibers from the posterior Fusiform (Fu) and Lingual (Li) gyri as well as the lateral surface. Essentially a stream of fibers was recorded reaching the ventral temporal pole cortex. Lateral extension of the dissection plane facilitated the identification of the DLOC branch of the ILF. Dissecting away the cortical grey matter and u fibers of the Superior, Middle (when present) and Inferior occipital gyri, as well as the ITG, along with the superficial white matter tracts of the occipital lobe. Thus, a fiber bundle was recognized traversing in a diagonal fashion the occipital lobe, consistent with the DLOC segment of the ILF which joined the main stem at the level of the ITG and FG.

Removing the cortex of the parahippocampal gyrus revealed a diagonal bundle of fibers fanning out deep in the collateral sulcus and - its anterior extension to the uncus- the rhinal sulcus. After following the aforementioned fibers posteriorly and along the cingulate gyrus and its isthmus, their C-shaped silhouette around the splenium of the Corpus callosum was unveiled thus making apparent that they constitute the inferior arm of the cingulum. The cingulate fibers terminate at the uncus and area 35 of the temporal pole.

At the lateral surface, after cortical grey matter removal of the temporal and frontal lobes, we recognized the MdLF at the level of the STG and the superior longitudinal fasciculus (SLF) complex at the anterior frontal lobe respectively. After dissection of the frontal connections and the frontal operculum, the insula and the cortex of the superior part of the STG were revealed. Careful removal of its grey matter revealed the MdLF fibers coursing through Heschl’s gyrus and terminating at the dorso-lateral TP. Further dissection of the insula disclosed the extreme and external capsules leading us to the temporal stem. At this level the UF was evident as it crossed the stem and was distributed along the dorsal surface of the pole, medial to the MdLF terminations. Progressive removal of MdLF fibers, revealed deeper terminations at the level of the STS.

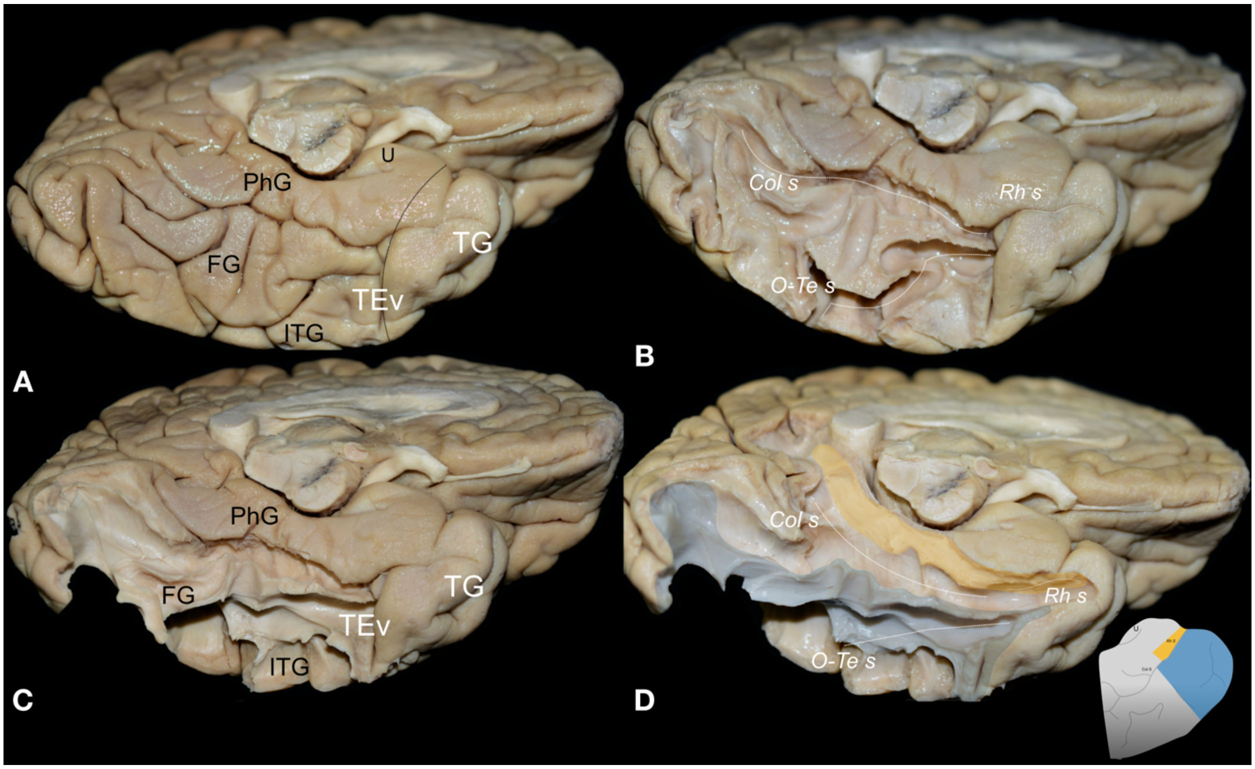


Fig 3: Inferior stepwise dissection of a left hemisphere **A:** Sulco-gyral anatomy. The black dotted line indicates the limit of the temporal pole region. **B:** Initial step of the dissection, U fibers of the FG and ITG. The Occipito-temporal and Collateral sulci are delineated with a white dotted line. The anterior extension of the Collateral sulcus at the polar region, the Rhinal sulcus (in this hemisphere a shallow sulcus) is delineated with a thin dotted line. **C:** Main stem of the ILF terminating at the posterior limit of the temporal pole region. The cortex of the PhG has been retained at this stage. **D:** Final stage of the dissection. The main stem of the ILF is shown in blue, terminating at the cortex corresponding to the TEv and ventral TG area. Dissection of the PhG reveals the fibers of the inferior arm of Cingulum (shown in yellow), terminating at the area 35. The inset illustrates the extent of cortical terminations of the two fasciculi in the ventral TP area. (FG: Fusiform Gyrus, ITG: Inferior Temporal gyrus, O-Te S: Occipito-temporal sulcus, PhG: Parahippocampal gyrus, Rs: Rhinal sulcus, U: Uncus)

To properly identify the distribution of the lateral surface fibers, we extended our dissection to the posterior temporal and parietal lobes, removing their u-fibers and the SLF/Arcuate complex. In this step of our dissection, we clearly recognized the MdLF fibers travelling towards the Superior Parietal Lobule (SPL) and the DLOC segment of the ILF traveling at an inferior level in a diagonal trajectory, lateral to the SS, to join its main stem at the basal surface.

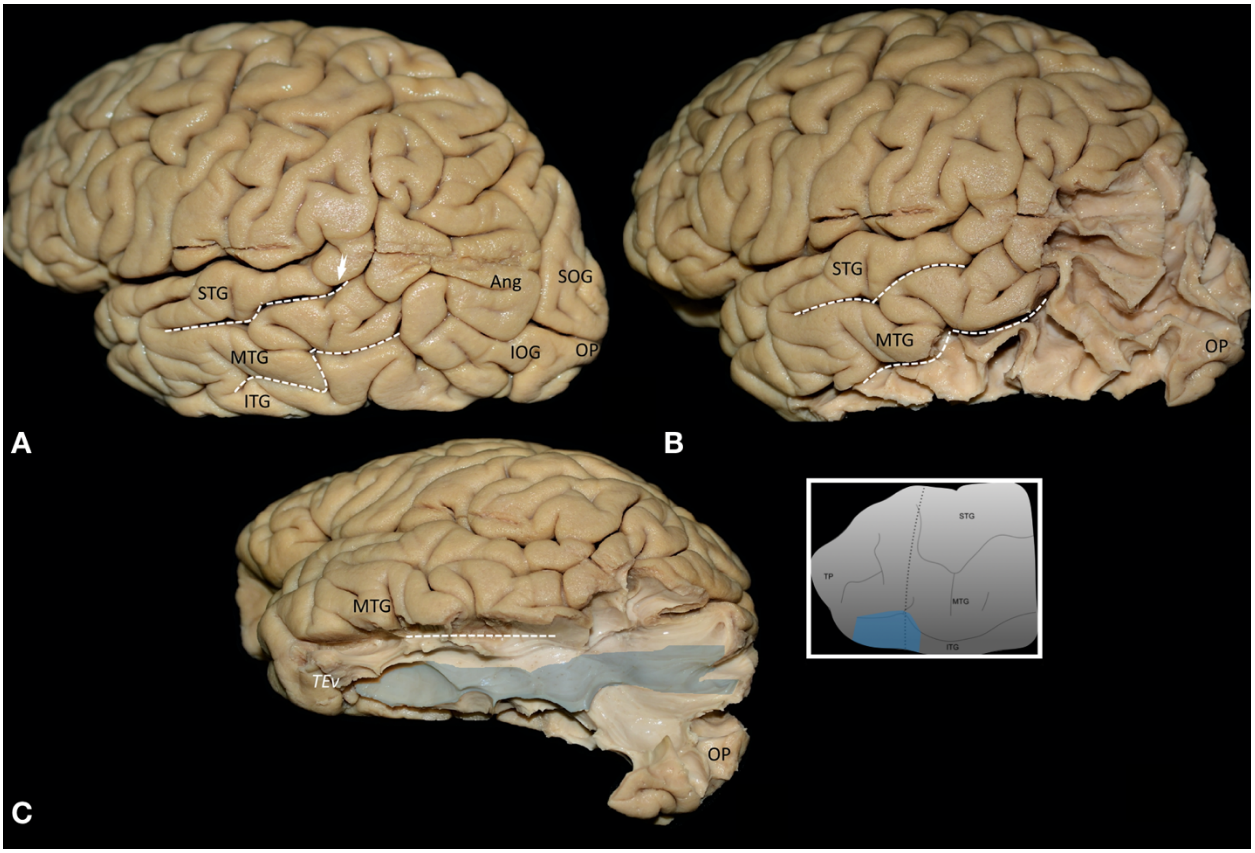


Fig 4: Lateral extension of the dissection of the same hemisphere as in Fig. 3. A: Sulco-gyral anatomy. The white dashed lines indicate the Superior (white arrow) and Inferior Temporal Sulci respectively. **B:** U fibers of lateral occipital and occipito-temporal junction. **C:** Final stage of the dissection. The DLOC segment of ILF is shown in blue as it joins the main stem of the fasciculus to terminate at the TEv region. The inset illustrates the extent of cortical terminations of the ILF at the ventrolateral TP. (Ang: Angular gyrus, IOG: Inferior Occipital gyrus, ITG: Inferior Temporal gyrus, MTG: Middle Temporal gyrus, OP: Occipital pole, SOG: Superior Occipital gyrus, STG: Superior Temporal Gyrus, TP: Temporal pole)

Removal of the remaining MdLF revealed the relationship between the UF, terminating at the dorso-medial part of the TP and the ILF terminating at the ventro-medial part. Further dissection of the ventral external capsule resulted in complete removal of the UF and its terminations to the TP. Dissection of the Lentiform nucleus disclosed the Anterior Commissure (AC) with its temporal branch in close proximity to the ILF and a part of it terminating supero-medialy to the ILF at the temporal pole. Finally, after AC removal a bundle originating from the midline, travelling superiorly to the optic tract, consistent with the Ansa Peduncularis, was recognized to terminate medial to the AC termination at the TP.

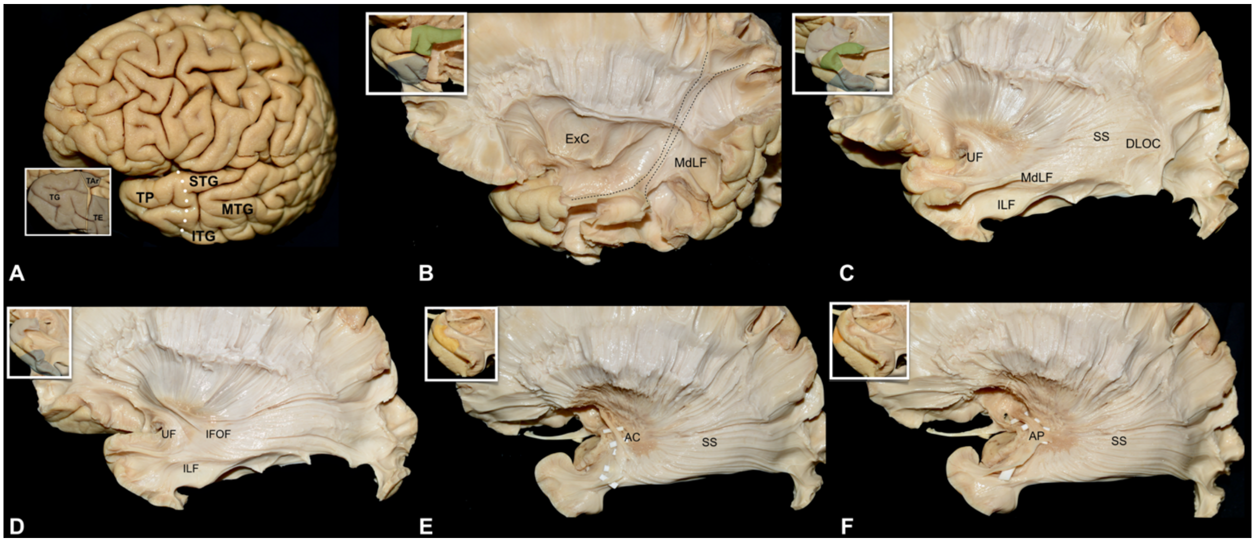


Fig 5: Stepwise dissection of the lateral surface of a left hemisphere. For each step of the dissection an inset is included in the upper-left corner. It demonstrates a concurrent anterior view of the TP cortex with the respective white matter tract terminations being illustrated in colour. The same colour coding is retained throughout the figure. **A:** Sulco-gyral anatomy of the temporal region before the dissection. The white dotted line demarcates the posterior limit of the TP cortex. The inset presents the parcellation of temporal pole cortex, for this hemisphere, as have been defined in Fig 1. **B:** MdLF dissected in a superior to inferior manner, traveling through Heschl's gyrus and terminating at the TAr area of the TP. The inset illustrates the relationship between the MdLF (green) and ILF (blue) terminations at the TP area. **C:** Further extension of the dissection through the lateral surface. The DLOC segment of the ILF is evident traversing lateral to the sagittal stratum. Most of MdLF fibers have been removed. The deepest MdLF

fibers are recognized terminating at the depths of the STS corresponding to TAp area. Inferiorly, the termination of the ILF is evident at the ventral TG and TEv areas. Superiorly, the fibers of UF (light grey) can be recognized travelling through the temporal stem and terminating at the dorsal TG region. The inset illustrates the relative anatomy of the terminations of the aforementioned white matter tracts. **D:** Removal of the remaining MdLF fibers reveals the UF and ILF terminations along the dorsal and ventral TG area respectively. The distinct termination pattern between them can be appreciated in the inset. **E&F:** Final stage of the dissection. The Anterior commissure is recognized terminating at the lateral portion of the remaining TP cortex. After its removal the ansa peduncularis fibers are recognized terminating medially. (AC: Anterior Commissure, AP: Ansa Peduncularis, DLOC: Dorsolateral segment of the ILF, ExC: External capsule, IFOF: Inferior Fronto-occipital Fasciculus, ILF: Inferior Longitudinal Fasciculus, ITG: Inferior Temporal gyrus, MdLF: Middle Longitudinal Fasciculus, MTG: Middle Temporal gyrus, SS: Sagittal stratum, STG: Superior Temporal Gyrus, TP: Temporal pole, UF: Uncinate Fasciculus)

White matter tracts morphology, trajectory, and connectivity

ILF

The major fiber bundle terminating at the TP area was the ILF. Its main stem displayed an antero-posterior trajectory along the basal surface of the hemisphere. The ILF fibers initiating from the Lingual gyrus, posterior FG and ITG together with fibers from the occipital pole, traveled in a longitudinal manner towards anterior temporal areas. A distinct fiber bundle keeping with the DLOC was consistently identified initiating from the lateral occipital cortex displaying an oblique trajectory lateral to the SS, that joined the main stem of the ILF at the level of the ITG or the FG. The ILF terminated at ventral and ventrolateral TP cortex areas. Interestingly, in several hemispheres, beneath the superficial u-fibers of the ITG, a second u-fiber system was recognized, running parallel to the main stem of the ILF, connecting the posterior TE area with postero-ventral ITG areas.

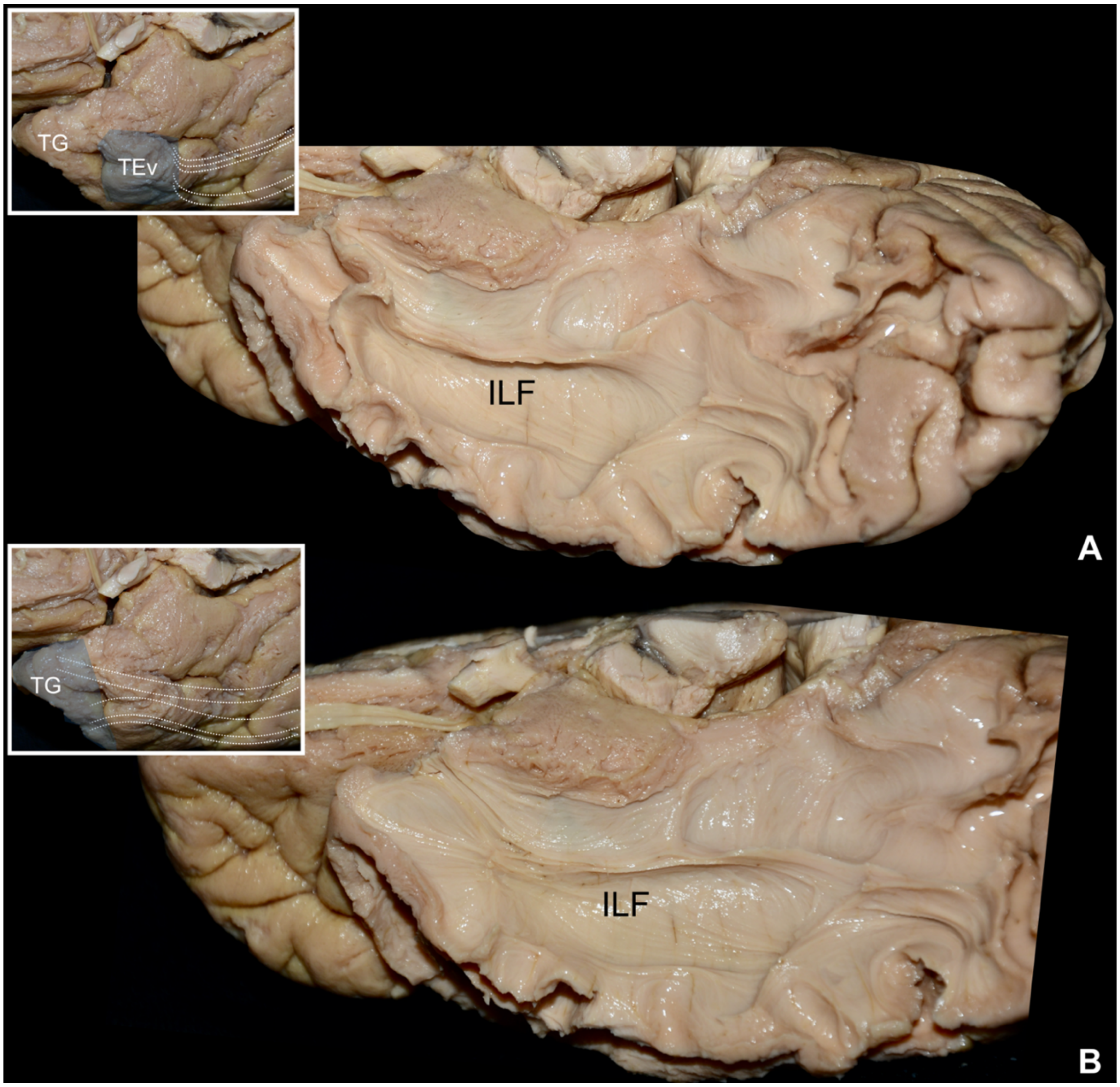


Fig 6: Termination patterns of ILF at the TP region in a right hemisphere. **A:** Termination at the posterior TEv region with anterior u-fiber extension towards the ventral TG area. The approximation of the cortical terminations is illustrated in the inset at the left-upper corner. **B:** Direct cortical terminations at the TG area of the TP. (ILF: Inferior Longitudinal Fasciculus)

<u>Inferior arm of Cingulum</u>

This C-shaped bundle was consistently identified running directly beneath the cingulate gyrus' cortex. Along its course through the cingulum, its shape followed the shape of overlying gyrus. It started at the level of the anterior cingulate gyrus, narrowing within the cingulate isthmus. Eventually one part terminated at the uncus whereas a second part fanned out further anteriorly, towards the ventromedial TP cortex.

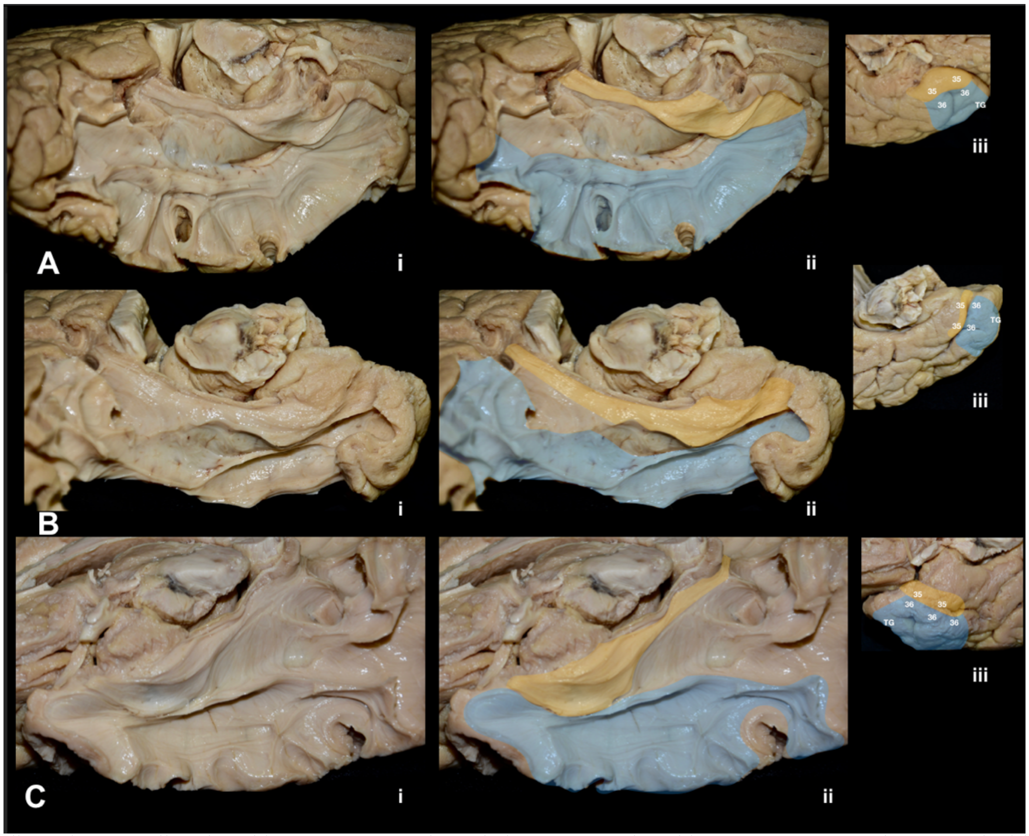


Fig 7: Termination pattern of Inferior arm of Cingulum in 3 basal dissections. **A&B:** Basal dissection in two left hemispheres. Cingulum fibers are shown in yellow, whereas blue represents the main stem of the ILF. **C:** Basal dissection of a right hemisphere. **i** The final step of the dissection revealing the white matter tracts along their course. **ii** The white matter tracts are demarcated with colour. **iii** The relative anatomy of TP cortical terminations is illustrated retaining the same colour coding. Along the lateral edge of the hemispheres **A** and **C,** a u fiber system is evident, running parallel to the main stem of the ILF, connecting the Inferior Temporal gyrus and Fusiform gyrus to ventro-lateral TP areas.

MdLF

This white matter bundle was consistently recognized terminating at the supero-lateral region of the TP cortex. Fibers running relatively superficial displayed an antero-lateral to postero-medial trajectory. Particularly, fibers initiating at the level of the STG were recognized directly beneath the TP cortex and followed until the SPL cortex. At the level of the temporoparietal junction, they were consistently identified deep to the SLF/AF complex and displayed posterior terminations at the level of the SPL and the Parieto-occipital arcus (POA). On the other hand, the fibers displaying the most anterior terminations at the level of the STS followed a more longitudinal trajectory posteriorly terminating at the level of the lateral Occipital lobe, medial to the DLOC segment of the ILF.

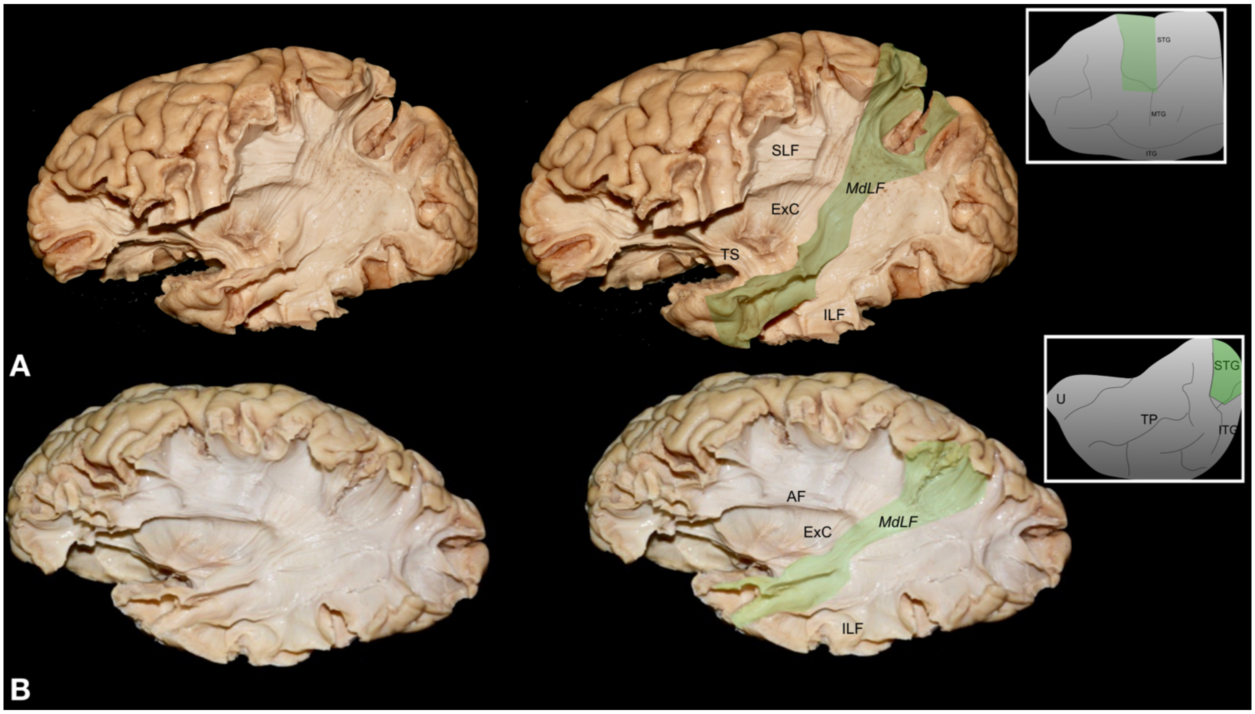


Fig 8: MdLF termination at the TP. **A&B:** Lateral to medial dissection of two left hemispheres. The course of the white matter tract is evident along the lateral surface and is shown in green. Insets present the TP cortex where MdLF terminations were discovered in our study. (AF: Arcuate Fasciculus, ExC: External capsule, ILF: Inferior Longitudinal Fasciculus, ITG: Inferior

Temporal gyrus, MdLF: Middle Longitudinal Fasciculus, MTG: Middle Temporal gyrus, SLF: Superior Longitudinal Fasciculus, STG: Superior Temporal Gyrus, TP: Temporal pole, TS: Temporal Stem, U:Uncus)

UF

The UF was identified consistently as part of the temporal stem and the ventral external capsule. After removing the insular surface and the extreme capsule, the fibers of the UF ventrally and inferior fronto-occipital fasciculus (IFOF) dorsally were clearly recognized. Superficial UF fibers, with their characteristic hook-like appearance, were recognized to start at the level of the pars orbitalis and the posterior orbital gyrus. Deeper fibers were recognized to initiate from the gyrus rectus and medial cortical regions ventral to the Putamen. All these fibers travelling through the temporal stem were distributed to the dorsal surface of the TP, anterior to the insular cortex.

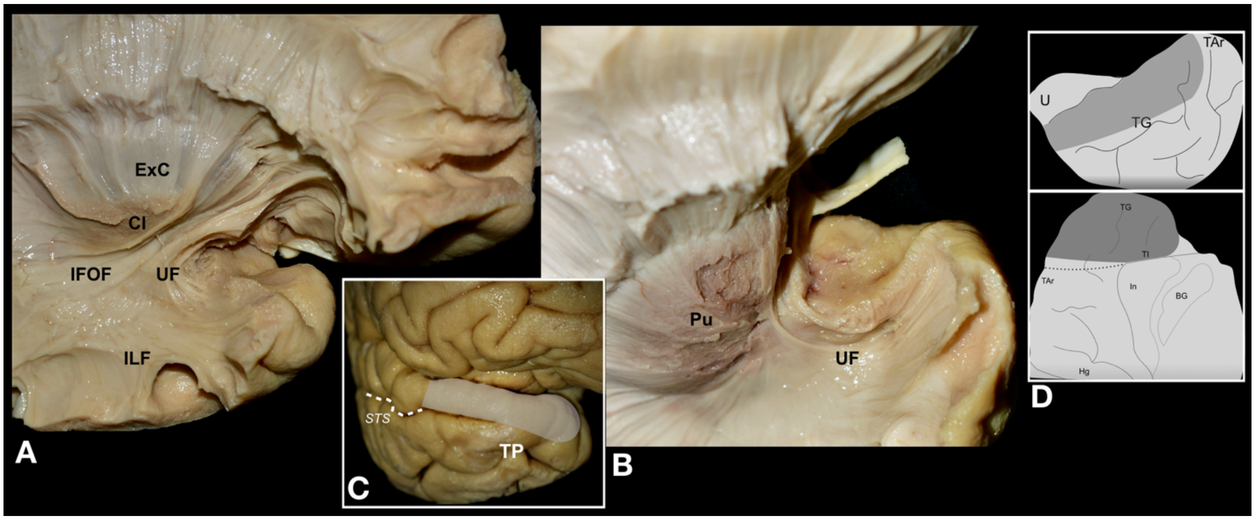


Fig 9: Termination pattern of UF to the TP, in a right hemisphere. **A:** Lateral view at the level of the external capsule, the temporal stem is recognized ventral to the Claustrum. UF terminates at areas TG and TI. **B:** Superior view after removing the external capsule and a major part of the temporal stem. Deep UF fibers travel antero-ventral to the Putamen terminating at areas TI and TG. **C:** Anterior view of the TP cortex in the same hemisphere. UF terminations are represented in grey. **D:** Graphic representation of the UF termination area along the TP cortex (*up: Anterior view, down: Superior view*) (BG: Basal Ganglia, Cl: Claustrum, ExC:

External capsule, Hg: Heschl's gyrus, IFOF: Inferior Fronto-occipital Fasciculus, ILF: Inferior Longitudinal Fasciculus, In: Insula, Pu: Putamen, STS: Superior Temporal sulcus, TP: Temporal pole, UF: Uncinate Fasciculus, U: Uncus)

AC

The AC fibers were recorded to initiate from the midline crossing anterior to the Internal Capsule fibers, after the complete removal of the Lentiform nucleus. The Gratiolet's canal, that encloses these fibers while exiting the level of the basal ganglia, was always opened in order to dissect the two fiber streams of the AC. The posterior fiber stream travelled posteriorly inside the SS, lateral to the optic radiation, towards the posterior temporal lobe. The anterior fiber stream was significantly thinner and terminated at the TP region.

AP

The most hidden fasciculus of the limbic system was recognized travelling deep to the AC fibers. It initiated from the midline as 1-2 streams of fibers ventral to the rostrum of the corpus callosum (CC) and the posterior gyrus rectum. It travelled in an "S" like fashion through the Substantia Innominata and divided in two segments, a posterior joining the SS deep to the AC fibers and an anterior towards the TP cortex.

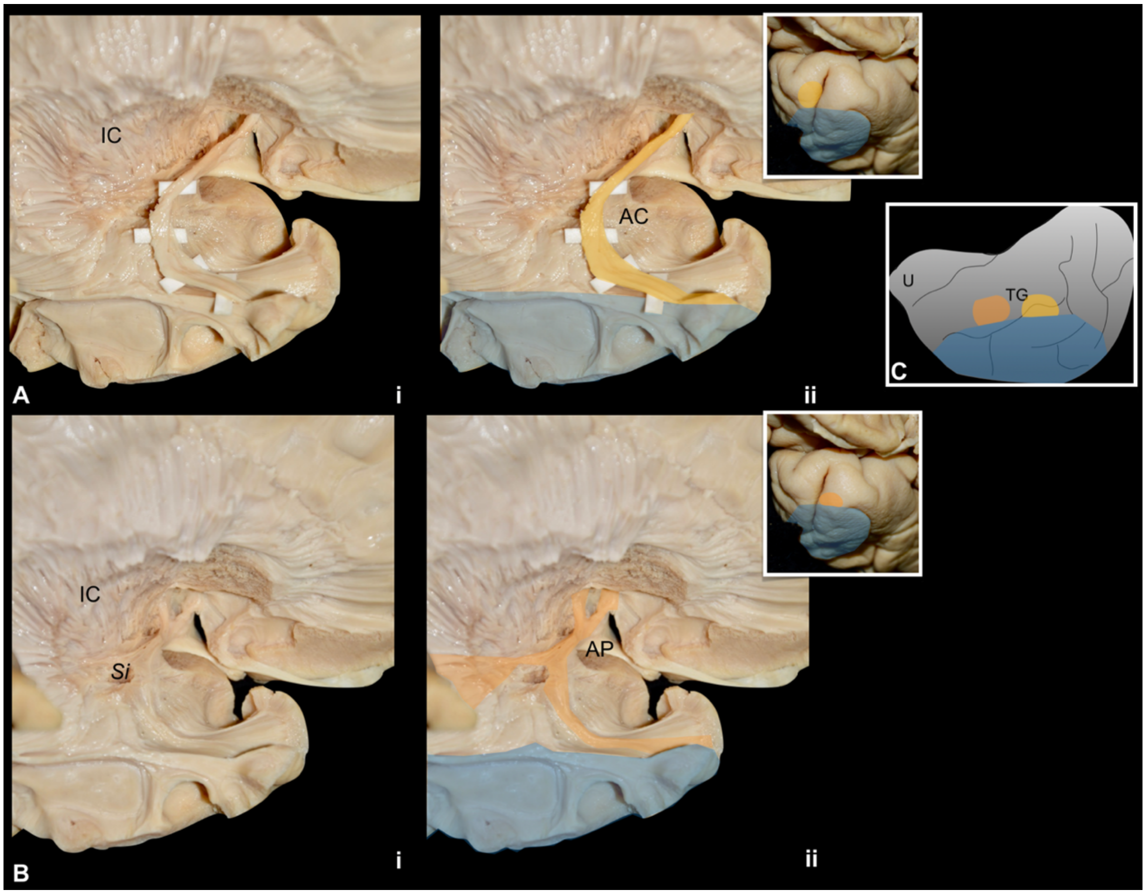


Fig 10: Termination of AC and AP at the TP, in a right hemisphere. The UF fibers along with the Putamen have been completely removed, revealing the vertical fibers of the Internal Capsule. **Ai:** Termination of AC at lateral TG area, directly superior to ILF. **Aii:** Colour demarcation of AC (dark yellow) and ILF (blue) termination at TP. In the inset the TP terminations of each white matter tract are illustrated retaining the same colour coding **Bi:** After removal of AC fibers, the fibers of AP are revealed around Substantia Innominata and terminate anteriorly, directly medial to AC. **Bii:** Colour demarcation of AP (orange) and ILF termination at TP. In the inset the TP terminations of each white matter tract are illustrated, once more, retaining the same colour coding C: Graphic representation of the relative anatomy of AC, AP and ILF terminations at the TG area (anterior view). (AC: Anterior Commissure, AP: Ansa Peduncularis, IC: Internal Capsule, Si: Substantia innominata, U: Uncus)

Temporopolar terminations and termination patterns

ILF

The most superficial fibers of ILF terminated at the level of the anterior TEv region. Interestingly, in 29.4% of hemispheres where the horizontal sulcus at the posterior limit of the TP was present, the fiber tracts terminated at the level of the posterior TEv and a u-fiber system at the depth of the sulcus connected the bundle with the anterior TEv and the ventral TG areas. In 70.6% of the hemispheres the majority of the ILF fibers terminate directly to TP cortical areas without any mediation from TP u-fibers. After removal of the superficial fibers, the main stem of the ILF terminated further anterior to the ventral, ventromedial and ventrolateral TP. This part of the fasciculus connected with most of the ventral TG area and the anterior part of area 36, as well as the inferior TEd and anterior TEv areas.

Inferior arm of cingulum

Following the cingulate isthmus and traveling directly under the cortical grey matter of the parahippocampal gyrus, the inferior arm of the cingulum fanned out at the level of the hippocampus covering medially the depth of the collateral sulcus. Its terminations extend along the uncus and the anterior area 35 of the TP.

MdLF

The anterior terminations of this fiber tract cover the lateral surface of the anterior temporal lobe, namely the anterior parts of the STG and STS. The most superficial fibers, traversing through Heschl's gyrus, terminate at the TAr region whereas the deeper fibers of the fasciculus, display terminations at the TAp region, superiorly to the ILF terminations.

UF

This c-shaped fiber fasciculus crosses to the temporal lobe through the temporal stem and is distributed throughout dorsal cortical areas of the TP. Specifically, in our dissections it terminated at the level of the dorsal TG and the TI area anterior to the uncus.

AC

After complete removal of UF and lentiform nucleus the AC, with its characteristic bicycle-handle appearance was recognized displaying direct cortical terminations at the middle part of the lateral TG region between UF and ILF terminations.

AP

This deep fiber tract arose through the Substantia Innominata, anterior to the internal capsule. Its terminations were recorded at the middle part of the medial TG, dorsal to ILF, ventral to UF and medial to AC terminations.

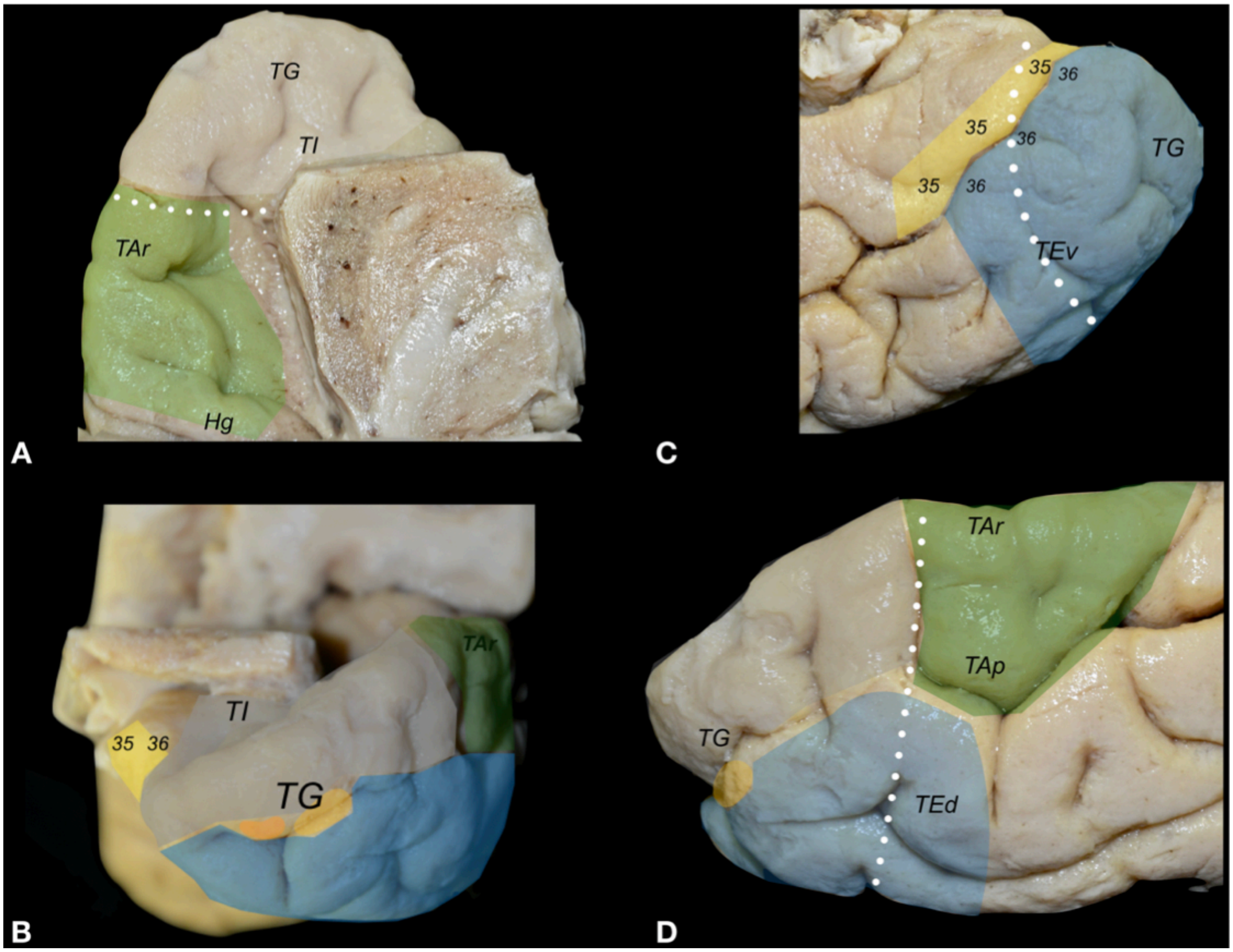


Fig 11: Colour map of the TP region illustrating the comparative anatomy of the white matter tracts' terminations as were revealed in our study. The same colour coding was retained, namely ILF – blue, MdLF – green, UF – light grey, Inferior Arm of cingulum – light yellow, Anterior Commissure – dark yellow, Ansa Peduncularis – Orange. The regions according to Ding's map are mentioned in each view, as were defined in Figure 1. **A:** Superior view, **B:** Anterior view, **C:** Infero-medial view, **D:** Lateral view.

Subcortical corelative anatomy of the TP

Dorsally, the fibers of the MdLF, located directly beneath the STG cortex, terminate at the most dorsolateral part of the TP, the TAr area with a few deeper fibers terminating ventrally and more anteriorly at the TAp area. Medial to the TAr area, we find the fibers of the UF spreading across the dorsal part of the TP cortex, namely the dorsal TG and TI areas. Directly beneath the UF, we find the thin terminations of the AC lateral and AP medial, recognized only after complete removal of the UF. These two thin fiber tracts serve as an anatomical landmark separating the terminations of the UF dorsally and the ILF ventrally. On the basal surface we recognize the ILF terminations covering the majority of the ventral polar surface, namely the anterior TEv, ventral TG and area 36 while medially the terminations of the inferior arm of the cingulum extend along the medial bank of the rhinal sulcus, the area 35. Therefore, it is evident that the two major fasciculi of the temporal pole exert a discrete termination pattern. The UF is constantly dorsal to the ILF within the TG area, with no terminations ventral to the AC and AP.

3.3 RESULTS: MIDDLE LONGITUDINAL FASCICULUS

White Matter Dissection 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 the hemisphere are evident (Step 1). 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). 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). 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.

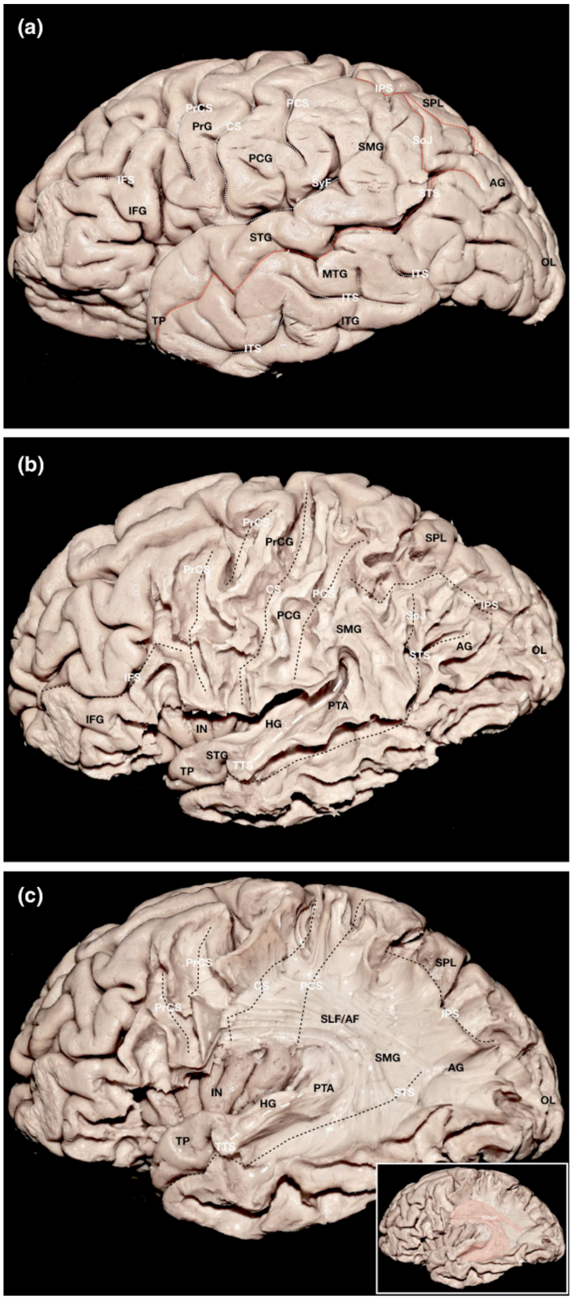


Fig. 12: **Cortical and superficial subcortical anatomy.**

(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 Transverse 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 Kalyvas et al by permission of Springer Nature, Brain Structure & Function

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 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 supramarginal gyrus (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) (Rhoton Jr 2002, Alves, Ribas et al. 2012, Maldonado, de Champfleur et al.

2013). Removing the U-fibers of the TPO junction, unveils MdLF fibers continuing further posteriorly to enter the occipital lobe (Step 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). 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). 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.

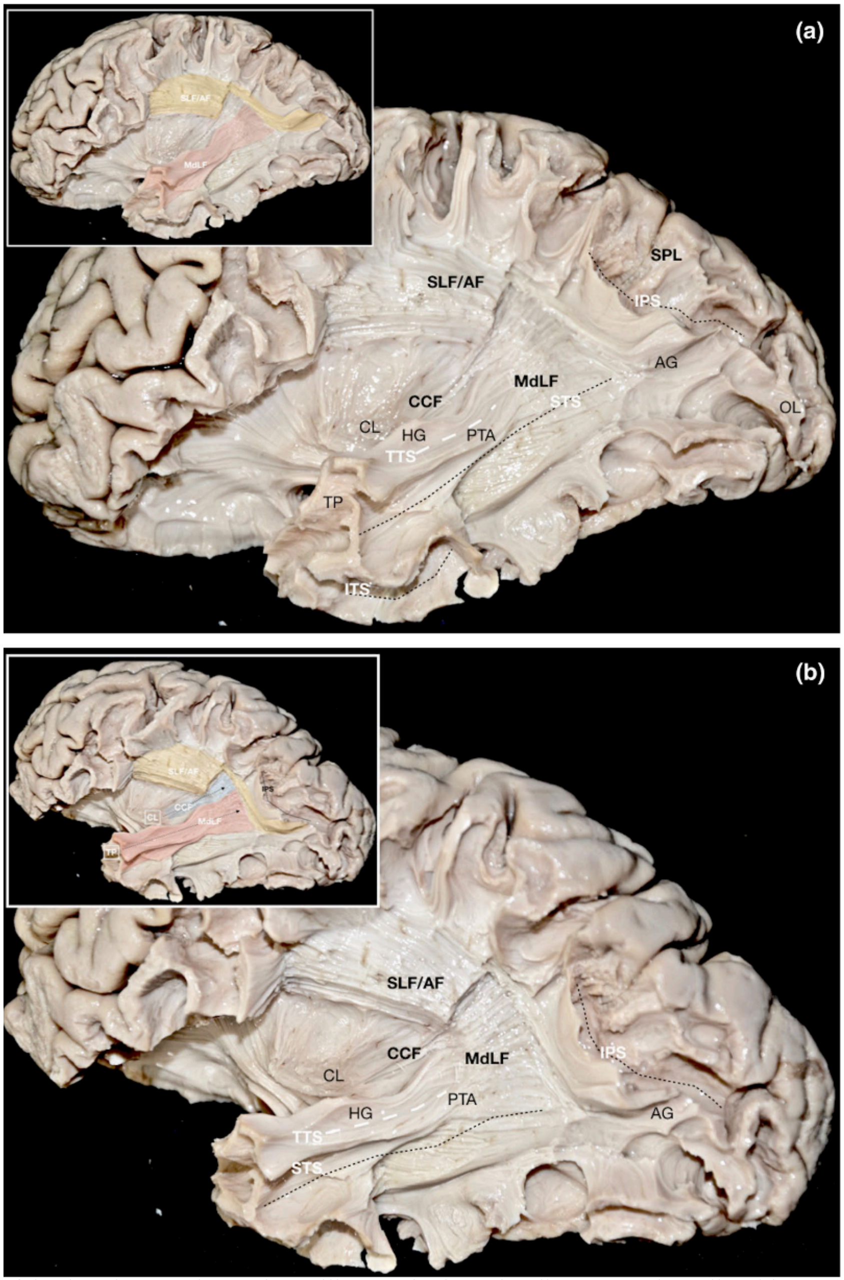


Fig. 13: Relationship between the MdLF and the IPL. Correlative anatomy with respect to the SLF and CCF (Step 3)

(a) Same specimen as in Fig. 12. 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 Kalyvas et al by permission of Springer Nature, Brain Structure & Function

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).

Trajectory and morphology of the MdLF

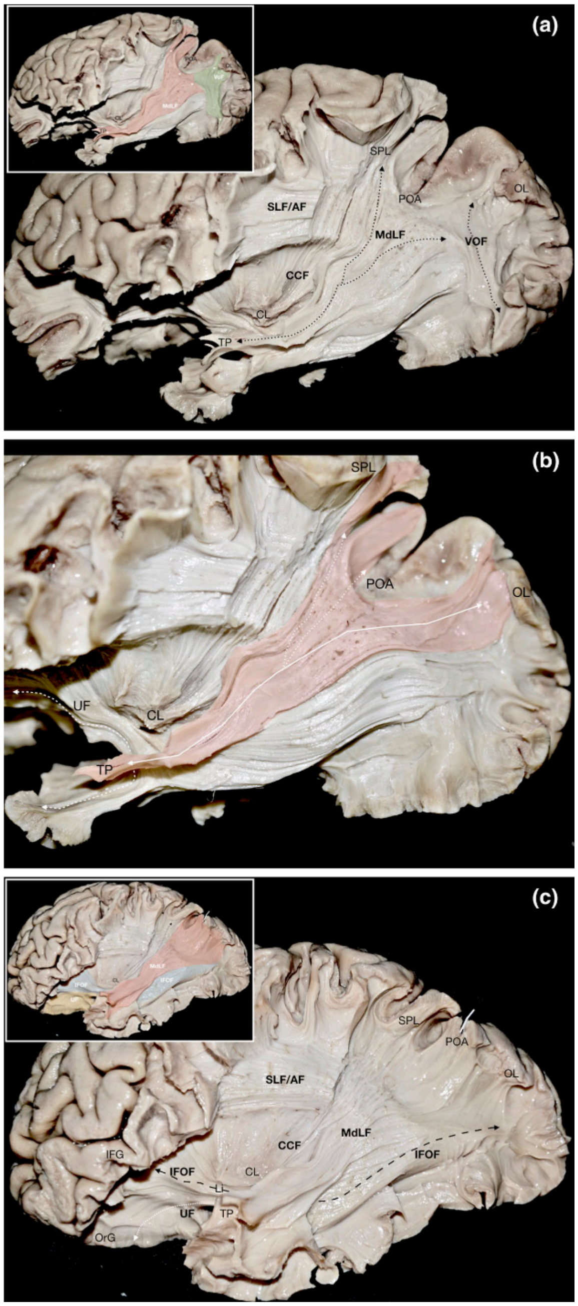
The MdLF was invariably identified and recorded as a white matter bundle travelling under the U-fibers of the anterior STG/STS area and medial to both the U-fibers and the SLF/AF complex at the posterior temporal lobe and IPL. It was documented to connect the STG to the SPL and parieto-occipital area, 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. 14: 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. 14a. 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. 12. 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 Kalyvas et al by permission of Springer Nature, Brain Structure & Function

Subcortical Correlative anatomy of the MdLF

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. 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.

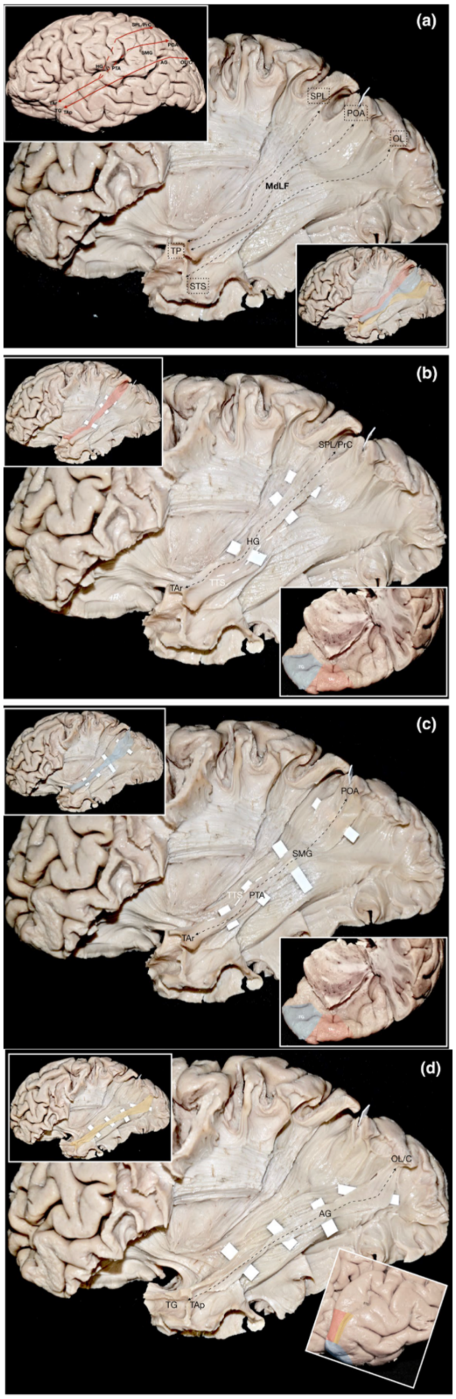


Fig. 15: Connectivity and segmentation pattern (Step 6)

(a) Left hemisphere - Same as in Fig. 12. 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 Kalyvas 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.

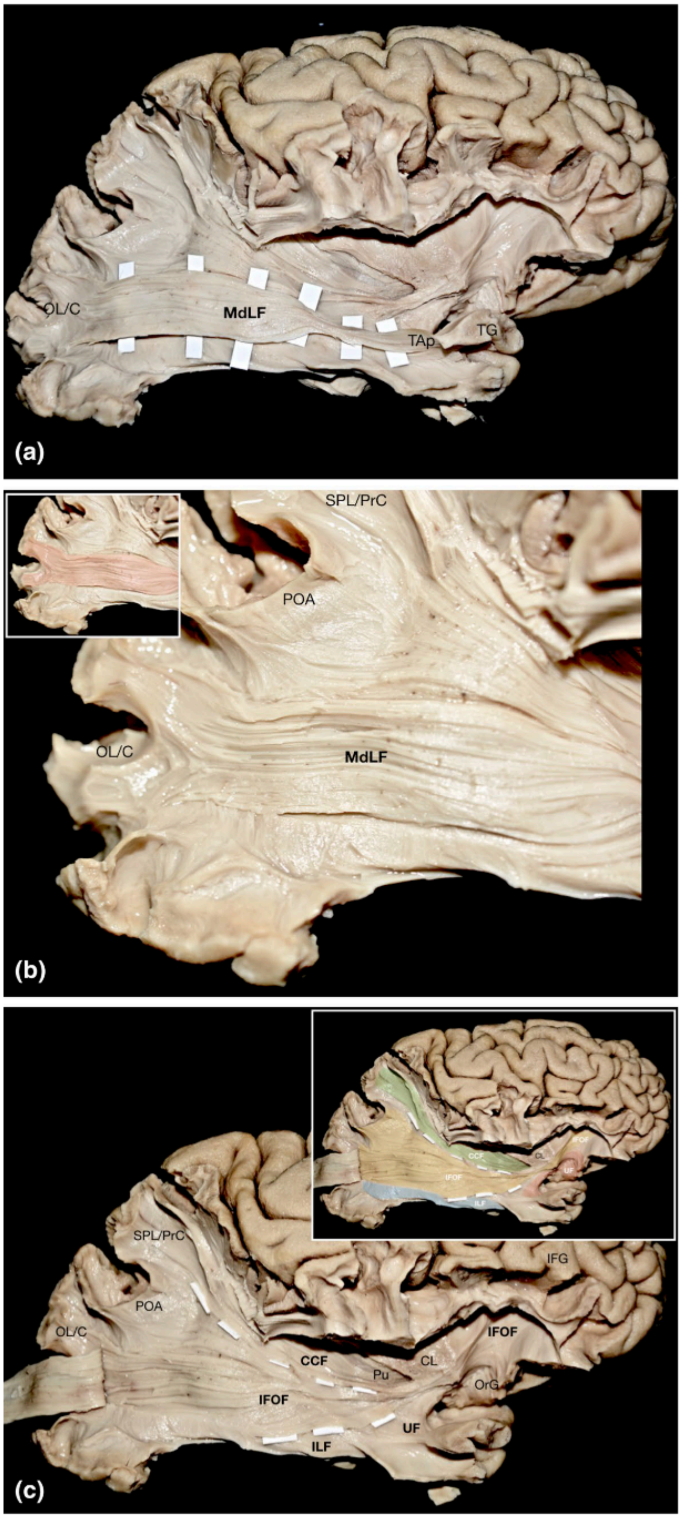


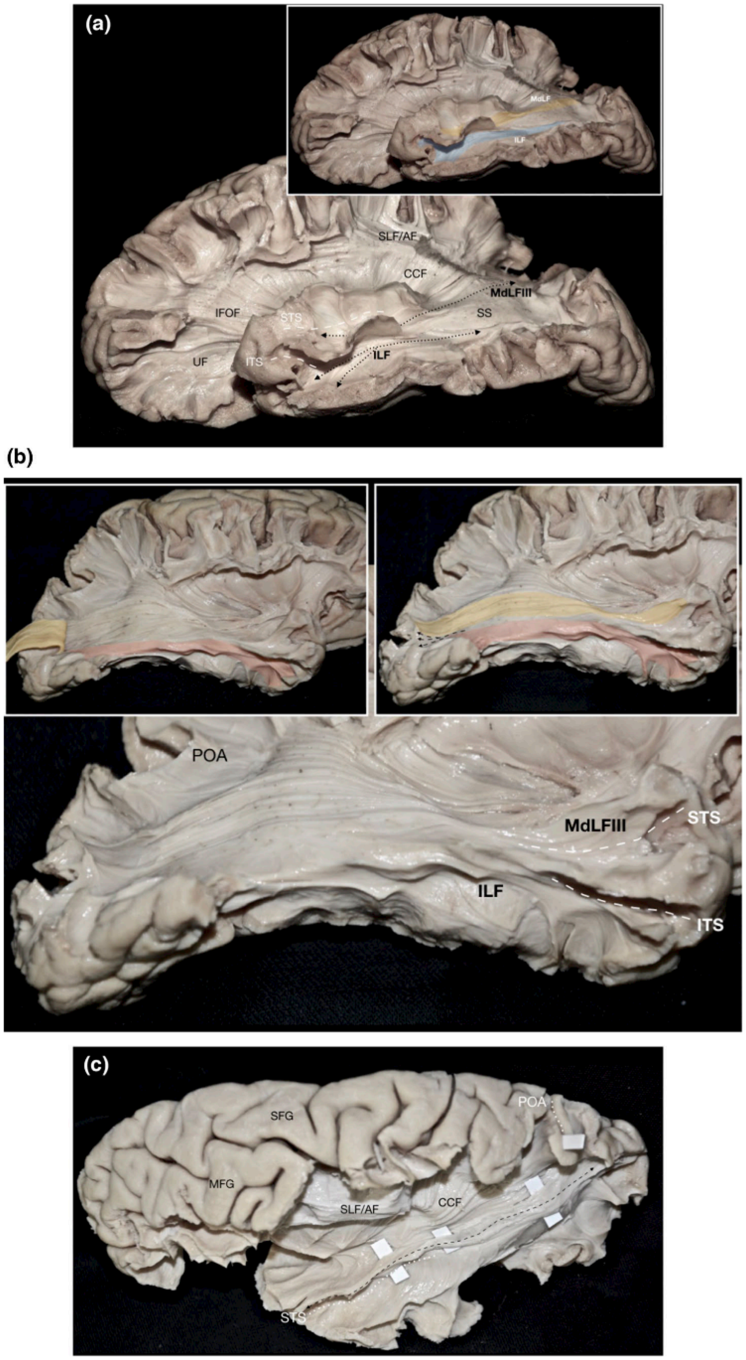
Fig. 16: MdLF Occipital terminations and relationship with deeper fiber tracts (Step 7)

(a) Different specimen. Right lateral side. Hyper-selective dissection of the MdLF-III.

(b) 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). 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 Kalyvas et al by permission of Springer Nature, Brain Structure & Function

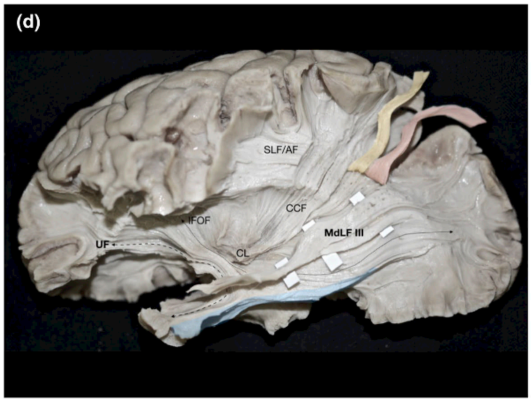
Fig. 17: MdLF III correlative anatomy with respect to ILF at the sulcal and deep subcortical levels.



(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.

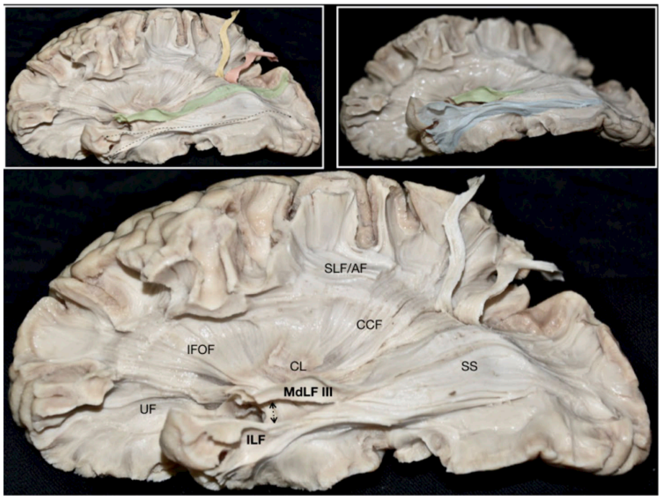
(b) Right hemisphere. Inferolateral view. Again, MdLF III and ILF anterior terminations at the level of the STS and ITS/ventral TP, respectively. ILF fibers are seen turning towards the medial TP at the most anterior aspect of the tract. Posteriorly both tracts merge with the sagittal stratum and share 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) 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) 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.

(e)



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 Kalyvas et al by permission of Springer Nature, Brain Structure & Function

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

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.

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.

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. More specifically, the most inferior fibers of the MdLF are apparent at the level of the STS 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. 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. Again, the ILF fibers terminate distinctly more anteriorly in the temporal pole. Importantly, the ILF fibers turn towards the medial TP at the most anterior aspect of the tract. 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. 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.

Segmentation and connectivity pattern

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. 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, we used a similar nomenclature and we defined the three MdLF segments as MdLF-I, MdLF-III and MdLF-III.

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. 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. This segment travels parallel and posterolateral in relation to the claustrocortical fibers of the dorsal external capsule.

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). The MdLF-II lies more posteriorly, inferiorly and medially when compared to the MdLF-I and in an oblique and posteriorly directed course.

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. 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.

3.4 RESULTS: FIFTH COMPONENT OF THE CINGULUM BUNDLE

Fiber Dissection

Upon removing the cortex and superficial U-fibers of the parieto-occipital sulcus (POS), calcarine fissure, cuneus, precuneus, posterior cingulate area, lingual, parahippocampal and fusiform gyri, we invariably expose a group of fibers seen to radiate from the area of the posterior precuneus (BA7 - anterior bank of the POS) to the basal temporo-occipital junction (BA37 - middle third of the fusiform gyrus). This distinct white matter bundle, previously described as CB-V, follows the trajectory of the POS, bends around the splenium of the Corpus Callosum, then curves caudo-medially passing under the posterior half of the proximal calcarine fissure to reach the Posterior Parahippocampal Area and further dives under the collateral sulcus in a deeper plane to terminate to the middle third of the fusiform gyrus (BA 37). In 80% of cases, (12/15 hemispheres), fibers of the CB-V were also recorded to terminate at the medial temporal lobe and more specifically at the lateral piriform area (BA35).

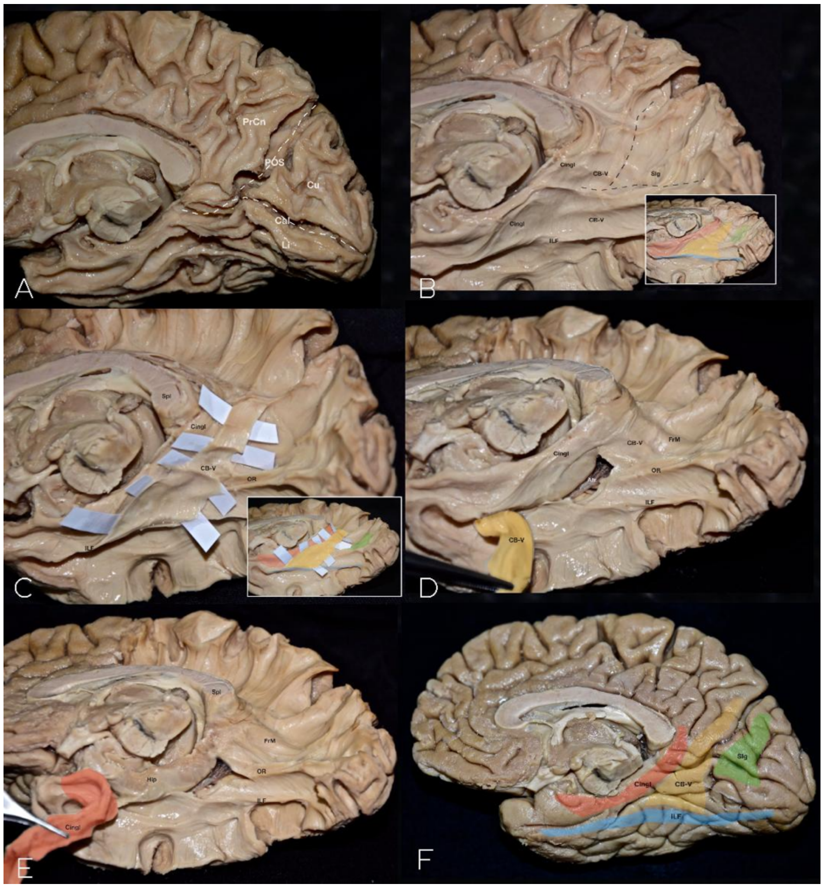
This fiber tract follows a dorso-medial to ventrolateral trajectory and usually exhibits three medially projecting knees, specifically at the level of the Forceps Major, Retrosplenial Cortex and parahippocampal gyrus. It displays a triangular silhouette with the narrowest part seen in the area of the posterior precuneus and the widest part in the area of the fusiform gyrus. There were no differences observed between left/right hemispheres, concerning the tract's thickness, connectivity pattern or morphology.

Spatial Relationship of CB V with Adjacent Fiber Tracts: Inferior arm of the Cingulum and CB-V.

Fibers of the inferior arm of the cingulum originate from frontal cortices and bend around the splenium of the corpus callosum in an almost parallel trajectory to the mid-sagittal plane, whereas CB-V fibers originate at the precuneus and run in an oblique dorsolateral to ventromedial direction, crossing the parasagittal plane. Although inferior to the level of the splenium these two bundles exhibit what is widely known as a “kissing pattern” of fiber distribution, indeed the white matter dissection technique allowed us to specifically differentiate the fibers of the CB-V, which are encountered more lateral and caudal in relation to the fibers of the inferior arm of the cingulum.

Fig.18: Progressive dissection of a right hemisphere. Medial views

A: Gray matter has been removed. The superficial U-fibers are apparent. The contour of the main sulci is illustrated.



B: Upon removing the superficial U-fibers, the inferior arm of the cingulum, CB-V, ILF and Sledge runner fasciculus are depicted. Inset: The aforementioned fasciculi are highlighted in red, yellow, blue and green color respectively.

C: The fibers of the CB-V are followed along their trajectory, from the posterior precuneus to the area of the fusiform gyrus and medial temporal lobe. CB-V fibers can be dissected without affecting the structural integrity of the inferior arm of the cingulum. These two fiber systems appear with a kissing configuration but without intermingling. Inset: The inferior arm of the cingulum, CB-V, sledge runner fasciculus and ILF are highlighted in red, yellow, blue and green color respectively.

D: Fibers of the CB-V are followed towards the medial temporal lobe. The structural integrity of the inferior arm of the Cingulum remains intact.

E: The inferior arm of the cingulum is gradually dissected. Its inferior terminations follow a trajectory that is medial in relation to that of CB-V.

F: The anatomical silhouette of the inferior arm of the cingulum (red), CB-V (yellow), Sledge runner fasciculus (green) and ILF (blue) is superimposed on the medial surface anatomy.

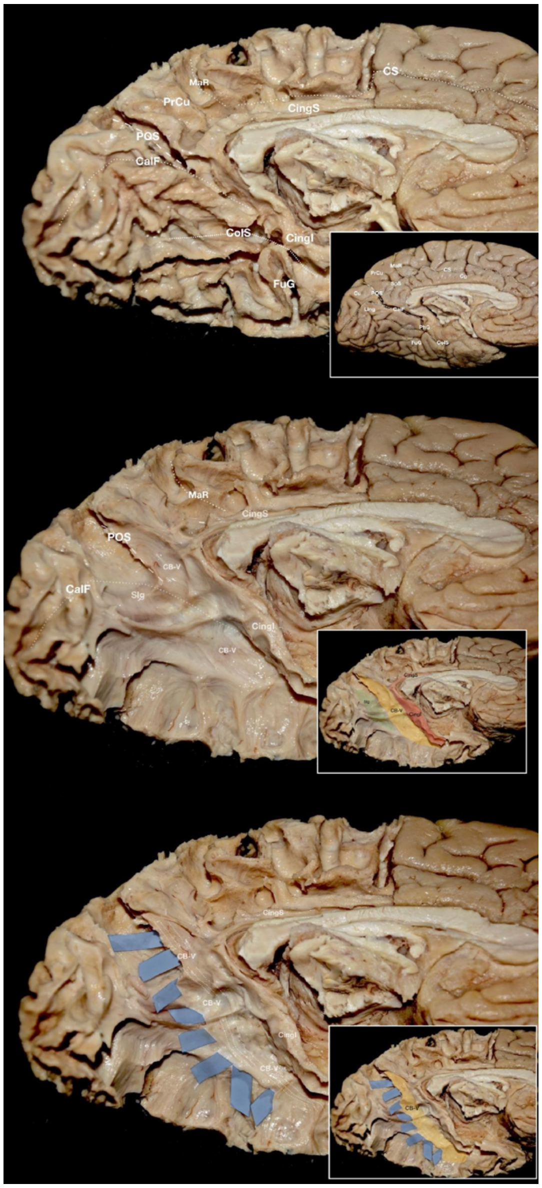
Cal= Calcarine Fissure, CB-V= Cingulum Bundle V, CingI= Inferior arm of the cingulum, Cu= Cuneus, FrM= Forceps Major, Hip= Hippocampus, ILF= Inferior Longitudinal Fasciculus, Li= Lingual Gyrus, OR= Optic radiation, POS= Parieto-occipital Sulcus, PrCn= Precuneus, Slg= Sledge runner fasciculus, Spl= Splenium of the Corpus Callosum

Sledge Runner Fasciculus and CB-V.

We observed the fibers of the cingulum lying adjacent to the fibers of the SR. This relation was particularly tight with regard to the most anteroinferior part of the SR, which runs deep to the isthmus of the cingulate gyrus and posterior part of the parahippocampal gyrus.

The Sledge Runner Fasciculus (SRF) is an adjacent fiber tract which also travels in the depth of the POS, at the same plane and in a close spatial relationship with the CB-V. However, in contrast to CB-V, which stems from the anterior bank of the POS (caudal precuneus), the SRF originates at the posterior bank of the POS (rostral cuneus) and travels in an oblique rostro-ventral direction following a shorter trajectory and terminating at the RSC, parahippocampal place area (PPA) and anterior lingula. CB-V and SRF fibers are seen to cross the deep segment of the POS and most probably share common terminations in the PPA area.

Fig. 19: Progressive dissection of a left hemisphere. Medial views.



A: Superficial U-fibers exposed. The contour of the main sulci is illustrated. Inset: The superficial landmarks including the sulci and gyri are marked.

B: U-fibers removed and the inferior arm of the cingulum, CB-V and Sledge runner fasciculus are depicted. The Sledge runner fasciculus resides caudally with its fibers running from the anterior cuneus towards the PPA and RSC. CB-V is located between the Sledge runner and Inferior arm of the cingulum. Its fibers travel anterior to the POS from the posterior precuneus to the middle third of the fusiform gyrus. Anterior to CB-V, the inferior arm of the cingulum projects and terminates to medial temporal structures. Inset: These tracts are highlighted in yellow (CB-V), red (inferior arm of the cingulum) and green (sledge runner fasciculus) color respectively.

C: CB-V is gradually dissected, starting from the posterior precuneus to the fusiform gyrus. CB-V and inferior arm of the cingulum run as independent pathways. Inset: The CB-V is highlighted in yellow color.

CalF= Calcarine fissure (distal part), CB-V= Cingulum Bundle V, Cg= Cingulate Gyrus, CingI= Inferior arm of the Cingulum, CingS= Superior Arm of the Cingulum, ColS= Collateral Sulcus, CS= Cingulate Sulcus, Cu= Cuneus, FuG= Fusiform Gyrus, Ling= Lingual Gyrus, MaR= Marginal Ramus of the Cingulate Sulcus, PhG= Parahippocampal Gyrus, POS= Parieto-occipital Sulcus, PrCu= Precuneus, Slg= Sledge runner Fasciculus, SpS= Subparietal Sulcus

Forceps Major and CB-V

The forceps major, also known as posterior forceps, consists of fibers originating from the splenium of the corpus callosum that travel towards the occipital cortex. When compared to the CB-V, the fibers of this bundle are seen to reside in a deeper plane and follow a perpendicular trajectory thus creating a superior knee in the dorsal half of the CB-V.

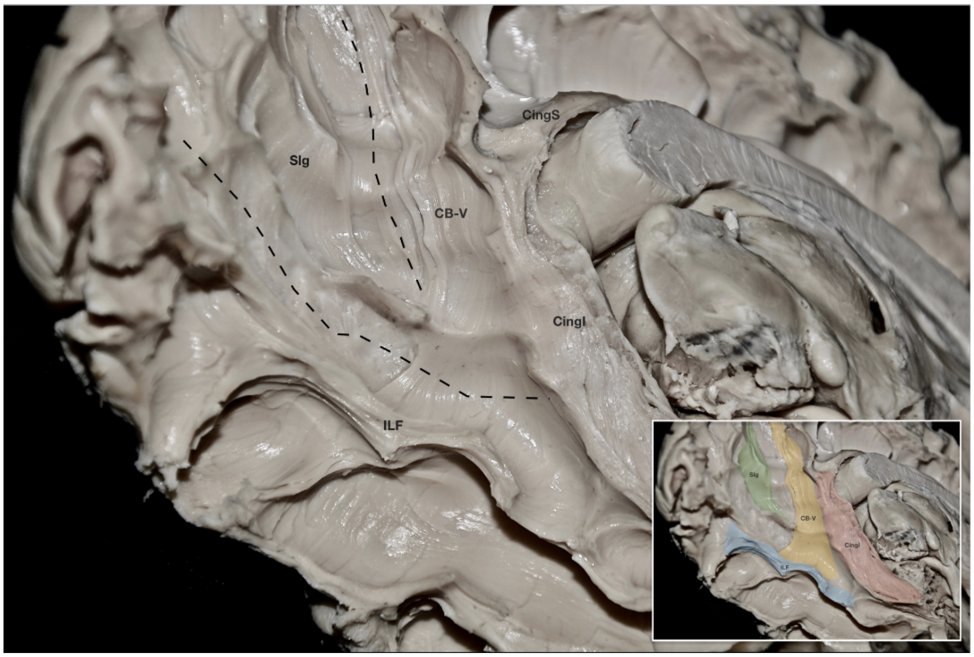


Fig. 20: Left hemisphere. Infero-medial view. The spatial relationship of the inferior arm of the cingulum, ILF, CB-V and Sledge runner is illustrated.

The Sledge runner fasciculus follows a short trajectory from the anterior cuneus towards the PPA and RSC and is located caudal to the CB-V. CB-V is seen to have a longer configuration, originating from the posterior precuneus and traveling mainly towards the fusiform gyrus. It exhibits a “funnel like” shape with its narrowest part seen in the area of posterior precuneus and its wider in the fusiform area. The stem of the ILF travels within the fusiform gyrus, keeping a perpendicular trajectory to that of CB-V and Slg. Interestingly, the inferior terminations of the CB-V penetrate the fibers of the ILF to terminate in the mid-fusiform gyrus. The inferior arm of the cingulum curves around the splenium of the corpus callosum to terminate to the medial temporal lobe. Inset: The correlative anatomy of the four fasciculi is illustrated. Red: Inferior arm of the cingulum. Yellow: CB-V. Green: Slg. Blue: ILF. CB-V= Cingulum Bundle V, CingI= Inferior arm of the Cingulum, CingS= Superior Arm of the Cingulum, ILF= Inferior Longitudinal Fasciculus, Slg= Sledge runner Fasciculus

ILF

ILF fibers run in the axial plane in the depth of the fusiform gyrus. CB-V fibers originate from the precuneus and terminate at the mid-portion of the fusiform gyrus, abutting the fibers of the middle third of the ILF in a perpendicular fashion. The CB-V fibers that continue towards the medial temporal pole, travel in a direction parallel to that of the ILF.

Fig. 21: Right hemisphere. Infero-medial view CB-V and adjacent fasciculi illustrated in relation to the sulcal anatomy.

The silhouette of the main sulci including the Collateral, Occipito-temporal and Parieto-occipital sulci is depicted. CB-V travels anterior to the POS while Slg resides posteriorly. ILF is confined within the fusiform gyrus. The inferiormost fibers of the CB-V travel below the depth of the collateral sulcus terminating in the area of the mid-fusiform gyrus. Inset: The Inferior arm of the cingulum, CB-V, Slg and ILF area highlighted with red, yellow, green and blue color respectively. The silhouette of the main sulci is also marked for orientation purposes. CB-V = Cingulum Bundle V, CingI = Inferior arm of the Cingulum, ColS= Collateral Sulcus, OccTemp= Occipitotemporal Sulcus, OR = Optic Radiation, POS= Parieto-occipital sulcus, Slg = Sledge runner Fasciculus, Spl = Splenium of the Corpus Callosum.Inset: The inferiormost terminations of the Sledge runner and CB-V are highlighted in green and yellow color respectively. The Sledge runner terminates in the area of the retrosplenial cortex (1) and parahippocampal place area (2), while the CB-V reaches the middle part of the fusiform gyrus, which corresponds to the fusiform face area (3), and the medial temporal structures (4). ILF is highlighted in blue color.

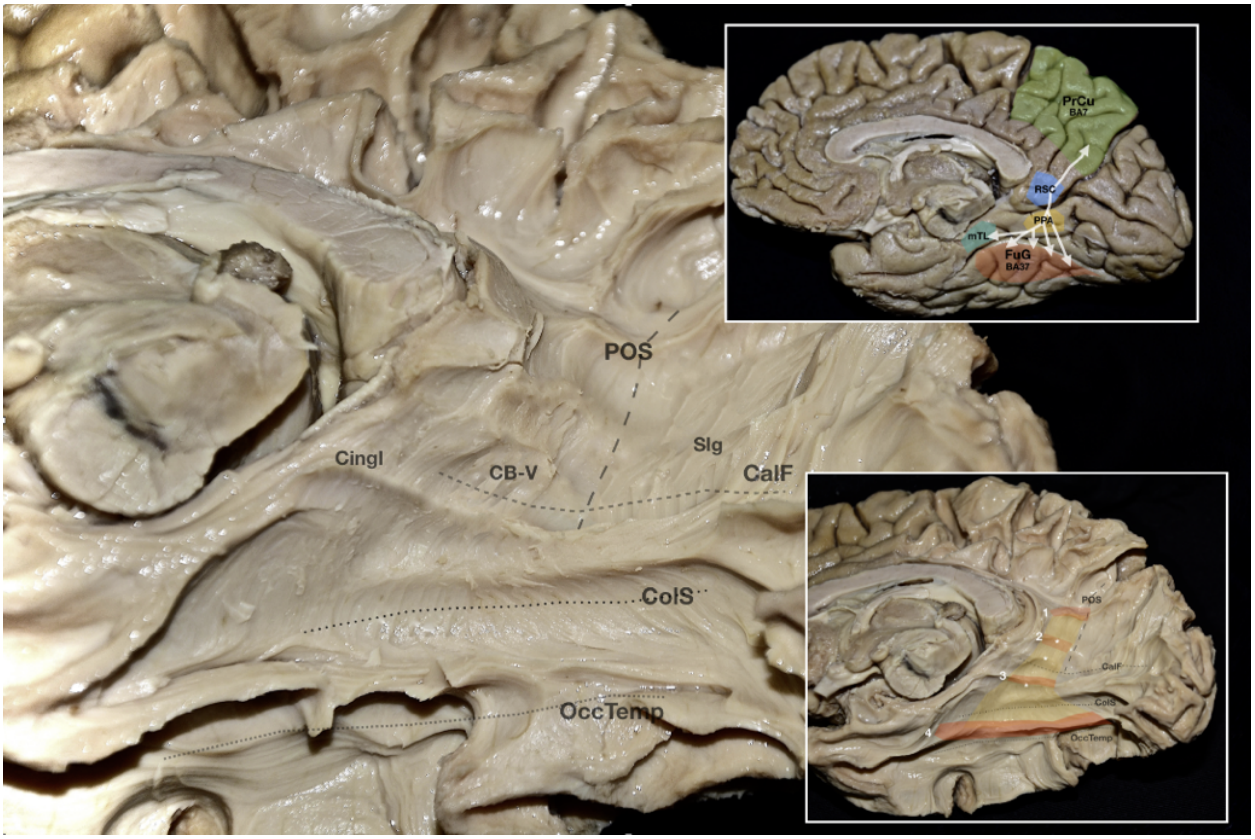


Fig. 22: Infero-medial view of a right hemisphere. Morphology and connectivity of the CB-V illustrated.

CB-V can be seen running at the level of the anterior bank of the POS. Its fibers spread towards the fusiform area and medial temporal lobe. Its narrowest part corresponds to the area of the posterior precuneus while the widest to the area of the fusiform gyrus. CB-V exhibits 3-4 medially projecting “knees”. These “knees” usually appear near the level of the RSC and PPA. Four termination zones can be appreciated. The superior terminations of the CB-V project towards the posterior precuneus. Two termination zones are recorded at the level of the RCS and PPA. The inferior terminations of the CB-V radiate in a wide area corresponding to the middle and, sometimes, posterior aspect of the fusiform gyrus and part of the pyriform cortex. Upper Inset: The trajectory of the CB-V superimposed on the superficial anatomy. Terminations cover a wide area including the posterior precuneus(green), RSC(blue), PPA(yellow), Fusiform gyrus(Red) and medial temporal lobe (magenta). Lower Inset: The “knees” of the CB-V are marked with stars. The termination zones are highlighted with red color: 1= posterior precuneus, 2=Retrosplenial Cortex 3= Parahippocampal place area 4= fusiform gyrus and medial temporal lobe.

CalF= Calcarine Fissure, CB-V= Cingulum Bundle V, CingI= Inferior arm of the cingulum, ColS= Collateral Sulcus, FuG= Fusiform Gyrus, mTL= Medial Temporal Lobe, OccTemp= Occipitotemporal Sulcus, POS= Parieto-occipital Sulcus, PPA= Parahippocampal place area, PrCu= Precuneus, RSC= Retrosplenial Cortex, Slg= Sledge runner Fasciculus

Connectivity

In all cases, we found CB-V fibers terminating in the area of caudal precuneus (BA7), PPA and Mid-Fusiform gyrus (BA 20&37). Fibers of the CB-V were also recorded to terminate in the Retrosplenial Area (BA29&30) in 93% of cases (14/15). In 80% (12/15) of specimens, we additionally encountered fibers of the CB-V in the lateral piriform cortex (BA35).

3.5 RESULTS: UNCINATE FASCICULUS

Mapping the orbitofrontal terminations of the uncinate fasciculus.

Upon removing the grey matter of the four orbital gyri, gyrus rectus, inferior and middle frontal gyrus, anterior part of STG, MTG , ITG and temporal operculum we expose the superficial short U-fibers and gain access to the insular surface. We then peel away the cortex of the limen insula, anterior insular surface and insular apex to reveal fibers of the extreme capsule. Dissecting the most superficial part of the extreme capsule at the level of the limen insula and insular apex aids in the exposure of the main stems of the uncinate and occipitofrontal fasciculi. By following the direction of these fibers under the microscope we were able to adequately distinguish the two tracts, since they display different trajectories and termination patterns i.e. the uncinate fasciculus curves around the limen insula in a hook shape fashion to radiate to the temporal pole while the occipitofrontal fasciculus travels diagonally through the anterior part of the insula to fan out to the middle and posterior temporo-occipital cortices. At this point, we consistently recorded the most superficial fibers of the uncinate fasciculus - what we define as the first layer of uncinate fibers - to terminate to the area of the posterior orbital gyrus and adjacent posterior part of the pars orbitalis, after exhibiting a short course.

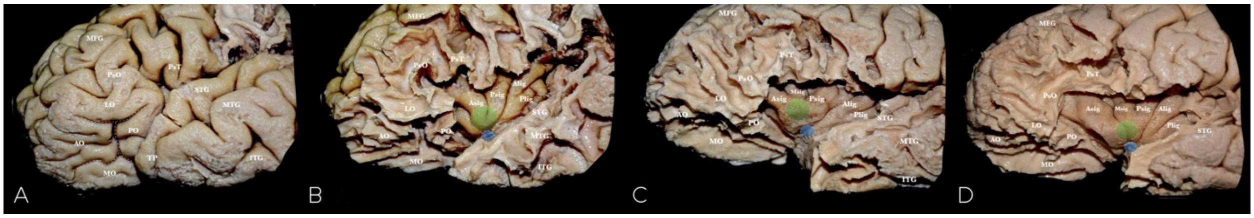


Fig 23: A Lateral aspect of a left hemisphere. The regional surface anatomy is illustrated. Inferolateral view of a left hemisphere. The surface anatomy of the orbitofrontal area is depicted. The cruciform sulcus divides the basal frontal area into four orbital gyri. **B, C, D** Variations of the insular surface anatomy. Lateral aspect of three left hemispheres. The cortex of the orbital surface, inferior frontal gyrus, part of the middle frontal gyrus and anterior temporal lobe has been removed and the short arcuate fibers become apparent. In **C** and **D** the temporal pole has also been removed for better access to the insular and orbitofrontal areas. The morphological variation of the surface anatomy of the insula is illustrated particularly with regard to the area of the insular apex. Green disk =Insular Apex, Blue disk=Limen insula, AO=anterior orbital gyrus, MO=medial orbital gyrus, LO=lateral orbital gyrus, PO=posterior orbital gyrus, PsO=pars orbitalis, PsT=pars triangularis, RS= sulcus of Rolando, STG= superior temporal gyrus, MTG=middle temporal gyrus, ITG=inferior temporal gyrus. Asig=anterior short insula gyrus, Msig=middle short insular gyrus, Psig=posterior short insular gyrus, Alig=anterior long insular gyrus, Plig=posterior long insular gyrus.

Progressive dissection of the orbitofrontal area, part of the lateral prefrontal u-fibers of the inferior frontal gyrus and inferior part of the middle frontal gyrus, helps identifying the trajectory of the second fiber layer of the uncinate fasciculus. These fibers, which are longer in relation to those of the first layer, are consistently recorded to terminate to the posterior two thirds of the gyrus rectus. At this stage of dissection, we did not track any fibers branching off the main stem of the uncinate fasciculus and projecting towards the inferior or middle frontal gyri.

Proceeding deeper and removing the u fibers of the gyrus rectus, we expose the third fiber layer of the uncinate fasciculus, seen to travel towards the medial surface of the hemisphere and to wrap around the ventral surface of the putamen.

Differentiating the stems of the uncinate and occipitofrontal fasciculus at the area of the insular apex.

By following the trajectory and direction of the fibers seen to travel through the anterior part of the temporal stem – an area where the two tracts lie in a very close proximity- we were able to thoroughly distinguish the uncinate from the occipitofrontal fasciculus. In that respect, fibers that were found to curve around the limen insula and project towards the temporal pole were designated to belong to the uncinate fasciculus, whereas fibers that were recorded to pass posterior to the limen insula, obliquely through the temporal stem and towards the temporo-occipital area were defined as occipitofrontal fibers. In all specimens studied, the area of the insular apex i.e. the area that the short insular gyri converge to form a pyramidal prominence, proved to be a crucial landmark with regard to the topographical differentiation of these subcortical pathways. More specifically, all fibers that reside ventral to the area of the insular apex belong to the stem of the uncinate fasciculus whereas fibers that travel just under and dorsal to the level of the insular apex clearly belong to the stem of the occipitofrontal fasciculus. In that way, we could confidently follow the fibers of the uncinate fasciculus up to their respective frontal terminations.

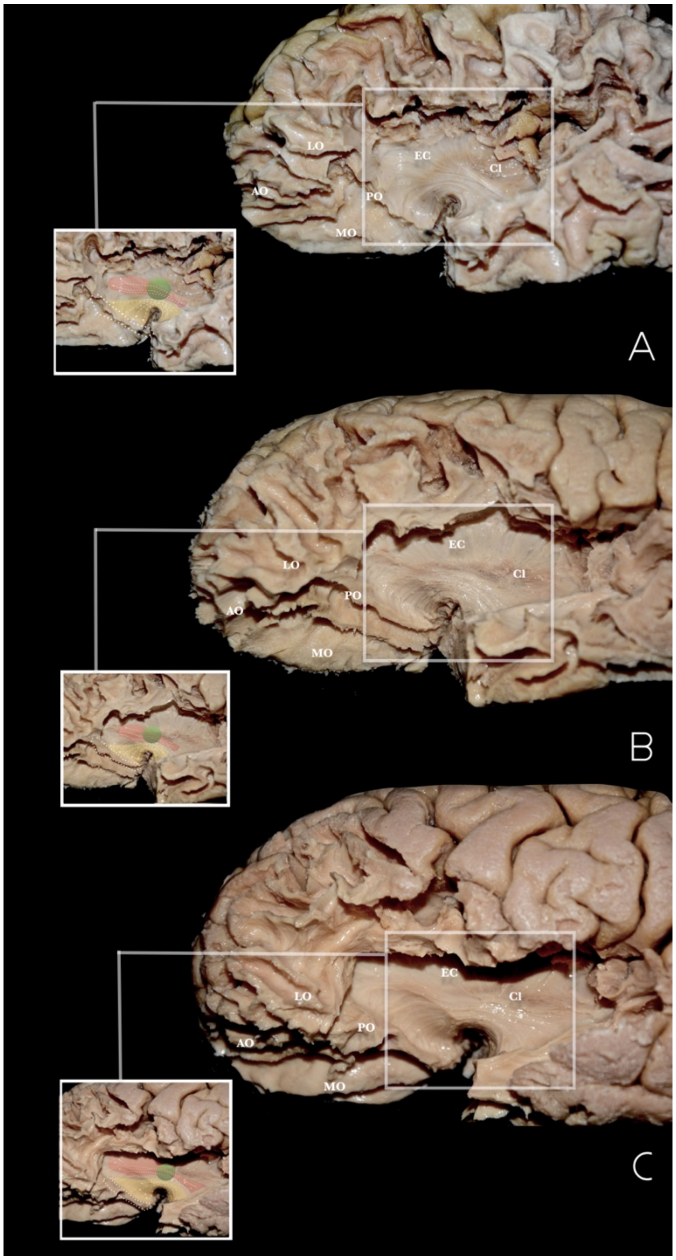


Fig 24: A, B, C. The first fiber layer of the uncinate fasciculus is illustrated. The insular apex is introduced as a surface landmark for differentiating the uncinate from the occipitofrontal fasciculus. Progressive dissection of the short arcuate fibers of the anterior insular and orbitofrontal areas reveals the first layer of fibers of the uncinate fasciculus – marked with the yellow bundle - which are followed and seen to terminate to the posterior orbital gyrus and pars orbitalis – dotted area. Fibers proved to belong to the occipitofrontal fasciculus – marked in the magnified area with the red bundle - are also evident, travelling in proximity to the uncinate fasciculus. The area of the insular apex is marked with a green disk. Note that in all cases, fibers that travel just under and dorsal to the area of the insular apex are occipitofrontal fibers whereas those that lie ventrally to the insular apex belong to the uncinate fasciculus. Yellow bundle= trajectory of the first layer of the uncinate fasciculus, Red bundle= trajectory of the occipitofrontal fasciculus, Green disk=insular apex, AO=anterior orbital gyrus, LO=lateral orbit gyrus, MO=medial orbital gyrus, PO=posterior orbital gyrus, Cl=claustrum

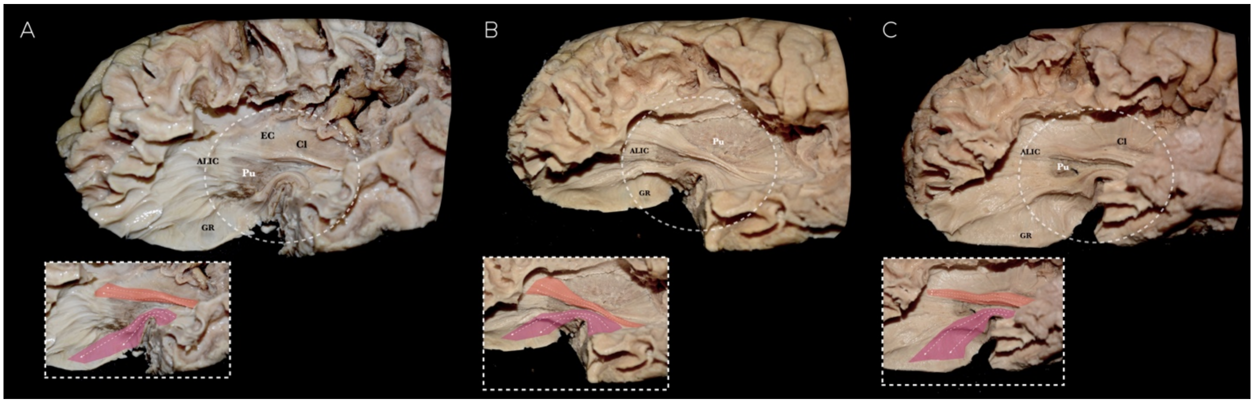


Fig 25: A, B, C Same specimens and same views as above. Revealing the second layer of the uncinate fasciculus. Progressive dissection reveals the second layer of uncinate fibers radiating to the posterior two thirds of the gyrus rectus. At this stage, a clear cleavage plane between the stems of the uncinate and inferior occipitofrontal fasciculi can be developed. Between these two fiber pathways, the plane of dissection deepens so as to reveal the ventral surface of the putamen centrally and the lateral part of the anterior limb of the internal capsule at the periphery. Pink bundle = trajectory of the second layer of the uncinate fasciculus, Orange bundle = trajectory of the occipitofrontal fasciculus. ALIC=anterior limb of the internal capsule, Pu=putamen, GR=gyrus rectus, Cl=claustrum, EC=external capsule.

Exploring the ventromedial frontal terminations of the uncinate fasciculus. Evidence from Medial to Lateral dissections.

We applied stepwise medial to lateral dissections focused on the ventromedial frontal area to identify and record the regional distribution of the fibers of the uncinate fasciculus. Upon removing the cortex, we expose the short arcuate U fibers connecting the cingulate gyrus with the paraolfactory gyrus and gyrus rectus. Further dissection displays the ventral fibers of the cingulum radiating to the area of the paraolfactory gyrus. We then consistently identified a group of fibers seen to terminate to the posterior third of the paraolfactory gyrus and exhibiting a close spatial relationship with the fibers of the ventral end of the cingulum. These fibers were carefully followed along their course and were found to merge with the main stem of the uncinate fasciculus.

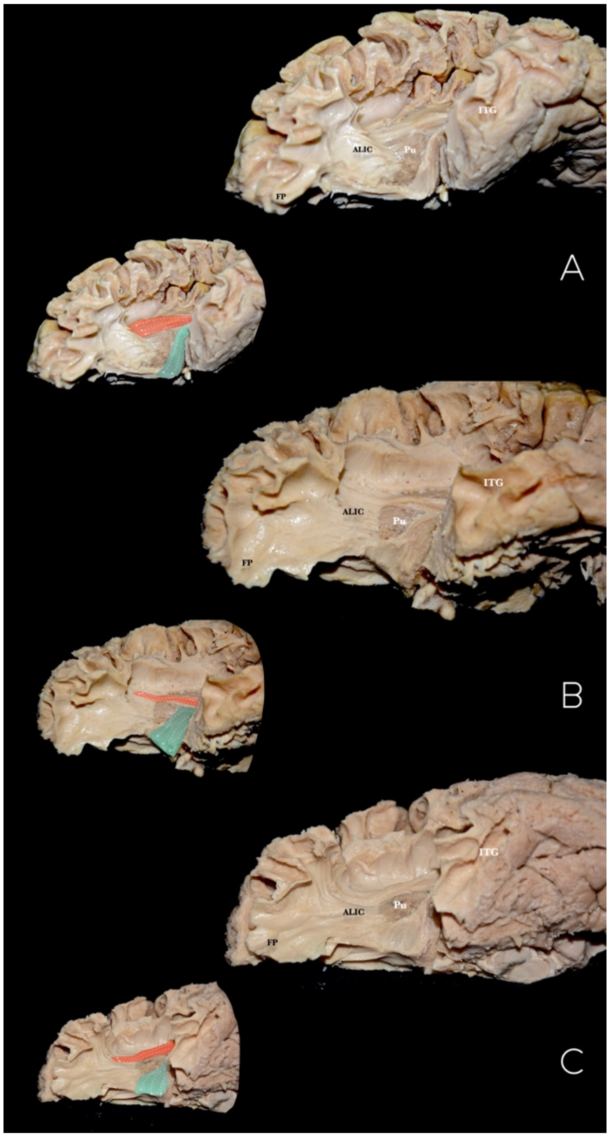


Fig 26: A, B, C Inferior views of the same specimens as above. Exposing the third layer of fibers of the uncinate fasciculus. Progressive dissection exposes the third layer of uncinate fibers seen to radiate towards the medial surface of the hemisphere. These fibers are exposed and their termination pattern illustrated in Figure 25. Green bundle= trajectory of the third layer of uncinate fibers, Orange bundle= trajectory of the occipitofrontal fasciculus, Pu=putamen, ALIC=anterior limb of the internal capsule, FP=frontal pole, ITG=inferior temporal gyrus.

We invariably identified three consecutive fiber layers seen to radiate from the main stem of the uncinate fasciculus and recorded to terminate to the posterior area of the orbitofrontal territory, pars orbitalis and ventromedial frontal lobe- Brodmann areas 11, 47 and 25 respectively. It is therefore clear that the frontal terminations of this tract project to the posterior orbitofrontal region and that there are no fibers documented to follow a more dorsal trajectory towards the prefrontal cortex of the inferior, middle or superior frontal gyrus.

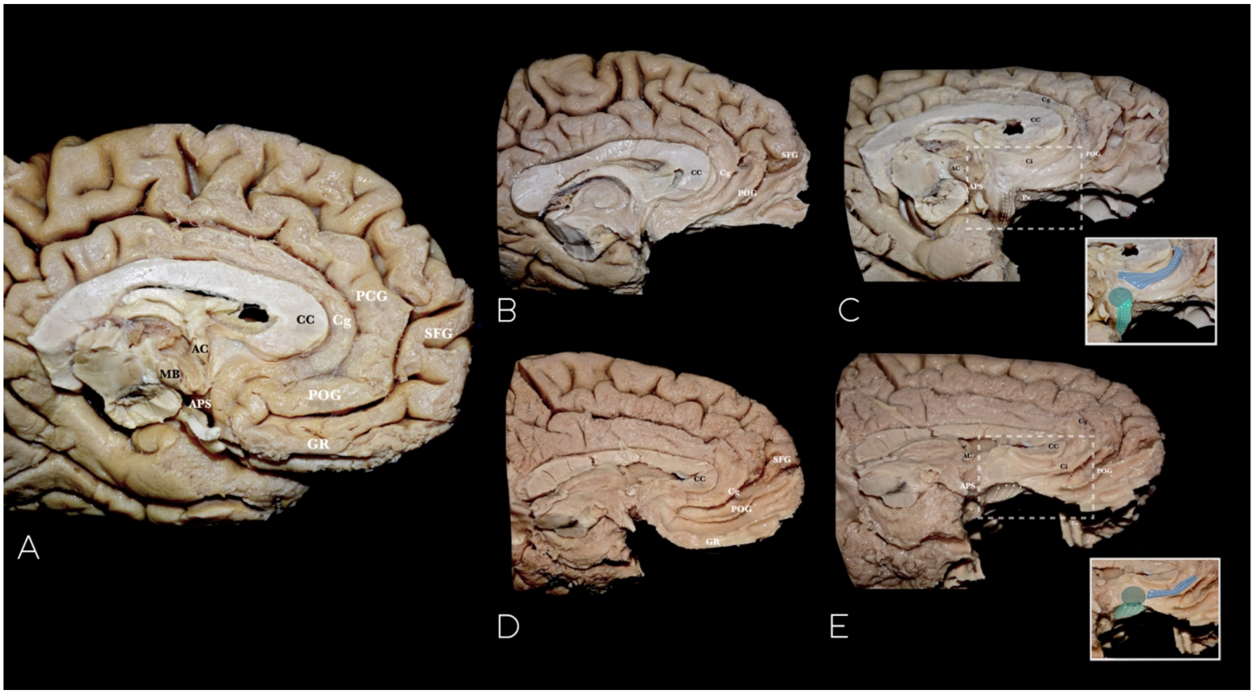


Fig 27: Medial view of a left hemisphere. A, The regional surface anatomy is illustrated. The para-cingulate gyrus continues ventrally as the paraolfactory gyrus. The gyrus rectus continues as the superior medial frontal gyrus. The mammillary body, the anterior commissure and the anterior perforated substance are also illustrated. **B, C** Exposing the short arcuate fibers. Medial views of two left hemispheres. Upon removing the cortex of paraolfactory gyrus, gyrus rectus and cingulate gyrus the short arcuate u fibers connecting adjacent gyri are exposed. **D, E** Medial aspect of the third layer of the uncinate fasciculus. Infero-medial views of the specimens in Figures 25 B and 25 C. Progressive fiber dissection reveals the fibers of the third layer of the uncinate fasciculus –illustrated as a green bundle in the magnified area - that are followed to their lateral extension . These fibers are documented to terminate to the posterior paraolfactory gyrus –green disk in the magnified area- close to the ventral end of the cingulum – deep blue bundle. Green bundle = trajectory of the third layer of the uncinate fasciculus, Green disk=posterior end of the paraolfactory gyrus, Deep blue bundle=Cingulum, CC=corpus callosum, PCG=paracingulate gyrus, CG=cingulate gyrus, POG=paraolfactory gyrus, SFG=superior frontal gyrus, GR=gyrus rectus, APS=anterior perforated substance, AC=anterior commissure, MB=mammillary body

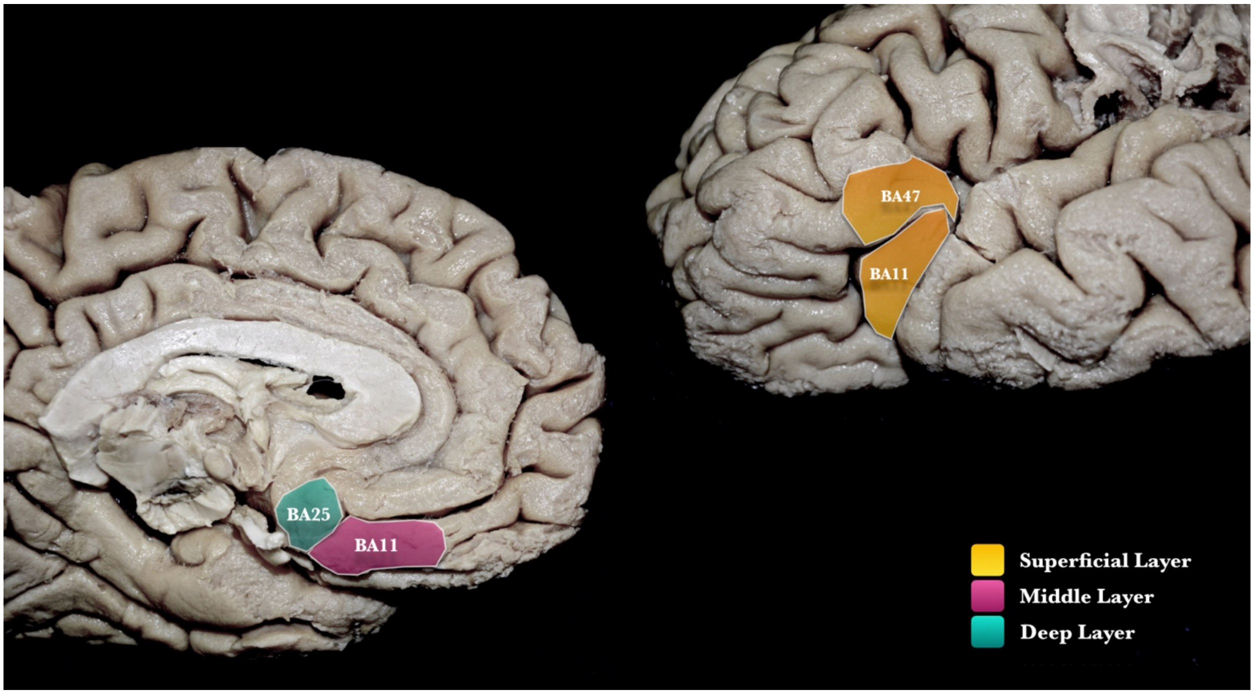


Fig 28: The termination areas of uncinate fasciculus projected in the surface anatomy of the frontal lobe. The lateral and medial aspects of the same specimen are displayed. The first layer projects in the posterior orbital gyrus and the adjacent segment of the pars orbitalis – Brodmann areas 11and 47. The second layer terminates to the gyrus rectus – Brodmann area 11 - and the third layer ends to the posterior third of the paraolfactory gyrus – Brodmann area 25. Yellow area=first layer, Pink area=second layer, Green area=third layer.

CHAPTER 4: DISCUSSION

4.1 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 (Makris, Papadimitriou et al. 2009). 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) (Makris, Preti et al. 2013, Makris, Preti et al. 2013, Maldonado, de Champfleur et al. 2013, Menjot de Champfleur, Lima Maldonado et al. 2013, Wang, Fernandez-Miranda et al. 2013, Makris, Zhu et al. 2017, Conner, Briggs et al. 2018, Tremblay, Perron et al. 2019). In this vein, although the main body of DTI data converge on the robust connectivity between the STG and AG (Makris, Papadimitriou et al. 2009, Makris, Preti et al. 2013, Makris, Preti et al. 2013, Menjot de Champfleur, Lima Maldonado et al. 2013, Makris, Zhu et al. 2017, Tremblay, Perron et al. 2019), the two available anatomic reports suggest otherwise(Maldonado, de Champfleur et al. 2013, Wang, Fernandez-Miranda et al. 2013). 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 (Maldonado, de Champfleur et al. 2013, Wang, Fernandez-Miranda et al. 2013).

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 anatomic 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 (Maldonado, de Champfleur et al. 2013, Wang, Fernandez-Miranda et al. 2013). 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 (Le Bihan, Poupon et al. 2006, Oouchi, Yamada et al. 2007, Johansen-Berg and Rushworth 2009, Vos, Jones et al. 2011, Fernandez-Miranda, Pathak et al. 2012). 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 (Koutsarnakis, Liakos et al. 2015, Gungor, Baydin et al. 2017) and exhibiting abundant fibers radiating towards the IPS and AG (Monroy-Sosa, Jennings et al. 2019) 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. 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. 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 (Makris, Preti et al. 2013, Makris, Preti et al. 2013, Menjot de Champfleur, Lima Maldonado et al. 2013, Makris, Zhu et al. 2017, Tremblay, Perron et al. 2019) the study by Conner and colleagues places the MdLF further posteriorly along the temporal lobe (Conner, Briggs et al. 2018). 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 (Maldonado, de Champfleur et al. 2013, Wang, Fernandez-Miranda et al. 2013). In this study, we have vividly demonstrated and consistently recorded all three segments of the MdLF to terminate in different areas of the TP. 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 (Ding, Van Hoesen et al. 2009). 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. Our results therefore suggest that the anterior terminations of the MdLF-I and II reside at the TAr area, while these of the MdLF-III correspond to the areas TG and TAp (Ding, Van Hoesen et al. 2009)

Functional Considerations and segmentation pattern of the MdLF

Early theories have hypothesized that the MdLF is a component of the language pathway (Makris and Pandya 2009, Makris, Papadimitriou et al. 2009). 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 (Hickok and Poeppel 2007, Gow Jr, Segawa et al. 2008), 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 (Makris, Zhu et al. 2017). Regarding the non-dominant hemisphere, the MdLF has been associated with visuospatial processing due to its parietal connections (Galati, Committeri et al. 2001, Galletti and Fattori 2002, Macaluso, Driver et al. 2003). Beyond language and visuospatial functions, the MdLF has been also linked to the integration of higher order auditory and audiovisual functions (Makris, Preti et al. 2013, Wang, Fernandez-Miranda et al. 2013, Makris, Zhu et al. 2017) with very recent findings strongly implicating this tract in speech perception and auditory processing ability in noise (Tremblay, Perron et al. 2019)(table 3).

In line with our results, evidence from previous anatomical (Maldonado, de Champfleur et al. 2013) and anatomo-tractographic studies (Wang, Fernandez-Miranda et al. 2013) 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 (De Witt Hamer, Moritz-Gasser et al. 2011).

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 (Makris, Papadimitriou et al. 2009, Makris, Preti et al. 2013, Makris, Preti et al. 2013, Wang, Fernandez-Miranda et al. 2013) and the present study. Conversely, it has been well documented that tracts crucial for language, such as the AF (Matsumoto, Okada et al. 2008) and SLF (Makris, Kennedy et al. 2004), exhibit considerable asymmetry in terms of volume and FA, according to language lateralization (Catani, Allin et al. 2007). 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. We have thus demonstrated the MdLF-I to course always through the anterior transverse gyrus (Heschl's Gyrus) and the MdLF-II to travel just under the cortex of the posterior transverse gyri/posterior transverse area. 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 (Liegeois-Chauvel, Musolino et al. 1991, Howard, Volkov et al. 1996, Howard, Volkov et al. 2000, Lewald and Getzmann 2011). In that respect, although assumptions on the role of the MdLF in higher auditory processing have been previously made (Wang, Fernandez-Miranda et al. 2013, Burks, Boettcher et al. 2017), 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 (Ding, Van Hoesen et al. 2009) According to functional studies in non-human primates, the area TAr i.e. the equivalent of the dorsolateral TP, has been implicated in high order auditory processing (Hackett, Stepniewska et al. 1999, Romanski, Bates et al. 1999, Poremba, Saunders et al. 2003) with remarkable neural activities being detected following specific vocal calls (Poremba, Malloy et al. 2004). 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 (Seltzer and Pandya 1978, Seltzer and Pandya 1991).

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 (Warren, Zielinski et al. 2002, Krumbholz, Schönwiesner et al. 2004, Brunetti, Belardinelli et al. 2005, Tata and Ward 2005, Tata and Ward 2005, Zimmer and Macaluso 2005) while areas in or anterior to Heschl's gyrus subserve the processing of phonetic stimuli (Binder, Frost et al. 2000, Obleser, Boecker et al. 2006) and pitch characteristics (Warren and Griffiths 2003). Further, similar to the well-established dorsal and ventral visual streams, the existence of respective parallel auditory pathways is also advocated by field researchers (Rauschecker and Tian 2000, Tian, Reser et al. 2001, Lomber and Malhotra 2008, Rauschecker and Scott 2009). 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 (Ahveninen, Jaaskelainen et al. 2006). 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 (Jääskeläinen, Ahveninen et al. 2004).

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 (Ding, Van Hoesen et al. 2009) 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 (Seltzer and Pandya 1978, Seltzer and Pandya 1991, Ding, Van Hoesen et al. 2009) to the AG and occipital lobe/cuneus, could potentially play a role in the integration of auditory and visual information (Makris, Zhu et al. 2017).

Finally, studies in patients with Semantic Dementia (Mummery, Patterson et al. 2000, Galton, Patterson et al. 2001, Davies, Graham et al. 2004, Nestor, Fryer et al. 2006, Noppeney, Patterson et al. 2007, Lambon Ralph and Patterson 2008) and herpes simplex virus encephalitis (HSVE) (Kapur, Barker et al. 1994, Lambon Ralph, Lowe et al. 2007, Noppeney, Patterson et al. 2007) as well as data from positron emission tomography (PET) (Devlin, Russell et al. 2000, Visser, Jefferies et al. 2010) and repetitive transcranial magnetic stimulation (rTMS) (Pobric, Jefferies et al. 2007, Lambon Ralph, Pobric et al. 2008) 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 (DeWitt and Rauschecker 2013, DeWitt and Rauschecker 2016). 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 (Roux, Minkin et al. 2015). 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.

4.2 FIFTH COMPONENT OF THE CINGULUM BUNDLE

The idea of segmentation of major association tracts such as the Superior Longitudinal Fasciculus and Cingulum has been enthusiastically gaining ground in the field of human brain connectivity as it refines brain circuitry in a more accurate manner. Indeed, a few studies focusing on the anatomy of different components of the SLF, ILF, Arcuate Fasciculus, as well as the cingulum, have been recently published.(Wu, Sun et al. 2016, Panesar, Yeh et al. 2018, Panesar, Belo et al. 2019) According to this approach, these fiber pathways can be studied as individual anatomo-functional entities as they exhibit distinctive connectivity in terms of axonal termination patterns, while their structure and function can be conceptualized as the cluster effect of smaller tributaries that converge and contribute to the formation of a main subcortical "river".

In this context, Wu and colleagues, in an anatomo-tractographic study proposed a nuanced segmentation of the cingulum bundle based on the different connectivity of each component. The authors use the term CB-V to describe the segment of the cingulum that connects the precuneus with temporo-basal and temporo-mesial structures. Further, in a study by Jones and colleagues the same bundle -described as the "parahippocampal cingulum"- was recorded to interconnect the posterior precuneus, posterior cingulate cortex and medial temporal pole.(Jones, Christiansen et al. 2013) However, to our knowledge current literature is quite limited on this medially projecting parieto-temporal pathway and therefore its very existence, topography, morphology and intricate anatomical characteristics remain vague to date. With this in mind, we strived to provide original, human, ex vivo, direct structural evidence on the existence of CB-V as a discrete component of the cingulum bundle and further on the direct axonal connectivity between the precuneal territory and mesio-temporal regions.

Our results demonstrate that the CB-V exhibits extensive cortical projections and termination points to the caudal precuneus. Findings in healthy individuals suggest that the precuneus is the core structure of the default mode network.(Fransson and Marrelec 2008, Utevsky, Smith et al. 2014) The idea of the Default Mode Network (DMN) has derived from the classical studies of Shulman (1997) and Raichle (2001).(Raichle, MacLeod et al. 2001, Greicius, Krasnow et al. 2003, Cavanna and Trimble 2006) The authors using data stemming from functional imaging (fMRI and PET) observed a group of cortical areas in the human brain, including the posterior cingulate cortex(PCC), medial prefrontal cortex (mPFC) and precuneus, that were consistently found to exhibit reduced activity during non-self-oriented and goal directed tasks. In light of this observation, the term “Default Mode” was coined by Raichle.(Raichle 2015) The very same areas show significant co-activation during resting-state conditions and theoretically support a default-mode of brain function activated during day-dreaming, self-oriented and theory-of-mind related tasks. This task-negative network allegedly participates in high order amodal functions such as self-awareness, mind-wandering and future planning.(Greicius, Krasnow et al. 2003, Vatansever, Menon et al. 2015)

Moreover, the precuneal lobule is consistently found to be activated in a broad range of high-order functions such as navigation, memory retrieval, attention, intelligence comparison, visuo-spatial imagery, representational similarity analysis (RSA) and transitive reasoning.(Marchette, Vass et al. 2014, Paladini, Muri et al. 2017, Rosen, Stern et al. 2018) In the same vein, data stemming from a recent repetitive transcranial magnetic stimulation (rTMS) study documented the precuneus to be involved in the process of updating place representations during self-motion.(Muller, Riemer et al. 2018) Additionally, the CB-V is recorded to project to the cortex of the PPA, which is consistently seen to participate in the visuo-spatial circuitry involving location representation, context retrieval as well as perception and utilization of spatial landmarks.(Epstein, Patai et al. 2017)

Another key hub area participating in the "navigation pathway" is the retrosplenial cortex also known as retrosplenial complex area (RSC). This region encodes visual information and supports navigation, orientation and spatial memory.(Epstein, Patai et al. 2017) According to our results, the CB-V exhibits its higher fiber density on this brain region. Similarly, and slightly anteriorly the parahippocampal gyrus was also found to be one of the areas that CB-V fibers constantly radiate. This specific region is implicated in high-level visuospatial perception and memory processing and, as recently demonstrated, the underlying structural architecture of these two aforementioned discrete functions is parceled along the longitudinal axis.(Baumann and Mattingley 2016) More specifically, visuospatial perception is localized at the posterior half of the parahippocampal gyrus whereas the anterior half is involved in contextual memory processing**.** CB-V also exhibits profound cortical projections to the fusiform gyrus and particularly to the Fusiform Face Area (FFA). FFA has been extensively implicated in face recognition, facial expression perception and visual word recognition but it has also been documented to participate in a handful of other visual and memory cognitive processes such as visual mental imagery and visual memory. (Harvey and Burgund 2012) The possible functional implications of the CB-V are summarized in Table 1.

We have therefore provided direct structural evidence on the existence, topography, morphology and axonal connectivity of a thus far vague and ambiguous white matter pathway previously coined in the neuroscientific literature as the CB-V. This separate bundle of fibers was recorded to participate in the connectivity of high order cerebral areas such as the caudal precuneus, PPA, RSC and FFA.

Micro-surgical Corridors to Trigonal/Peritrigonal Lesions and possible clinical repercussions with respect to the CBV.

CB-V underlies a wide cerebral area which extends from the precuneus to the fusiform gyrus. This region is exposed and manipulated in an effort to elegantly approach and resect lesions residing in or around the atrium of the lateral ventricle. Trigonal/Peritrigonal lesions, have been traditionally accessed through a variety of surgical approaches including the posterior transcallosal corridor or the transcortical operative variants through the inferior parietal lobule or posterior temporal lobe. However, the neurological sequelae linked with these surgical trajectories - including disconnection syndromes, damage to the optic radiations, dyslexia, agraphia, apraxia, motor disturbances and high incidence of epileptic seizures- have paved the way towards more sophisticated routes in the era of modern Microneurosurgery.

In this context, Yasargil was the first to describe the parieto-occipital interhemispheric trans-precuneus approach for the treatment of Peritrigonal lesions.(Tokunaga, Tamiya et al. 2006) This surgical avenue was further elaborated by Goel in 1995 who proposed the contralateral interhemispheric transfalcine transprecuneus approach (CITP) to avoid the ill effects of excessive brain retraction.(Bohnstedt, Kulwin et al. 2015, Xie, Sun et al. 2015) Although elegant, these surgical pathways have to inevitably manipulate, retract or even transgress the cortex and white matter of the precuneus and neighboring structures. As shown in the current study, the CB-V radiates to this very same area, lying just laterally to the superficial u-fibers of the posterior precuneus and connecting this cortical hub to the PPA, FFA, Retrosplenial Cortex and Lateral Piriform Cortex therefore participating in a multimodal association network believed to integrate visuospatial, facial, self-relevant and other type of cues with mnemonic functions. Interrupting this network could potentially result in disconnection syndromes involving spatial and episodic memory, awareness as well as the ability to recognize faces.

The supracerebellar transtentorial transcollateral sulcus (STTS) approach described by Kawashima and colleagues is an alternative sophisticated corridor for accessing atrial and peri-atrial lesions.(Zhao, Borba Moreira et al. 2019) Through a wide transsulcal opening of at least 3cm of the collateral sulcus, the surgeon can allegedly access trigonal/peritrigonal lesions without damaging the optic radiations. However, doubts have been raised with regard to the visual-related morbidity of this approach since the route provided by the collateral sulcus may involve damaging the anterior bundle of the optic radiations.(Koutsarnakis, Kalyvas et al. 2018) Additionally and in a hodotopical point of view, by interrupting the inferior part of the CB-V within the fusiform gyrus may impede the flow of information arising from BA37 (FFA) relevant to face and word recognition to the precuneal hub.

Limited data exists with regard to memory and supramodal integration deficits following CITP/ STTS approaches.(Tokunaga, Tamiya et al. 2006) This could be possibly attributed to the fact that a thorough pre-operative and post-operative neuropsychological battery is required to assess deficits in high-order functions subserved by fine tracts such as the CB-V, something that is not routinely applied in the daily management of such patients. However, in the modern era of extensive multidisciplinary research into the brain connectome, the Neuro-oncology surgeon should be an integral part of scientific groups exploring cerebral structure to function relationships not only by providing in-vivo data though brain mapping techniques but also by investigating the cortico-subcortical architecture through anatomical fiber dissections.

4.3 UNCINATE FASCICULUS

Ever since the seminal fiber dissection study on the structure of the human uncinate fasciculus by Ebeling and Von Cramon, most of the current anatomo-imaging literature has converged towards a common topographical and morphological architecture of the tract. According to this, the uncinate fasciculus connects the pars orbitalis, lateral and medial orbital gyri, gyrus rectus and subcallosal area with the anterior part of the superior, middle and inferior temporal gyri and uncus by travelling in a hook-like shape around the limen insula and through the anterior third of the temporal stem. This anatomical description, with some minor differences concerning the frontal terminations of the tract, is encountered in the majority of studies of research groups that have shed light into the cerebral subcortical architecture and brain anatomo-functional connectivity(Ebeling and von Cramon 1992, Ture, Yasargil et al. 2000, Catani, Howard et al. 2002, Kier, Staib et al. 2004, Peuskens, van Loon et al. 2004, Fernandez-Miranda, Rhoton et al. 2008, Wang, Sun et al. 2008, Peltier, Verclytte et al. 2010, Martino, De Witt Hamer et al. 2011, Thiebaut de Schotten, Dell'Acqua et al. 2012, Bhatia, Henderson et al. 2017, Gungor, Baydin et al. 2017).

However, recent evidence stemming primarily from tractographic protocols suggests a wider distribution pattern of the frontal terminations of the tract, thus introducing ambiguity and perplexity on its structural silhouette. More specifically, apart from the orbitofrontal cortex and pars orbitalis, which are constantly and traditionally described as cortical termination territories, Hau and colleagues have proposed that the uncinate fasciculus additionally radiates to a large area of the dorsolateral and ventrolateral prefrontal cortices including the superior, middle and inferior frontal gyri (Hau, Sarubbo et al. 2016, Hau, Sarubbo et al. 2017). In a similar vein, a tractographic study by Leng et al and a fiber dissection investigation by Baydin and colleagues demonstrated widespread terminations of the tract to the inferior and middle frontal gyri, lending support to the emerging concept of a more extended pattern of axonal connectivity than previously believed (Leng, Han et al. 2016, Baydin, Gungor et al. 2017).

In an effort to elucidate this controversial topic we employed focused white matter dissections with the aim to identify, follow and record the topographical pattern of the frontal termination of the uncinate fasciculus. We intentionally used the fiber dissection technique as our stand-alone method of investigation since it has been microscopically documented to preserve the anatomical integrity of the neural axons, thus providing structural evidence of high accuracy. Additionally, we opted to implement a method that will offer robust and direct anatomical data and is currently considered as the gold standard technique for validating results coming from tensor tractographic studies (Thomas, Ye et al. 2014, Knosche, Anwander et al. 2015, Maier-Hein, Neher et al. 2017, Aydogan, Jacobs et al. 2018, Schilling, Gao et al. 2018, Sinke, Otte et al. 2018, Schilling, Petit et al. 2020).

With this method of investigation in our armamentarium we invariably identified three consecutive and discrete layers of uncinate fibers that were found to project and terminate in three distinct cerebral areas. More specifically and in a latero-medial direction of dissection, the first and most superficial layer was seen to terminate to the posterior orbital gyrus and adjacent part of the pars orbitalis, the second, intermediate layer projects to the posterior two thirds of the gyrus rectus and the third, deeper layer was documented to radiate to the posterior one third of the paraolfactory gyrus. All these fiber layers were meticulously followed along their trajectory and were found to blend into the main stem of the uncinate fasciculus. In Table 1 we provide a summary of the pertinent literature and compare the available data to our study.

We were very diligent in the process of differentiating the fibers of the uncinate from those of the occipitofrontal fasciculus, since we believe that this is the most crucial step in defining the spatial relationship of these tracts and, in our view, is the main source of confusion and perplexity that has currently emerged. In this vein, special attention has to be paid to the narrow insular area where the stems of these two pathways meet and travel in close proximity, since the correct differentiation of these tracts at this point will accurately disclose their respective frontal termination pattern. To this end, one has to follow the trajectory of the fibers either to the anterior temporal lobe for the uncinate fasciculus or to posterior temporo-occipital areas for the occipitofrontal tract. In this endeavor, we have consistently identified the area of the insular apex to be the most important surface landmark in differentiating with confidence these adjacent tracts. Indeed, in all studied specimens the fibers seen to travel ventrally in relation to the insular apex, were recorded to belong to the stem of the uncinate fasciculus whereas the fibers that course just under and dorsal to the level of the insular apex proved to belong to the stem of the occipitofrontal bundle since they all radiate to posterior temporo-occipital cortices. Hence, by following the trajectory of the designated uncinate fibers we could thoroughly map their frontal termination pattern. In that respect and with a high level of accuracy, we did not disclose any uncinate fibers to project and radiate towards the inferior, middle and superior frontal gyri apart from the area of the pars orbitalis. On the contrary, fibers that project from temporo-occipital areas blend to form the main stem of the occipitofrontal fasciculus and fan out to project and terminate abundantly to dorsolateral and ventrolateral prefrontal cortices.

We strongly believe that the current controversy regarding the distribution pattern of the frontal termination of the uncinate fasciculus mainly derives from the different methods that research groups have utilized to differentiate and allocate adjacent fibers either to the uncinate or to the occipitofrontal fasciculus. Because the area where the stems of the tracts meet is very narrow and their respective regional morphology quite similar, the level of difficulty and uncertainty increases for tractographic and white matter dissection techniques to accurately map the respective connectional anatomy of the tracts. In a further step, both tensor and non-tensor DTI protocols are proved to be prone to false positive results, mainly due to noisy peaks or ambiguous bending and fanning fiber populations(Jones 2003, Alexander and Barker 2005, Le Bihan, Poupon et al. 2006, Fernandez-Miranda, Pathak et al. 2012). This effect is accentuated when long distance connections are explored, as the reconstruction error accumulates with each tracking step. Current literature has particularly stressed the fact that, even in ideal experimental conditions, the accuracy of an indirect method like the diffusion weighted imaging (DWI) is suboptimal and the application of a direct anatomical procedure is mandatory for validating or ruling out tractographic data. In this context, the white matter dissection technique stands as a direct anatomical process providing structural evidence of high accuracy and reproducibility, should it be properly employed (see Study strengths and limitations).

Our results are largely in agreement with the classical description of the tract and support its' structure to function relationship (Ebeling and von Cramon 1992, Kier, Staib et al. 2004, Peuskens, van Loon et al. 2004, Peltier, Verclytte et al. 2010, Papagno, Miracapillo et al. 2011, Von Der Heide, Skipper et al. 2013). Although the pertinent literature on the functional significance of the uncinate fasciculus and its possible involvement in conditions such as anxiety, epilepsy, autism, frontotemporal dementia and antisocial behavior is quite extensive and in a way "generalistic", indeed there is converging evidence that the tract is primarily associated with certain aspects of episodic memory, language and social-emotional processing. More specifically, the role of the dominant uncinate fasciculus in language is linked to processes that underpin the explicit lexical retrieval of certain aspects of semantic memory as those implicated in the proper name retrieval of famous faces. Sound evidence for this claim has been provided by the elegant study of Papagno and colleagues (Papagno, Miracapillo et al. 2011), in which the pre- and post-operative status of proper famous faces name retrieval was assessed and was found to be impaired in patients submitted to obligatory removal of the anatomical area of the uncinate fasciculus. More basic linguistic processes such as speech production, speech comprehension, phonology, semantics, and syntax do not appear to be associated with the function of the uncinate fasciculus and therefore the current notion that advocates a more widespread projection of the tract to specific language related cortices is not favorable. Further and in relation to memory and emotion, the tract seems to play a crucial role in linking temporal cortical areas that are implicated in encoding and storing mnemonic and emotionally colored representations to regions of the orbitofrontal cortex that are believed to assign values of reward or punishment to the presented stimuli and consequently underlie associative learning, behavioral shaping and decision making (Tsapkini, Frangakis et al. 2011) (Lu, Crosson et al. 2002, Semenza 2011, Von Der Heide, Skipper et al. 2013, Waldron, Manzel et al. 2014). In other words, the uncinate fasciculus is potentially involved in the connectivity of areas that integrate memory and executive functions in a way that memory based representations alter the way we behave(Von Der Heide, Skipper et al. 2013). A good body evidence both on human and non-human primates lends support to these contentions but clearly more data needs to be aggregated for a better understanding of the tract's anatomo-functional significance.

The concept of the "insular apex" in differentiating the IFOF from the UF and its potential implication in clinical practice.

As shown in the Results section, the area of the insular apex was consistently observed and recorded to be a crucial landmark with regard to the accurate differentiation of the IFOF and UF stems. In most of cases, the insular apex is a prominent area of convergence of the short insular gyri and is usually visible just under and medial to the triangular part of the inferior frontal gyrus. The relationship between the pars triangularis and insular apex is well known and is mainly attributed to the fact that the triangular part is retracted upwards, thus leaving a window of vision to the insular surface. This "insular window" is covered by arachnoid membrane and has been traditionally used by neurosurgeons as a safe and effective corridor to access insular and middle cerebral artery (MCA) lesions.

By introducing the area of the insular apex as a landmark related to subcortical structures and particularly to the structural architecture of the IFOF, one could potentially improve the spatial resolution of subcortical brain mapping carried out when treating patients harboring tumors in and around the insula. In these cases the proper identification and preservation of the IFOF, which serves as the primary ventral semantic language pathway, is imperative in decreasing language related morbidity and in achieving an optimal onco-functional balance in each patient. In other words, when the insular apex comes into view, the surgeon can form a mental picture of the trajectory and subcortical architecture of the IFOF, which will subsequently allow for a faster and more effective brain mapping strategy. This accurate knowledge of the cortical and subcortical anatomy, what is known as the “3D surgical view”, supplemented with the proper use of the intraoperative neuronavigation system is the cornerstone in optimizing outcomes in the field of surgical neurooncology.

Last but not least and in the context of DWI based tractography, the area around the insular apex can be used for the placement of regions of interest (ROIs) in order to accurately delineate and differentiate the IFOF from the UF. This can theoretically improve the spatial resolution of both tensor and non-tensor tractographic protocols, which are abundantly used not only for practical intraoperative purposes but also for contemporary neuropsychological research.

4.4 OTHER WHITE MATTER TRACTS ARISING/TERMINATING FROM/TO TEMPORAL POLE

The ILF was identified as the major tract terminating at the TP with its main stem displaying an antero-posterior trajectory along the basal surface of the hemisphere. The ILF fibers initiating from the Lingual gyrus, posterior Fu and ITG together with fibers from the occipital pole, traveled in a longitudinal manner towards anterior temporal areas. The ILF terminated at ventral and ventrolateral TP cortex areas. Taking into consideration the connection patterns of the ILF involving the temporal pole as well as visual occipital and inferior temporal associative areas, it is hypothesized that this tract is subserving the ventral visual stream believed to be fundamental for object recognition (Ungerleider and Haxby 1994). Awake cortical stimulation studies have failed to prove a role of this pathway in speech and semantics–two cognitive functions that are usually mapped and monitored in the operating theater (Mandonnet, Nouet et al. 2007). As such, an abrupt injury of the ILF is predominantly linked with dysfunction of visual cognition (e.g., visual agnosia, prosopagnosia, and alexia) (Herbet, Zemmoura et al. 2018). Furthermore, DTI metrics of the left ILF have been recently found to be significantly lower in patients with visual hallucinations in schizophrenia suggesting a potential role of the ILF in the underlying pathophysiology (Ashtari, Cottone et al. 2007). Gradual atrophy of the ILF in neurodegenerative diseases affecting the temporal pole such as semantic dementia and posterior cortical atrophy, may partly interpret the progressive nature of semantic and lexical access difficulties (Migliaccio, Agosta et al. 2012). Although ILF subserves seemingly lateralized functions, findings from awake electrocortical stimulation and mapping indicate that when injury of ILF’s anterior part ensues, the contralateral ILF can compensate in a dynamic fashion. The significant neuropsychological compromise seen in disruption of the tract in either acute or chronic disease also concur with this hypothesis (Herbet, Zemmoura et al. 2018).

The AC fibers were recorded to initiate from the midline crossing anterior to the Internal Capsule fibers, after the complete dissection of the Lentiform nucleus. The posterior fiber stream travelled posteriorly inside the SS, lateral to the optic radiation, towards the posterior temporal lobe. The anterior fiber stream was significantly thinner and terminated at the TP region. Different pathologies have been linked with structural and functional changes in the AC such as genetic (mutations in Pax6), trauma (diffuse axonal injury) and neuropsychological disorders (schizophrenia) (Wilde, Bigler et al. 2006, Yousefi 2012, Corcoba, Steullet et al. 2016). From an evolutionary perspective, the association between AC and CC can be characterized collateral and reciprocal with CC compensating for most functions subserved by AC. As such, not unexpectedly, various studies advocate for a compensatory role of AC in callosal agenesis, as a regressive compensatory mechanism (Muralidharan, Peeples et al. 2017). The compensatory roles played by these two structures become apparent in attention studies. The allocation of attention to action depends on neocortical systems and in the association with subcortical formations such as the basal ganglia and the thalamus. As such, the AC has been hypothesized as a potential mediator in the connection between vision, attention, and action.

The AP, by many known as the most hidden fasciculus of the limbic system was recognized travelling deep to the AC fibers. It initiated from the midline as 1-2 streams of fibers ventral to the rostrum of the CC and the posterior gyrus rectum. It travelled in an “S” like fashion through the Substantia Innominata and divided in two segments, a posterior joining the SS deep to the AC fibers and an anterior towards the TP cortex. In view of the anterior component’s morphology and trajectory it seems that it constitutes part of the amygdalothalamic pathway. The latter, has been recorded to connect the anterior temporal cortex and amygdala to the medial thalamus and is also known as inferior thalamic peduncle or extracapsular thalamic peduncle (Klingler and Gloor 1960, Peuskens, van Loon et al. 2004, Baydin, Yagmurlu et al. 2015, Li, Ribas et al. 2020). This fiber bundle is a reciprocal connection of the amygdala to the diencephalon, wherein the amygdala may regulate the cerebral cortex indirectly via the amygdalothalamic pathway, while the the thalamus regulates the amygdala directly, thus, potentially modulating the limbic system (Kamali, Riascos et al. 2018).

CHAPTER 5: CONCLUSIONS

5.1 MIDDLE LONGITUDINAL FASCICULUS

Focused fiber micro-dissections were employed to clarify the structural architecture of a recently identified tract known as the MdLF. 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.

5.2 FIFTH COMPONENT OF THE CINGULUM BUNDLE

Through the fiber micro-dissection technique we provide data supporting the existence of the Cingulum Bundle-V as a discrete subcomponent of the cingulum pathway. We further provide solid structural background on the direct axonal connectivity of the precuneus and medial temporal pole, cerebral territories that are heavily implicated in the neural circuit of core cognitive functions such as face and word recognition, facial expression perception, spatial navigation and updating, visuo-spatial perception memory and imagery. This constant anatomo-functional “dialogue” between these regions through discrete white matter pathways, provides useful insights on the adjustment and integration of the neural inputs and correlates of complex social cognition. Lastly, awareness is also raised with regard to the involvement of the CBV in microneurosurgical corridors employed to access lesions residing in or around the atrium of the lateral ventricle.

5.3 UNCINATE FASCICULUS

By using the white matter dissection technique, we were able to provide direct anatomical evidence of high sensitivity and accuracy on the intricate morphological pattern of the frontal termination of the uncinate fasciculus. We consistently disclosed terminations of the tract on the posterior orbital gyrus, pars orbitalis, gyrus rectus and posterior part of the paraolfactory gyrus. We did not record any fibers projecting from the main stem of the uncinate fasciculus and radiating towards the cortices of the superior, middle or inferior frontal gyrus apart from the pars orbitalis. This finding seems to be consistent with the putative functional significance of the tract. To our knowledge, the insular apex is introduced for the first time in the relevant literature as a crucial landmark with regard to the accurate topographical differentiation of the uncinate from the occipitofrontal fasciculus in the area where the main stems of these fasciculi converge. In that respect, axons that travel ventrally to the insular apex belong to the uncinate stem whereas fibers that reside just under and dorsal to the insular apex are documented to radiate from the stem of the occipitofrontal fasciculus. This finding could potentially inform surgical practice by refining the spatial resolution of awake subcortical mapping and by improving the accuracy of in vivo DTI fiber dissection protocols used for preoperative planning.

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 (Zemmoura, Blanchard et al. 2016). 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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