NATIONAL AND KAPODISTRIAN UNIVERSITY OF ATHENS MEDICAL SCHOOL
DEPARTMENT OF ANATOMY

SURFACE ANATOMY AND WHITE MATTER CONNECTIVITY OF THE PREMOTOR AND MOTOR AREAS

PHD DOCTORAL THESIS
SPYRIDON G. KOMAITIS, MD, MSC
ATHENS 2021

ΕΘΝΙΚΟ ΚΑΙ ΚΑΠΟΔΙΣΤΡΙΑΚΟ ΠΑΝΕΠΙΣΤΗΜΙΟ ΑΘΗΝΩΝ ΙΑΤΡΙΚΗ ΣΧΟΛΗ

ΕΡΓΑΣΤΗΡΙΟ ΑΝΑΤΟΜΙΑΣ

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ΕΠΙΦΑΝΕΙΑΚΗ ΑΝΑΤΟΜΙΑ ΚΑΙ ΥΠΟΦΛΟΙΩΔΕΙΣ ΣΥΝΔΕΣΕΙΣ ΤΗΣ ΠΡΟΚΙΝΗΤΙΚΗΣ ΚΑΙ ΚΙΝΗΤΙΚΗΣ ΧΩΡΑΣ

ΔΙΔΑΚΤΟΡΙΚΗ ΔΙΑΤΡΙΒΗ

ΣΠΥΡΙΔΩΝ Γ. ΚΩΜΑΪΤΗΣ, ΝΕΥΡΟΧΕΙΡΟΥΡΓΟΣ

ΑΘΗΝΑ 2021

ACKNOWLEDGEMENTS

As a child, I developed a special curiosity for everything that surrounds me. The man who made me love medicine, science and the universe was my father. It was also my father who introduced me to neurosciences. When I was 12 years old, he gifted me a book entitled "Phantoms in the Brain: Probing the Mysteries of the Human Mind". This was the period when I fell in love with the exploration of the mysteries of the human brain: an endeavor that would lead me to becoming a neurosurgeon and eventually, 15 years later, would introduce me to a special place where all the sulci and gyri, all the complex territories and structures that have been haunting generations of neuroanatomists and neuroscientists for centuries, would unravel in front of my eyes: The Athens Microneurosurgery Laboratory. The place where most of this work took place. This would not only be a sanctuary full of neurosurgical miracles, but also a home where I would meet my neurosurgical family. My mentor in neurosurgery Professor George Stranjalis and my beloved friends and neurosurgical companions Dr Christos Koutsarnakis, Dr Aristotelis Kalyvas, Dr Vangelis Drosos and Dr George Skandalakis. These are the people that share the same curiosity, the same dreams and the same passion for understanding how our mind works.

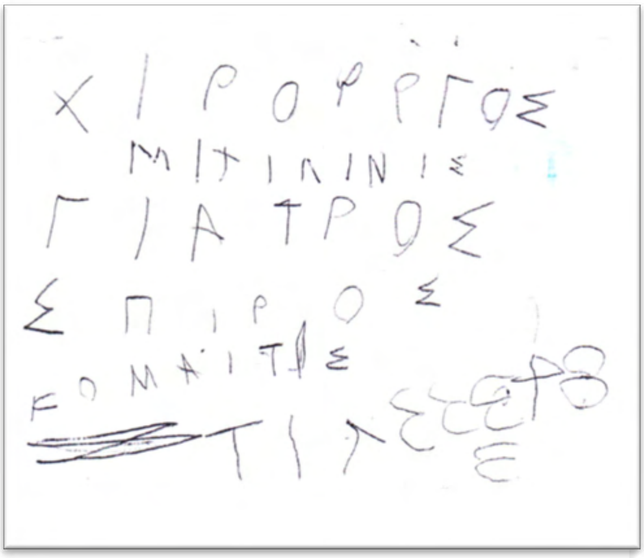
As the years passed and the idea of starting my PhD matured, I often wandered what would be the ideal subject to focus on. And it would not take long before the answer appeared unexpectedly in front of my eyes. It was in February 2018 while listening to Rachmaninoff's Pianoconcerto No2: Diving into the complex melodic texture while admiring the pianist's virtuosity, I was flummoxed by what is the most intricate and puzzling network within the human brain: the motor system. There, in front of my eyes, a constellation of sound, sentiments, experiences, actions, knowledge, mental preparation, all channeled through the motor areas into the complexity of a virtuoso's performance.

"How is this miraculous machine orchestrated? What are the anatomical substrates of our complex motor behavior?"

I only found droplets of answers within an ocean of questions while working in the lab for this thesis. I hope some of these answers will become a sparkle for future neuroscientists in this everlasting journey through the human mind.

For all their precious support and contribution, I would like to thank the members of my advisory committee, Associate Professor Maria Piagkou, Professor Emeritus Panagiotis Skandalakis, and Professor Theodoros Troupis.

Finally, a special thanks to my beloved mother that endured and continues to endure all the hard times.



ΧΙΡΟΡΡΓΟΣ
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“5-years old handwritten note: Surgeon – Doctor from Mytilene Spyros Komaitis”

“4-years old: Measuring blood pressure.”

“A few years later: Neurosurgical Family.”

To my father and mother

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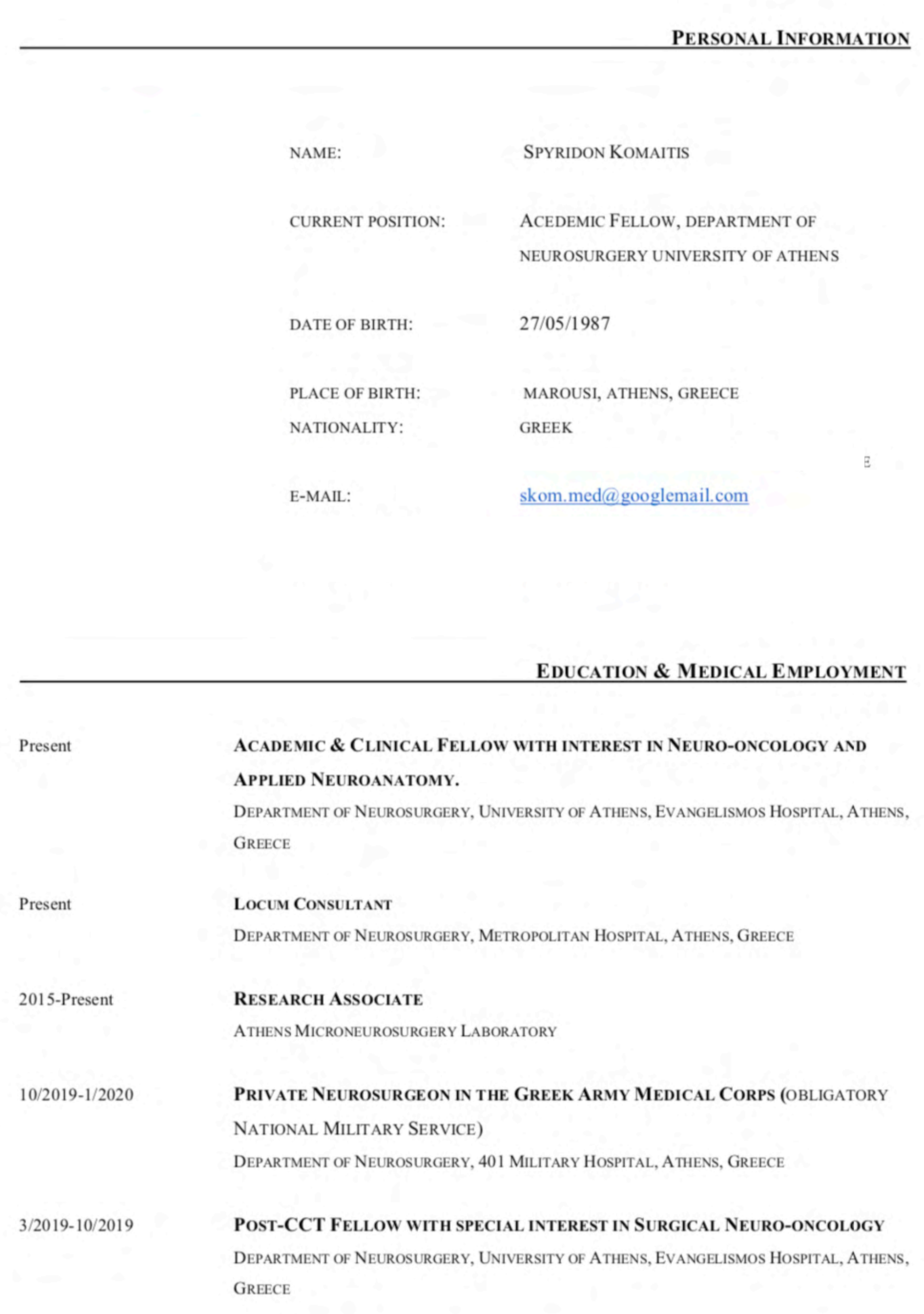
CURRICULUM VITAE



PERSONAL INFORMATION

NAME:	SPYRIDON KOMAITIS
CURRENT POSITION:	ACEDEMIC FELLOW, DEPARTMENT OF NEUROSURGERY UNIVERSITY OF ATHENS
DATE OF BIRTH:	27/05/1987
PLACE OF BIRTH:	MAROUSI, ATHENS, GREECE
NATIONALITY:	GREEK
E-MAIL:	skom.med@googlemail.com

EDUCATION & MEDICAL EMPLOYMENT

Present	**ACADEMIC & CLINICAL FELLOW WITH INTEREST IN NEURO-ONCOLOGY AND APPLIED NEUROANATOMY.** DEPARTMENT OF NEUROSURGERY, UNIVERSITY OF ATHENS, EVANGELISMOS HOSPITAL, ATHENS, GREECE
Present	**LOCUM CONSULTANT** DEPARTMENT OF NEUROSURGERY, METROPOLITAN HOSPITAL, ATHENS, GREECE
2015-Present	**RESEARCH ASSOCIATE** ATHENS MICRONEUROSURGERY LABORATORY
10/2019-1/2020	**PRIVATE NEUROSURGEON IN THE GREEK ARMY MEDICAL CORPS** (OBLIGATORY NATIONAL MILITARY SERVICE) DEPARTMENT OF NEUROSURGERY, 401 MILITARY HOSPITAL, ATHENS, GREECE
3/2019-10/2019	**POST-CCT FELLOW WITH SPECIAL INTEREST IN SURGICAL NEURO-ONCOLOGY** DEPARTMENT OF NEUROSURGERY, UNIVERSITY OF ATHENS, EVANGELISMOS HOSPITAL, ATHENS, GREECE

2/2019	**Successful Completion of Neurosurgery Specialty License Exams (FRCS Equivalent)**
6/2018-Present	**PhD Candidate** Department of anatomy, Medical School, University of Athens: "Surface anatomy and subcortical connections of the human motor and premotor areas"
10/2017-7/2019	**Master(MSc) of Science in applied neuroanatomy** Medical School, University of Athens
6/2014-2/2019	**Resident in Neurosurgery (CCT Equivalent)** Department of Neurosurgery, University of Athens, Evangelismos Hospital, Athens, Greece
6/2013-2/2014	**Core Surgical Training** General Hospital of Mytilene, Lesvos, Greece
4/2012-6/2012	**Rural Health Service** Agiasos, Lesvos, Greece
2005-2011	**Medical Degree, Medical School, Aristotle University of Thessaloniki, Greece** Grade: 8.42/10
2002-2005	**General Studies, Experimental High School of the University of the Aegean, Mytilene, Lesvos, Greece** Grade: "Excellent" ($19^{12/13}$ /20)

Awards & Scholarships

2005-2011	"Nikolaos Papadimitriou Foundation" Scholarship For excellent performance in Panhellenic National Examinations and excellent Performance in Medical School
2006-2007	"State Scholarships Foundation(IKY)" Scholarship For excellent performance in Medical School

Teaching Experience

2020-2021	Lecturer, MSc in Clinical and Experimental Neurosurgery, Medical School University of Athens, Greece
5/2019	Faculty Member - Speaker - Course Instructor: Neurosurgical Anatomy & White Matter Dissection, University of Athens, Evangelismos Hospital - Athens Microneurosurgery Laboratory – Hellenic Neurosurgical Society
5/2018	Speaker - Course Instructor: Neurosurgical Anatomy & White Matter Dissection, University of Athens, Evangelismos Hospital - Athens Microneurosurgery Laboratory – Hellenic Neurosurgical Society
5/2017	Speaker - Course Instructor: Neurosurgical Anatomy & White Matter Dissection, University of Athens, Evangelismos Hospital - Athens Microneurosurgery Laboratory – Hellenic Neurosurgical Society
4/2016	Course Instructor: White Matter Dissection, University of Athens, Evangelismos Hospital - Athens Microneurosurgery Laboratory – Hellenic Neurosurgical Society
9/2015	Course Instructor: Brain and Skull Base Anatomy, Laboratory for Education & Research in Neurosciences (LERNs) / Athens Microneurosurgery Laboratory, Attikon University Hospital, Athens, Greece
4/2015	Course Instructor: Neurosurgical Anatomy and White Matter Dissection, The Hellenic Neurosurgical Society & the Neurosurgical Clinic of University of Athens, Evangelismos Hospital
2013-2014	Clinical Instructor of Neurology: Nursing School – "Vostaneio" General Hospital, Mytilene, Lesvos, Greece

PUBLICATIONS

H-INDEX: 9

"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 Anatomoclinical Area."
Liakos F, **Komaitis S**, Drosos E, Neromyliotis E, Skandalakis GP, Gerogiannis AI, Kalyvas AV, Troupis T, Stranjalis G, Koutsarnakis C.World Neurosurg. 2021 Jun 15:S1878-8750(21)00837-8. doi: 10.1016/j.wneu.2021.06.012. Online ahead of print.PMID: 34144169

"Trends in hospital stay and outcome of CNS tumor patients in Greece during the socioeconomic crisis period (2010-2018): The case of the academic neurosurgical department at Evangelismos Hospital."
Kalamatianos T, Kalyvas A, **Komaitis S**, Stavridi K, Liouta E, Drosos E, Liakos F, Koutsarnakis C, Stranjalis G.Surg Neurol Int. 2021 May 3;12:211. doi: 10.25259/SNI_196_2021. eCollection 2021.PMID: 34084638

"Effects of brain radiotherapy on cognitive performance in adult low-grade glioma patients: A systematic review."
Koutsarnakis C, Neromyliotis E, **Komaitis S**, Mazarakis N, O'Hara DJ, Stranjalis G, Chumas P.Radiother Oncol. 2021 Jul;160:202-211. doi: 10.1016/j.radonc.2021.04.023. Epub 2021 May 6.PMID: 33964327

"The corticotegmental connectivity as an integral component of the descending extrapyramidal pathway: novel and direct structural evidence stemming from focused fiber dissections."
Komaitis S, Liakos F, Kalyvas AV, Drosos E, Skandalakis GP, Neromyliotis E, Gerogiannis A, Troupis T, Stranjalis G, Koutsarnakis C.Neurosurg Rev. 2021 Feb 10. doi: 10.1007/s10143-021-01489-2. Online ahead of print.PMID: 33564983

"Deciphering the frontostriatal circuitry through the fiber dissection technique: direct structural evidence on the morphology and axonal connectivity of the fronto-caudate tract."
Komaitis S, Koutsarnakis C, Lani E, Kalamatianos T, Drosos E, Skandalakis GP, Liakos F, Liouta E, Kalyvas AV, Stranjalis G.

"Machine learning in meningioma MRI: Past to present. A narrative review.

Neromyliotis E, Kalamatianos T, Paschalis A, **Komaitis S**, Fountas KN, Kapsalaki EZ, Stranjalis G, Tsougos I. J Magn Reson Imaging. 2020 Oct 2. doi: 10.1002/jmri.27378. Online ahead of print. PMID: 33006425

"Recent trends (2010-2018) in traumatic brain injury in Greece: results on 2042 patients."

Stranjalis G, Komaitis S, Kalyvas AV, Drosos E, Stavrinou L, Koutsarnakis C, Kalamatianos T., Injury. 2020 Jun 1:S0020-1383(20)30474-5. doi: 10.1016/j.injury.2020.05.045. Online ahead of print.PMID: 32536530

"A systematic review of surgical treatments of idiopathic intracranial hypertension (IIH)."

Kalyvas A, Neromyliotis E, Koutsarnakis C, Komaitis S, Drosos E, Skandalakis GP, Pantazi M, Gobin YP, Stranjalis G, Patsalides A.Neurosurg Rev. 2020 Apr 25. doi: 10.1007/s10143-020-01288-1. PMID: 32335853

“Dissecting the default mode network: Direct structural evidence on the morphology and axonal connectivity of the fifth component of the Cingulum Bundle.”
Skandalakis GP, Komaitis S, Kalyvas A, Lani E, Kontrafouri C, Drosos E, Liakos F, Piagkou M, Placantonakis D, Golfinos J, Fountas K, Kapsalaki E, Hadjipanayis C, Stranjalis G, Koutsarnakis C. J Neurosurg. 2020 Apr 24:1-12. doi: 10.3171/2020.2.JNS193177.

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

“Mapping the superficial morphology of the occipital lobe: Proposal of a universal nomenclature for clinical and anatomical use”
Koutsarnakis C, Komaitis S, Skandalakis G, Kalyvas A, Drosos E, Lani E, Emelifweonu J, Liakos F, Piagkou M, Stranjalis G. Neurosurg Rev. 2019 Nov 22. doi: 10.1007/s10143-019-01212-2. Online ahead of print.PMID: 31758336

“The Frontal Longitudinal System as revealed through the fiber micro-dissection technique: Structural evidence underpinning the direct connectivity of the prefrontal-premotor circuitry.
Komaitis S, Skandalakis G, Kalyvas A, Drosos E, Lani E, Emelifweonu J, Liakos F, Piagkou M, Stranjalis G, Koutsarnakis C. J Neurosurg. 2019 Oct 4:1-13. doi: 10.3171/2019.6.JNS191224. Online ahead of print.PMID: 31585424

“The dorsal component of the superior longitudinal fasciculus revisited. New insights from a focused dissection study.”
Komaitis S, Skandalakis G, Kalyvas A, Drosos E, Lani E, Emelifweonu J, Liakos F, Piagkou M, Stranjalis G, Koutsarnakis C. J Neurosurg. 2019 Mar 1:1-14. doi: 10.3171/2018.11.JNS182908. Online ahead of print.PMID: 30835690

“The carotico-clinoid bar: A systematic review and meta-analysis of its prevalence and potential implications in cerebrovascular and skull base surgery.”
Skandalakis GP, Koutsarnakis C, Pantazis N, Kalyvas A, Komaitis S, Lani E, Drosos E, Kalamatianos T, Hadjipanayis CG, Natsis K, Stranjalis G, Piagkou M.
World Neurosurg. 2019 Jan 21. pii: S1878-8750(19)30107-X. doi: 10.1016/j.wneu.2019.01.017. [Epub ahead of print] Review.PMID: 30677570

“Angiosarcoma-related cerebral metastases: a systematic review of the literature.”

Drosos E, Kalyvas A, Komaitis S, Lani E, Emelifweonu J, Liakos F, Piagkou M, Stranjalis G, Koutsarnakis C. Neurosurg Rev. 2019 Jun 4. doi: 10.1007/s10143-019-01127-y. Online ahead of print.PMID: 31165296

“Sledge Runner Fasciculus: Microanatomic architecture and Tractographic Morphology of a fiber tract subserving Spatial Navigation and Visuospatial imagery”

Koutsarnakis C, Kalyvas A, Skandalakis G, Karavasilis E, Christidi F, Komaitis S, Velonakis G, Liakos F, Emelifeonwu J, Kalamatianos T, Kelekis N, Stranjalis G. Brain Struct Funct. 2019 Apr;224(3):1051-1066. doi: 10.1007/s00429-018-01822-4. Epub 2019 Jan 3.PMID: 30607495

“Spinal Atypical rhabdoid teratoid tumor in an adult woman. A rare case report and review of the literature.”

Neromyliotis E, Kalyvas A, Drosos E, Komaitis S , Skandalakis G, Karavasilis E, Christidi F, Velonakis G, Liakos F, Emelifeonwu J, Kalamatianos T, Kelekis N, Stranjalis G, Koutsarnakis C. World Neurosurg. 2019 Aug;128:196-199. doi: 10.1016/j.wneu.2019.05.007. Epub 2019 May 10.PMID: 31082562

“Defining the relationship of the optic radiation to the roof and floor of the ventricular atrium: a focused microanatomical study.”

Koutsarnakis C, Kalyvas AV, Komaitis S, Liakos F, Skandalakis GP, Anagnostopoulos C, Stranjalis G. . J Neurosurg. 2018 May 4:1-12. doi: 10.3171/2017.10.JNS171836. Online ahead of print.PMID: 29726766

“Parietal association deficitis in patients harboring parietal lobe gliomas: a prospective study.”

Liouta E, Stranjalis G, Kalyvas AV, Koutsarnakis C, Pantinaki S,Liakos F, Komaitis S, Stavrinou LC. J Neurosurg. 2018 May 4;130(3):773-779. doi: 10.3171/2017.12.JNS171799.PMID: 29726775

“Finter tapping and verbal fluency post-tap test improvement in INPH: its value in differential diagnosis and shunt-treatment outcomes prognosis.”

Liouta E, Gatzonis S, Kalamatianos T, Kalyvas A, Koutsarnakis C ,Liakos F, Anagnostopoulos C, Komaitis S, Giakoumettis D, Stranjalis G. Acta Neurochir (Wien). 2017 Dec;159(12):2301-2307. doi: 10.1007/s00701-017-3301-2. Epub 2017 Aug 21.PMID: 28828534

“Letter to the Editor: White matter fiber tract architecture and ventricular surgery.”

Koutsarnakis C, Liakos F, Kalyvas A, Komaitis S, Stranjalis G. J Neurosurg. 2018 May 4:1-12. doi: 10.3171/2017.10.JNS171836. Online ahead of print.PMID: 29726766

“The Superior Frontal Transsulcal Approach to the anterior ventricular system: Exploring the sulcal and subcortical anatomy using anatomic dissections and DTI tractography.”

Faidon Liakos, MD; Aristotelis Vasileios Kalyvas, M.D., M.Sc.; Georgios P Skandalakis, BSc; Spyros Komaitis, MD; Fotini Christidi, MSc, PhD; Efstratios Karavasilis, MD; Evangelia Liouta, MSc; George

Stranjalis, MD, PhD. World Neurosurg. 2017 Oct;106:339-354. doi: 10.1016/j.wneu.2017.06.161. Epub 2017 Jul 8.PMID: 28698090

“Anaplastic lymphoma kinase expression and gene alterations in glioblastoma: correlations with clinical outcome.”
Karagkounis G, Stranjalis G, Argyrakos T, Pantelaion V, Mastoris K, Rontogianni D, Komaitis S, Kalamatianos T, Sakas D, Tiniakos D. J Clin Pathol. 2017 Jul;70(7):593-599. doi: 10.1136/jclinpath-2016-204102. Epub 2016 Dec 19.PMID: 27993946

“Complicated acute appendicitis within a right inguinal hernia sac (Amyand’s hernia): report of a case.”
Kouskos E, Komaitis S, Kouskou M, Despotellis M, Sanidas G. Hippokratia. 2014 Jan;18(1):74-6.PMID: 25125958

“Cardiovascular diseases in pregnancy.”
Godosis D, Komaitis S, Tziomalos K, Baltatzi M, Ntaios G, Savopoulos CG, Hatzitolios AI. Am J Cardiovasc Dis. 2012;2(2):96-101. Epub 2012 May 15.PMID: 22720198

COURSES & WORKSHOPS

9/2018	EMERGENCY NEUROLOGICAL LIFE SUPPORT, 251 AIRFORCE GENERAL HOSPITAL, ATHENS GREECE
5/2018	EANS TRAINING COURSE : TRAUMA AND FUNCTIONAL NEUROSURGERY, BELGRADE, MAY 2018
5/2017	NEUROSURGICAL ANATOMY – WHITE MATTER DISSECTION, MAY 29-31 2017, ATHENS MICRONEUROSURGERY LABORATORY
5/2017	EANS TRAINING COURSE: SPINE /PERIPHERAL NERVES, PRAGUE, MAY 2017
6/2016	THE 16TH HELSINKI LIVE DEMONSTRATION COURSE IN OPERATIVE MICRONEUROSURGERY, UNIVERSITY HOSPITAL OF HELSINKI, FINLAND
4/2016	WHITE MATTER DISSECTION, UNIVERSITY OF ATHENS, EVANGELISMOS HOSPITAL - ATHENS MICRONEUROSURGERY LABORATORY – HELLENIC NEUROSURGICAL SOCIETY
3/2016	LARISSA INTERNATIONAL NEUROVASCULAR COURSE “CEREBRAL ANEURYSMS”

11/2015	Neurosurgical Approaches to the Cranial Compartments, The Stewart Skills Laboratory, The Royal College of Surgeons of Edinburgh
9/2015	Surgical anatomy of cortical aereas and speech networks. Hellenic Neurosurgical Society Refresher Course
9/2015	Brain and Skull Base Anatomy, Laboratory for Education & Research in Neurosciences (LERNs) / Athens Microneurosurgery Laboratory
4/2015	Neurosurgical Anatomy and White Matter Dissection, The Hellenic Neurosurgical & the Neurosurgical Clinic of University of Athens, Evangelismos Hospital
1/2015	Skull base meningiomas(Posterior Fossa): Surgical Anatomy, Approaches, Complications. Hellenic Neurosurgical Socety Refresher Course
11/2014	44th Week of Exercise in Microsurgery, University of Ioannina Orthopedic Department Microsurgery Lab
11/2014	Anterior Cranial Fossa: Surgical techniques, Anatomy, Approaches Hellenic Neurosurgical Society Refresher Course
10/2014	Surgical Treatment of Craniosynostoses. Hellenic Neurosurgical Society Refresher Course
9/2014	Normal Pressure Hydrocephalus: Etiology, Pathophysiology and Treatment. Hellenic Neurosurgical Society Refresher Course
5/2012	Advanced Trauma and Life Support(ATLS), AHEPA Hospital Thessaloniki, Greece

ORAL PRESENTATIONS & POSTERS

"Subcortical connectivity of the premotor cortex"

Invited Lecture: Clinical and Experimental Neurosurgery MSc Programme 17/4/2021

"Superficial white matter pathways"

Invited Lecture: Clinical and Experimental Neurosurgery MSc Programme 27/3/2021

"Applied Neuroanatomy of the White Matter"

Invited lecture: 34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society

"The axonal connectivity of the premotor areas as revealed through fiber dissections: Shedding light on the structural correlates of complex motor behavior"

Komaitis S, Koutsarnakis C, Drosos E, Kalyvas A, Stranjalis G.

34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society

"Preoperative neurocognitive status predicts overall survival in dominant hemisphere primary glioblastoma"
Liouta E., Komaitis S., Koutsarnakis C., Kalyvas A. V., Drosos E., Stranjalis G
34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society

"The cingulum bundle V as revealed through the fiber microdissection technique: Structural data demonstrating the direct connectivity of the medial tempoo-parietal circuitry." Skandalakis G.P., Komaitis S., Kalyvas A. Lani E., Drosos E., Liakos F., Piagkou M., Placantonakis D.G., Golfinos J.G., Fountas K.
34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society

"The topography of the frontal terminations of the uncinate fasciculus revisited through focused fiber dissections"
Liakos F, Koutsarnakis C, Komaitis S, Skandalakis G, Piagkou M, Stranjalis G.

34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society

"Direct comparison between the Kawase's Approach and the Retrosigmoid intradural suprameatal(RISA) corridor to access the petroclival region using cadaveric dissections and CT quantitative volumetric analysis"

Stavrinou P., Koutsarnakis C., Drosos E., Komaitis S.3,4,6,7, Stranjalis G.3,4,7
34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society

"Neurosurgery and technology: a story of how the pieces fit together"

Invited lecture: in "eHealth and Telemedicine Management" Master's Degree in Rome Business School

"Treatment of cerebral metastases: The role of Neurosurgery and SRS/WBRT in the treatment of brain melanoma metastases."

Invited lecture: "Dilemmas and leading-edge subjects in oncology". 2-3 October 2020. Crowne Plaza Hotel, Athens, Greece

"Advances in minimally invasive treatment of ICH"

Invited lecture: 33rd Annual Congress Hellenic Neurosurgical Society, 4th Congress SeENS SouthEast Europe Neurosurgical Society.

"Surface Anatomy & Imaging Correlation"

Komaitis S Neurosurgical Anatomy and White Matter Dissection Course, June 1-2 2017, Athens Microneurosurgery Laboratory, Athens, Greece

"Management of Traumatic Brain Injury in the Emergency Department"

22nd Annual Conference of Continuing Medical Education, 13-17/2/2017, Evangelismos Hospital, Athens, Greece

"Epidural empyema as a late complication of complex epilepsy surgery."

Korfias S, Themistoklis K, Vlachakis E, **Komaitis S**, Giakoumettis D, Boviatsis K, Themistocleous M, Sakas D
XXII Congress of the European Society for Stereotactic and Functional Neurosurgery, 28 September – 1 October 2016, Madrid, Spain

"Typical versus non-typical idiopathic normal pressure hydrocephalus: the importance of cognition and gait characteristics in predicting tap test and shunt outcomes."

Liouta E, Gatzonis S, Kalyvas A, **Komaitis S**, Liakos F, Koutsarnakis C, Anagnostopoulos C, Stranjalis G. EANS 2016 Congress, September 4-8 2016, Athens, Greece

"Intracranial meningioma surgery in patients over 70 years old. One year morbidity and mortality."

Anagnostopoulos C, **Komaitis S**, Kalyvas A, Liouta E, Stranjalis G. EANS 2016 Congress, September 4-8 2016, Athens, Greece

"Giant malignant carcinoma of the paranasal sinuses with intracranial expansion: removal through extended transbasal approach and reconstruction of anterior fossa."

Kalyvas A, **Komaitis S**, Papadiochos I, Papadogeorgakis N, Stranjalis G. 30th Panhellenic Neurosurgery Congress

"Surgical treatment of meningiomas: A 5 year retrospective study."

Komaitis S, Kalyvas A, Mpanos S, Stranjalis G. 30th Panhellenic Neurosurgery Congress

"Microsurgical Anatomy of Orbitofrontal Arteries"

Mavridis IN, Kalamatianos T, Koutsarnakis C, **Komaitis S**, Stranjalis G. 30th Panhellenic Neurosurgery Congress

"Anatomical study: Approaching the frontal horn of the lateral ventricle through the cerebral isthmus."

Liakos F, Koutsarnakis C, **Komaitis S**, Themistoklis K, Stranjalis G. 29th Panhellenic Neurosurgery Congress

"The superior frontal transsulcal corridor to the anterior ventricular system. Exploring the sulcal and subcortical anatomy using white matter dissections and DTI tractography."

Liakos F, Koutsarnakis C, Kalyvas A, **Komaitis S**, Stranjalis G. EANS 2016 Congress, September 4-8 2016, Athens, Greece

MEMBERSHIP IN MEDICAL SOCIETIES

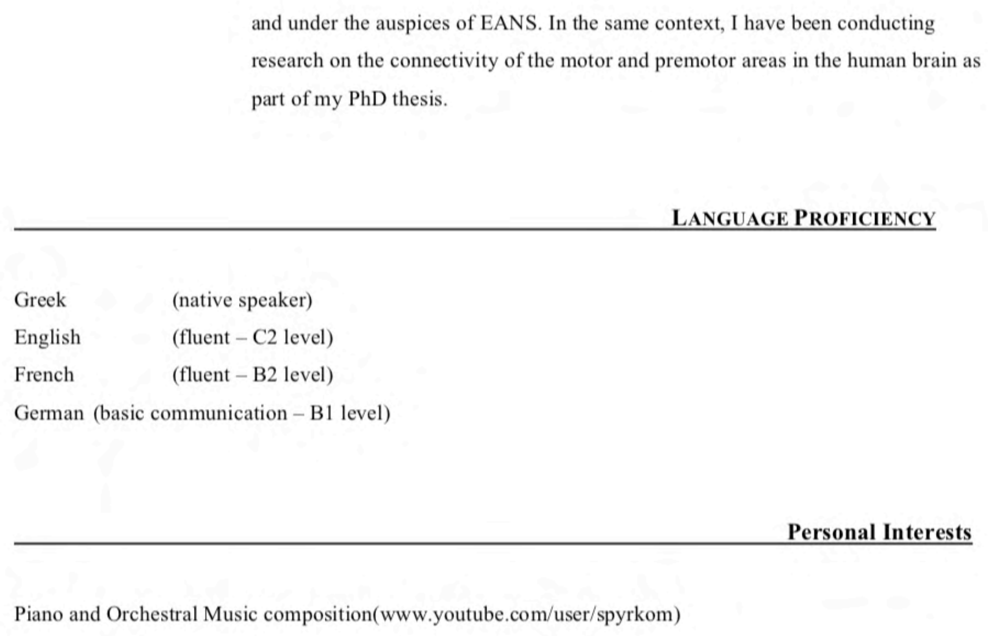
General Medical Council (Full registration with a licence to practice since May 15 2020.)
Medical Association of Athens
EANS Individual Member
Hellenic Neurosurgical Society (HNS)

REVIEWER IN PEER REVIEWED JOURNALS

OPERATIVE NEUROSURGERY
WORLD JOURNAL OF SURGICAL ONCOLOGY

RESEARCH

2015-Present	Since 2015 I have conducted research and published articles in high impact factors journals, in the field of White Matter Anatomy and Brain connectivity at the Athens Microneurosurgery Laboratory. Additionally, I have participated as an instructor/demonstrator and speaker in the annual International course on Neurosurgical Anatomy and White Matter Dissection from 2017 to 2019. As a Research Associate of the Microneurosurgery Laboratory I have co-organized the 3rd and 4th International Neurosurgical Anatomy and White Matter Dissection courses organized by the Academic Neurosurgery Department of the University of Athens



and under the auspices of EANS. In the same context, I have been conducting research on the connectivity of the motor and premotor areas in the human brain as part of my PhD thesis.

LANGUAGE PROFICIENCY

Greek	(native speaker)
English	(fluent – C2 level)
French	(fluent – B2 level)
German	(basic communication – B1 level)

Personal Interests

Piano and Orchestral Music composition(www.youtube.com/user/spyrkom)

LIST OF ABBREVIATIONS

Aar = Anterior ascending ramus of the Sylvian Fissure

ac = Anterior Commissure

ACC =Anterior Cingulate Cortex

AF =Arcuate Fasciculus

ALIC = Anterior Limb of the Internal Capsule

APS = Anterior Perforated Substance

ATR = Anterior Thalamic Radiation

BA = Brodmann’s Area

Caud = Caudate Nucleus

CB = Cingulum Bundle

CC= Corpus Callosum

CCg = Genu of the Corpus Callosum

CCs = Splenium of the Corpus Callosum

Cd = Caudate Nucleus

Cdb = Body of the Caudate Nucleus

Cdh = Head of the Caudate Nucleus

CdN= Caudate Nucleus (body)

CF = Calcarine Fissure

Cg = Cingulate Gyrus

Cgb = Body of the Corpus Callosum

CgG = Cingulate Gyrus

Cgra = Radiations of the cingulum towards the precuneus

Cgs = Cingulate Sulcus

Cgsa= Superior arm of the cingulum

CoR= Corona Radiata

CP= Cerebral Peduncle

CR = Corona Radiata

Crad = Callosal Radiations

CRT = Corticoreticular Tract

Cs = Centrum Semiovale

CS= Central Sulcus

CST = Corticospinal Tract

CTT = Corticotegmental Tract

DLPFC = Dorsolateral Prefrontal Cortex

DTI = Diffusion Tensor Imaging

FAT = Frontal Aslant Tract

FCT = Fronto-caudate Tract

FCTd = Dorsal component of the Fronto-caudate Tract

FCTdtz = Dorsal component of the Fronto-caudate Tract termination zone

FCTv = Ventral component of the Fronto-caudate Tract

FCTvtz = Ventral component of the Fronto-caudate Tract termination zone

FEF = Frontal Eye Fields

FLS = Frontal Longitudinal System

FLS(I) = Frontal Longitudinal System: Superior frontal longitudinal chain

FLS(S) = Frontal Longitudinal System: Inferior frontal longitudinal chain

fm = Foramen of Monro

FP= Frontal Pole

Fpo = Frontoparietal Operculum

FST = Frontostriatal Tract

FVF(l) = Lateral aspect of the 4th ventricle floor

FVF(m) = Medial aspect of the 4th ventricle floor

FVF = Floor of the 4th ventricle

Fx = Fornix

GP = Globus Pallidus

Hr = Horizontal ramus of the Sylvian Fissure

HT = Hypothalamus

IC = Internal Capsule

Ic = Inferior Colliculus

IFG = Inferior Frontal Gyrus

IFS = Inferior Frontal Sulcus

IntCps = Internal Capusle

Lc = Locus Coeruleus

Lgb = Lateral Geniculate Body

LN = Lentiform Nucleus

Mb = Midbrain

MCP = Middle Cerebellar Peduncle

MFG = Middle Frontal Gyrus

MFS = Middle Frontal Sulcus

mL = Medial lemniscus

Mn = Mesencephalic Nucleus

Mrg = Marginal ramus of the cingulate sulcus

OC = Optic Chiasm

OFC = Orbitofrontal Cortex

On = Olfactory Nerve

ON = Optic Nerve

OPPFC = Orbitopolar Prefrontal Cortex

OT = Optic Tract

Pc = Posterior Commissure

PcgG= Paracingulate gyrus

PcgS= Paracingulate sulcus

POS = Parieto-occipital Sulcus

PrC= Precentral Sulcus

PrCn(a) = Anterior Precuneus

PrCn(p) = Posterior Precuneus

Prcn = Precuneus

Pre-SMA = Pre-Supplementary Motor Area

PrG = Precentral Gyrus

PrOp = Pars Opercularis

PrOrb = Pars Orbitalis

PrS = Precentral Sulcus

PrT = Pars Triangularis

PtC = Postcentral Sulcus

PtG = Postcentral Gyrus

PtS = Postcentral Sulcus

Pv = Pulvinar

RF = Reticular Formation

Rn = Red Nucleus

SC = Superior Colliculus

SCP = Superior Cerebellar Peduncle

SFG = Superior Frontal Gyrus

SFS = Superior Frontal Sulcus

sL = Spinal lemniscus

SLF- Ip = Superior Longitudinal Fasciculus I – posterior segment

SLF-I = Superior Longitudinal Fasciculus I

SLF-Ia = Superior Longitudinal Fasciculus I – anterior segment

SLF-II = Superior Longitudinal Fasciculus II

SLF-III = Superior Longitudinal Fasciculus III

SLF-Ip = Superior Longitudinal Fasciculus I Posterior Part

SMA = Supplementary Motor Area

Sn = Substantia Nigra

Sn = Substantia Nigra

SP = Septum Pellucidum

SpS = Subparietal Sulcus

SpS = Subparietal sulcus

SS = Sagittal Stratum

St = Stria Terminalis

TEZ = Tegmental Entry Zone

Tgm(l) = Lateral Tegmental Area

Tgm(m) = Medial Tegmental Area

Tgm = Tegmentum

Th = Thalamus

tL = Trigeminal lemniscus.

TST = Tegmentospinal tracts

VCVS = Ventral Internal Capsule/ Ventral Striatum

VLPFC = Ventrolateral Prefrontal Cortex

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THESIS PUBLICATIONS

“The Corticotegmental connectivity as an integral component of the descending extrapyramidal pathway: Novel and direct structural evidence stemming from focused dissections.”

Komaitis S, Liakos F, Kalyvas AV, Drosos E, Skandalakis GP, Neromyliotis E, Gerogiannis A, Troupis T, Strranjalis G, Koutsarnakis C. Neurosurg Rev. 2021 Feb 10. doi: 10.1007/s10143-021-01489-2. Online ahead of print. PMID: 33564983

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“Dorsal component of the superior longitudinal fasciculus revisited. New insights from a focused dissection study.”

Komaitis S, Skandalakis G, Kalyvas A, Drosos E, Lani E, Emelifweonu J, Liakos F, Piagkou M, Stranjalis G, Koutsarnakis C. J Neurosurg. 2019 Mar 1:1-14. doi: 10.3171/2018.11.JNS182908. Online ahead of print.PMID: 30835690

PRESENTATIONS

“Neurosurgical Anatomy and White Matter Dissection: Surface Anatomy & Radiographic Correlation”

Komaitis S, Neurosurgical Anatomy and White Matter Dissection Course, May 6-7 2019, Athens Microneurosurgery Laboratory, Athens, Greece

“Introduction to the white matter anatomy of the human brain”

Komaitis S, Clinical and Experimental Neurosurgery MSc Program, Medical School, University of Athens, March 27 2021, Athens, Greece

“Integrating the motor circuitry: Evidence from focused white matter dissections”
Komaitis S, White Matter Dissection Course, May 17-18 2021, Athens Microneurosurgery Laboratory, Athens, Greece

“Subcortical Connections of the Premotor Cortex”

Komaitis S, Clinical and Experimental Neurosurgery MSc Program, Medical School, University of Athens, April 17 2021, Athens, Greece

“Applied neuroanatomy of the white matter”

Komaitis S, 34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society, 3-5 June 2021, Athens Greece

“The Axonal Connectivity of premotor areas revealed through fiber dissections: Shedding light on the structural correlates of complex motor behavior.”

Komaitis S, 34th Annual Congress of the Hellenic Neurosurgical Society and Joint Meeting with the Cyprus Neurosurgical Society, 3-5 June 2021, Athens, Greece

ABSTRACT

OBJECTIVE

To reveal the intrinsic architecture, morphology and spatial relationship of the white matter pathways implicated in the connectivity of motor/premotor cortex and SMA/pre-SMA complex that remains vague to this day.

METHODS

Thirty normal, adult, formalin-fixed cerebral hemispheres were explored through the fiber micro-dissection technique. Lateral to medial and medial to lateral dissections were performed in a tandem manner and under the surgical microscope.

RESULTS

We traced the subcortical architecture, spatial relationships and axonal connectivity of four major pathways: a) the dorsal component of the SLF (SLF-I) was found to reside in the medial aspect of the hemisphere and seen to connect the precuneus with the SMA and pre-SMA complex, b) the Frontal Longitudinal System (FLS) was consistently encountered as the natural anterior continuation of the SLF-II and SLF-III and connected the premotor and prefrontal cortices c) the Fronto-caudate Tract (FCT),a fan-shaped tract, was documented to participate in the connectivity of the prefrontal and premotor cortices to the head and body of the caudate nucleus and d) the Cortico-tegmental Tract(CTT) was invariably recorded to subserve the connectivity of the tegmental area with the motor/premotor areas and fronto-parietal cortex. No hemispheric asymmetries were recorded for any of the implicated pathways. Sub-segmentation systems were also introduced for each of the aforementioned tracts.

CONCLUSIONS

The structural connectivity and functional specialization of motor and premotor areas in the human brain remains vague to this day as most of the available evidence derives either from animal or tractographic studies. By using the fiber-microdissection technique as our main method of investigation, we provide sound structural evidence on the delicate anatomy of the related white matter pathways.

Keywords: Fiber tract, Motor cortex, Premotor cortex, Connectivity, White Matter

ΠΕΡΙΛΗΨΗ

ΣΚΟΠΟΣ

Σκοπός της παρούσας διατριβής είναι η μελέτη της αρχιτεκτονικής, της μορφολογίας και της συσχετιστικής ανατομίας των δεματίων λευκής ουσίας που εμπλέκονται στη συνδεσιμότητα του κινητικού και προκινητικού φλοιού καθώς και της επικουρικής και προ-εκπικουρικής περιοχής.

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

Αναζητήθηκε η υποφλοιώδης αρχιτεκτονική, η χωρική συσχέτιση και η συνδεσιμότητα τεσσάρων κυρίως μείζονων δεματίων: Α) Το ραχιαίο τμήμα του άνω επιμήκους δεματίου (SLF-I) ανευρέθηκε σταθερά στην έσω επιφάνεια του ημισφαιρίου να συνδέει το προσφηνοειδές λόβιο, την επικουρική και προ-επικουρική κινητική περιοχή. Β) Το Μετωπιαίο Επίμηκες Δεμάτιο(FLS) παρατηρήθηκε σταθερά ως μια πρόσθια συνέχεια του 2ου και 3ου τμήματος του άνω επιμήκους δεματίου(SLF II& SLF III). Το εν λόγω δεμάτιο συνδέει τον προκινητικό με τον προμετωπιαίο φλοιό. Γ) Το Μέτωπο-Κερκοφόρο Δεμάτιο (FCT) ένα ριπιδοειδές σύστημα ινών λευκής ουσίας, καταγράφηκε να συμμετέχει στη συνδεσιμότητα του προμετωπιαίου και προκινητικού φλοιού με την κεφαλή και το σώμα του κερκοφόρου πυρήνα. Δ) Το Φλοιο-καλυπτρικό δεμάτιο (CTT) ανευρέθηκε σταθερά να συνδέει τη μεσεγκεφαλική καλύπτρα με τον κινητικό/προκινητικό φλοιό και τον φλοιό της οπίσθιας κεντρικής έλικας. Κατά τις παρασκευές των εν λόγω δεματίων δεν παρατηρήθηκαν ημισφαιρικές ασυμμετρίες. Τέλος πρότυπα υποτμηματοποίησης προτάθηκαν για όλα τα δεμάτια.

ΣΥΜΠΕΡΑΣΜΑΤΑ

Η συνδεσιμότητα και η λειτουργική εξειδίκευση των κινητικών και προκινητικών περιοχών του ανθρώπινου εγκεφάλου παραμένει σε μεγάλο βαθμό ασαφής καθώς ο μεγαλύτερος όγκος πληροφοριών προέρχεται από μελέτες σε πειραματόζωα και δεσμιδογραφικές μελέτες. Χρησιμοποιώντας την τεχνική Παρασκευής της λευκής ουσίας κατά Klingler ως βασική μέθοδο διερεύνησης, η παρούσα μελέτη παρέχει δεδομένα και στοιχεία για την λεπτή ανατομία των σχετιζόμενων με τις παραπάνω περιοχές δεματίων.

Λέξεις Κλειδιά: Δεμάτια, Κινητικός φλοιός, Προκινητικός φλοιός, Συνδεσιμότητα, Λευκή Ουσία

CHAPTER 1: INTRODUCTION

1.1 A BRIEF HISTORICAL NOTE: THE MOTOR SYSTEM FROM JACKSON TO THE MODERN COGNITIVE/MOTOR MODEL.

More than a century ago John Hughlings Jackson, from Providence Green Yorkshire, full physician at the National Hospital for Neurology and Neurosurgery (then National Hospital for Paralysis and Epilepsy), was the first to support the notion that the cerebral cortex is the center of motor activity. By observing his wife's epileptic seizures, he described the widely known "Jacksonian" seizures that appear as localized motor convulsive seizures. Based on his observations, Jackson was led to the idea that epileptic seizures were nothing more than electrical discharges within the different territories of the brain. This was the basis of the theory of localization within the human cerebrum.


JOHN HUGHLINGS JACKSON (1835-1911)

GUSTAV FRITSCH AND EDWARD HITZIG

In 1970, Gustav Fritsch and Eduard Hitzig, lend support to Jackson’s theories as they managed to locate a motor area in the dog’s brain by stimulating the cortex while the animal was in an awake state. Fritsch and Hitzig, were led to two main ideas: 1) there is a motor area responsible for the movement of contralateral limbs. 2) There seems to be somatotopy within this area with specific loci provoking movements of specific muscle groups.

CHARLES SCOTT SHERRINGTON (RIGHT)

Following Fritsch and Hitzig's primitive experiments, Ferrier and later Sherrington -a British neurophysiologist and pathologist widely known for his studies on neuron activity, for the description of the synapses and for the 1932 Nobel Prize "for his discoveries regarding the functions of the neurons"- proceeded with more sophisticated experiments in non-human primates that led them to the description of an area around the central sulcus that corresponds to the sensorimotor cortex.

In 1936 Otfrid Foerster, from Breslau, a neurologist, student of Dejerine, Pierre Marie and Babinski, and personal physician of Lenin after his 1922 stroke, conducted important research on the motor command of the cerebral cortex

PENFIELD AND JASPER

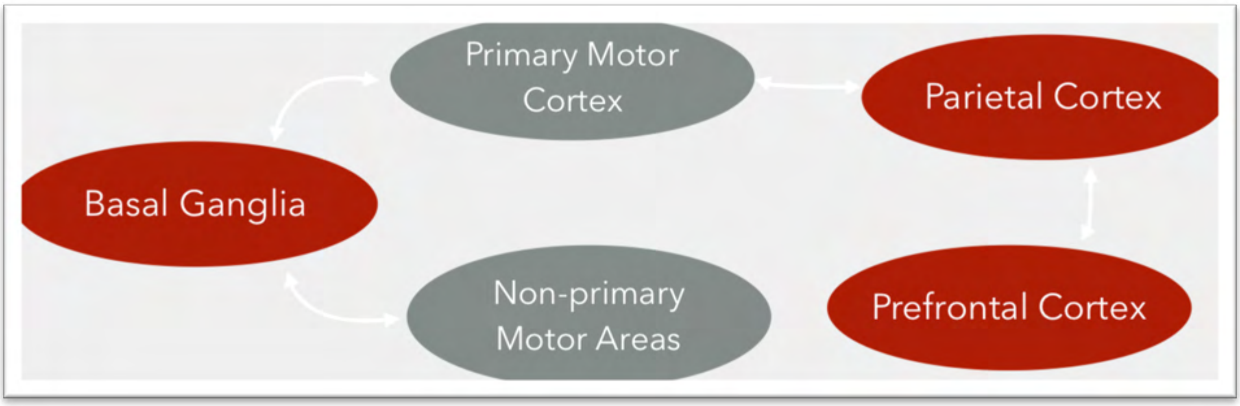
while operating on patients treated for epilepsy. Foerster's legacy passed on, to one of his most renown students: Wilder Penfield.

In 1929, Penfield became the first Professor of Neurosurgery in McGill. During this period, he was introduced to and closely collaborated with Herbert Jasper. A world renown epileptologist. Their fruitful collaboration led to the development of the so called "Montreal Procedure", an awake craniotomy with direct cortical stimulation for the resection of epileptogenic areas. Through this procedure Penfield grasped the opportunity to map and document the functional role of different cortical areas, developing his famous cortical maps and the homunculus. The human primary motor cortex, Brodmann's Area 4, was recorded and documented in detail for the first time in history.

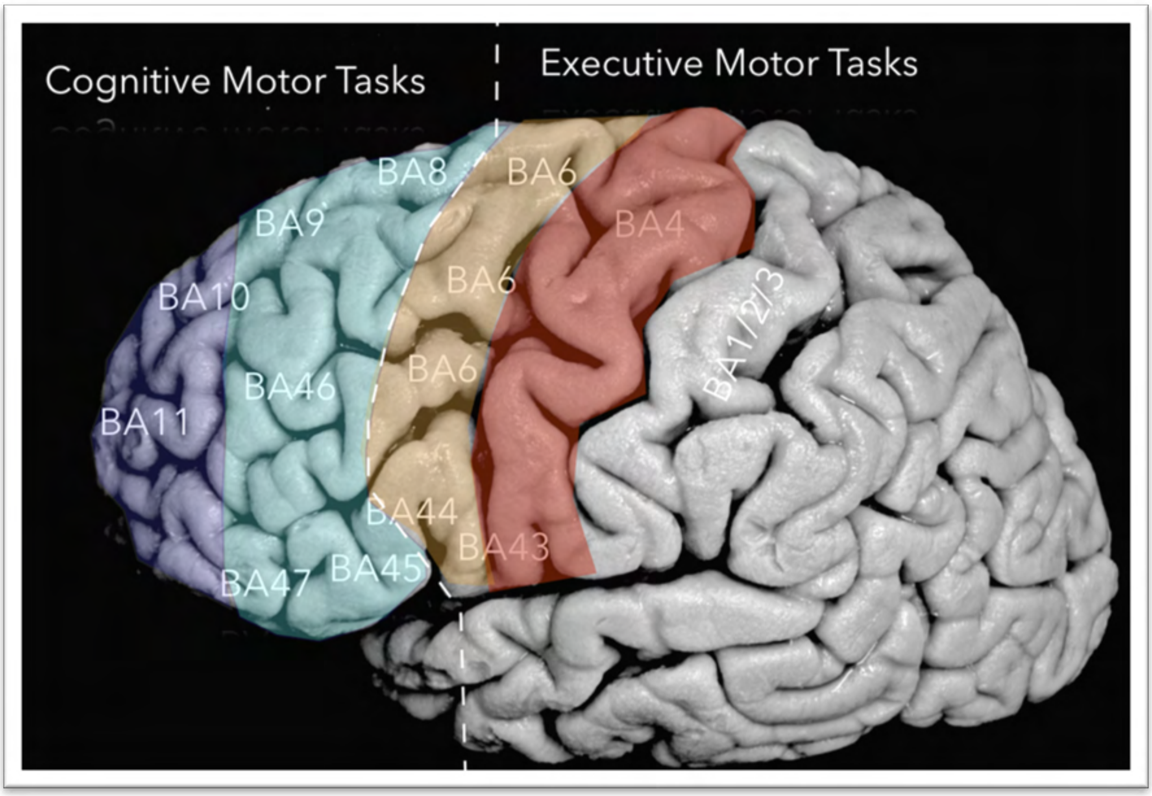
JOHN FULTON

During the following decades, many neurophysiologists with John Fulton among them, supported the notion that secondary motor areas, work hand with hand with the primary motor cortex to contribute to the programming, sequencing and fine tuning of motor actions. This idea was a cornerstone, leading to the description of the premotor and non-primary motor areas, including the Supplementary and pre-Supplementary Motor Area (SMA and pre-SMA) as well as the anterior cingulate cortex.

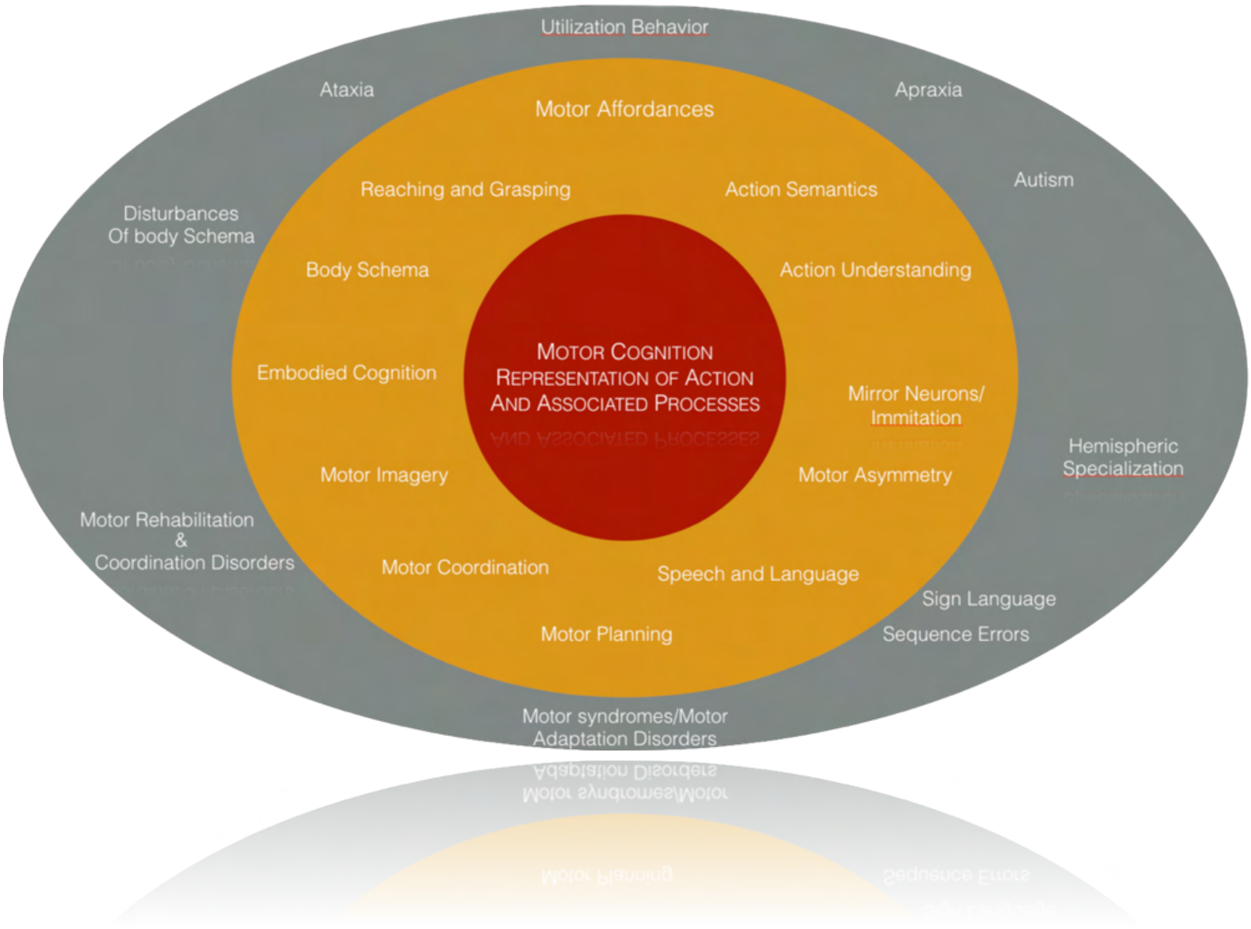
The introduction of the premotor and non-primary motor areas, paved the way towards the modern theory for the organization of the motor system in the human brain. During the 80s and 90s a number of neurophysiologists including Marc Jeannerod, postulated a novel theory: a wide network in the human brain including the parietal and prefrontal cortices as well as the basal ganglia participate in a complex network that gives birth to the so-called cognitive motor function. The latter includes processes like action understanding, action semantics, motor imagery, embodied cognition and imitation. This model surpasses the classical motor model and offers an intriguing and elaborate theory to support our current neuroanatomical and neurophysiological perception.



AREAS IMPLICATED IN COGNITIVE MOTOR FUNCTION



ALLOCATION OF FUNCTION WITHIN MOTOR/PREMOTOR/PREFRONTAL AREAS



COGNITIVE MOTOR FUNCTIONS AND ASSOCIATED CLINICAL SYNDROMES

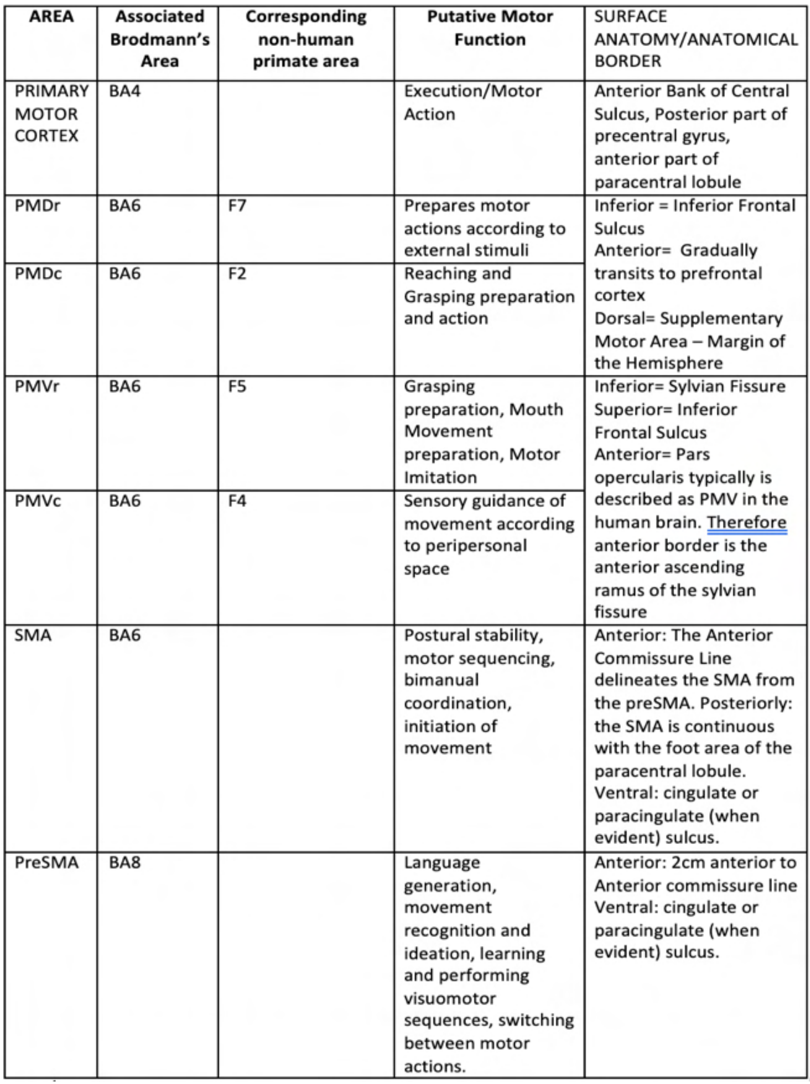
1.2 SURFACE ANATOMY OF THE MOTOR, PREMOTOR AND NON-PRIMARY MOTOR AREAS

1.2.1 ANATOMICAL DEFINITIONS AND SUPERFICIAL ANATOMICAL BORDERS BETWEEN MOTOR AND PREMOTOR AREAS.

In the human brain, the primary motor cortex is located in the anterior bank of the central sulcus as well as in the caudal part of the precentral gyrus. In cytoarchitectural terms and as described by Korbinian Brodmann, it is defined by two major characteristics. First, the presence of giant pyramidal neurons –known as Betz cells- in its fifth layer. Second, the lack of a well-defined fourth granular layer that categorizes the primary motor cortex(BA4) as a heterotypic cortex –meaning a part of the neocortex that deviates from the typical 6-layer pattern.

Along its rostral border, the primary motor cortex transits to a more granular cortex that gradually loses the population of giant Betz cells. This cortex represents Brodmann's area 6, also known as the primary motor cortex that could be perceived as a transitional area between the primary motor cortex –that is a heterotypic cortex- and the prefrontal cortex that is a typical neocortex. The premotor cortex is divided into a dorsal(PMd) and a ventral(PMv) aspect that present with functional variations. Additionally, each of these cortices is further divided into a rostral and a caudal part. Therefore, a rostral and a caudal dorsal premotor cortex(PMDr & PMDc) as well as a rostral and a caudal ventral premotor cortex(PMVr & PMVc) exist.

The non-primary motor areas, including the Supplementary Motor Area(SMA) and pre-Supplementary Motor Area(pre-SMA) – also described as mesial premotor cortex(MPMC)- are located in the medial aspect of the superior frontal gyrus and the anterior part of the paracentral lobule. They incorporate parts of Brodmann’s Areas 6&8.



AREA	Associated Brodmann’s Area	Corresponding non-human primate area	Putative Motor Function	SURFACE ANATOMY/ANATOMICAL BORDER
PRIMARY MOTOR CORTEX	BA4		Execution/Motor Action	Anterior Bank of Central Sulcus, Posterior part of precentral gyrus, anterior part of paracentral lobule
PMDr	BA6	F7	Prepares motor actions according to external stimuli	Inferior = Inferior Frontal Sulcus Anterior= Gradually transits to prefrontal cortex Dorsal= Supplementary Motor Area – Margin of the Hemisphere
PMDc	BA6	F2	Reaching and Grasping preparation and action	
PMVr	BA6	F5	Grasping preparation, Mouth Movement preparation, Motor Imitation	Inferior= Sylvian Fissure Superior= Inferior Frontal Sulcus Anterior= Pars opercularis typically is described as PMV in the human brain. Therefore anterior border is the anterior ascending ramus of the sylvian fissure
PMVc	BA6	F4	Sensory guidance of movement according to peripersonal space	
SMA	BA6		Postural stability, motor sequencing, bimanual coordination, initiation of movement	Anterior: The Anterior Commissure Line delineates the SMA from the preSMA. Posteriorly: the SMA is continuous with the foot area of the paracentral lobule. Ventral: cingulate or paracingulate (when evident) sulcus.
PreSMA	BA8		Language generation, movement recognition and ideation, learning and performing visuomotor sequences, switching between motor actions.	Anterior: 2cm anterior to Anterior commissure line Ventral: cingulate or paracingulate (when evident) sulcus.

MOTOR AND PREMOTOR AREAS - SURFACE ANATOMICAL BORDERS AND FUCNTION

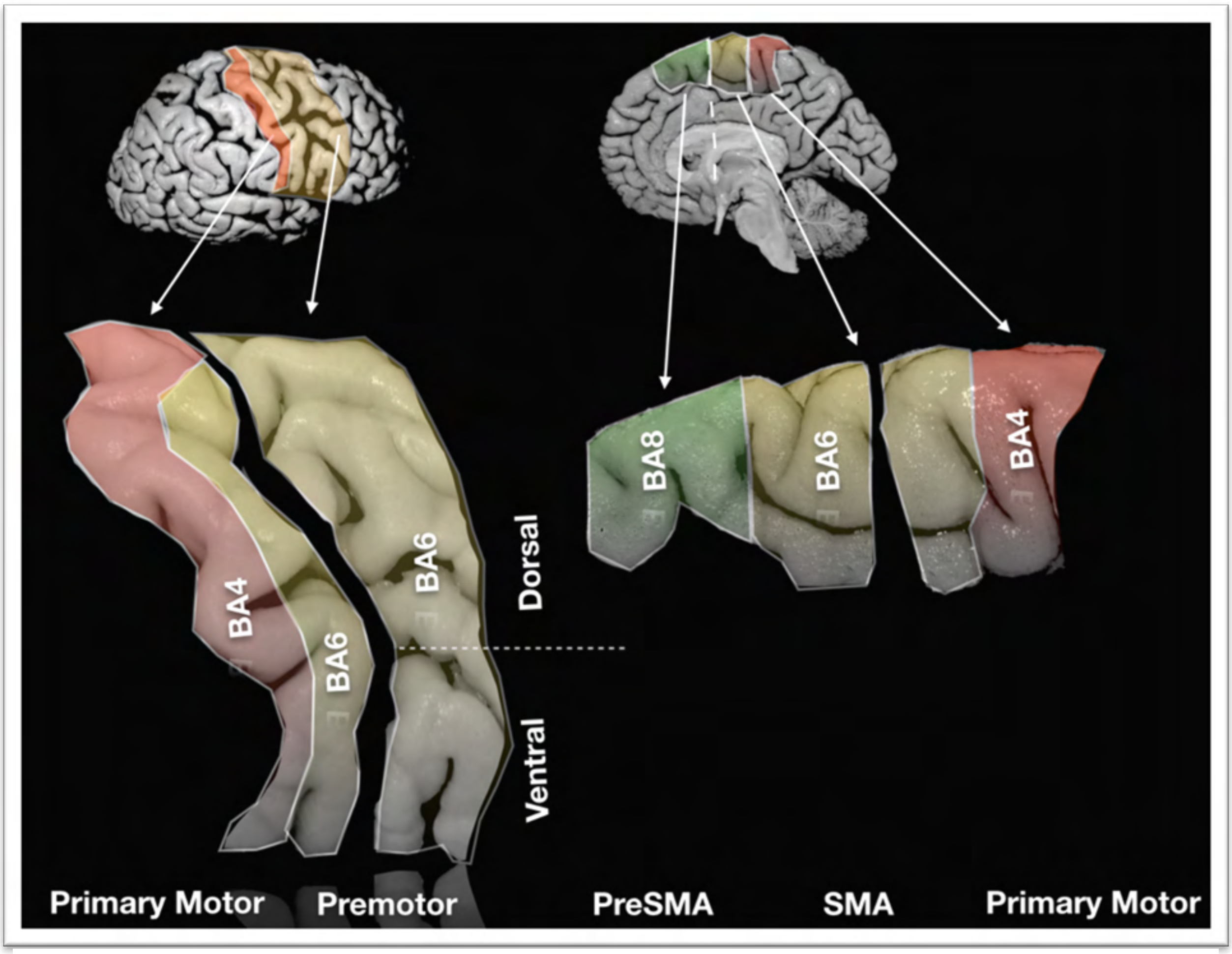


Figure.1.1. *Illustration of the surface anatomy corresponding to the primary motor, premotor and non-primary motor areas. The Primary motor cortex corresponding to Brodmann's area 4 is highlighted in red. The Premotor cortex (lateral aspect) and the Supplementary Motor Area (medial aspect) corresponding to Brodmann's area 6 is highlighted in yellow. The pre-Supplementary Motor area is highlighted in green. The border between the PMD and PMV, corresponding to the inferior frontal sulcus is illustrated with dotted line.*

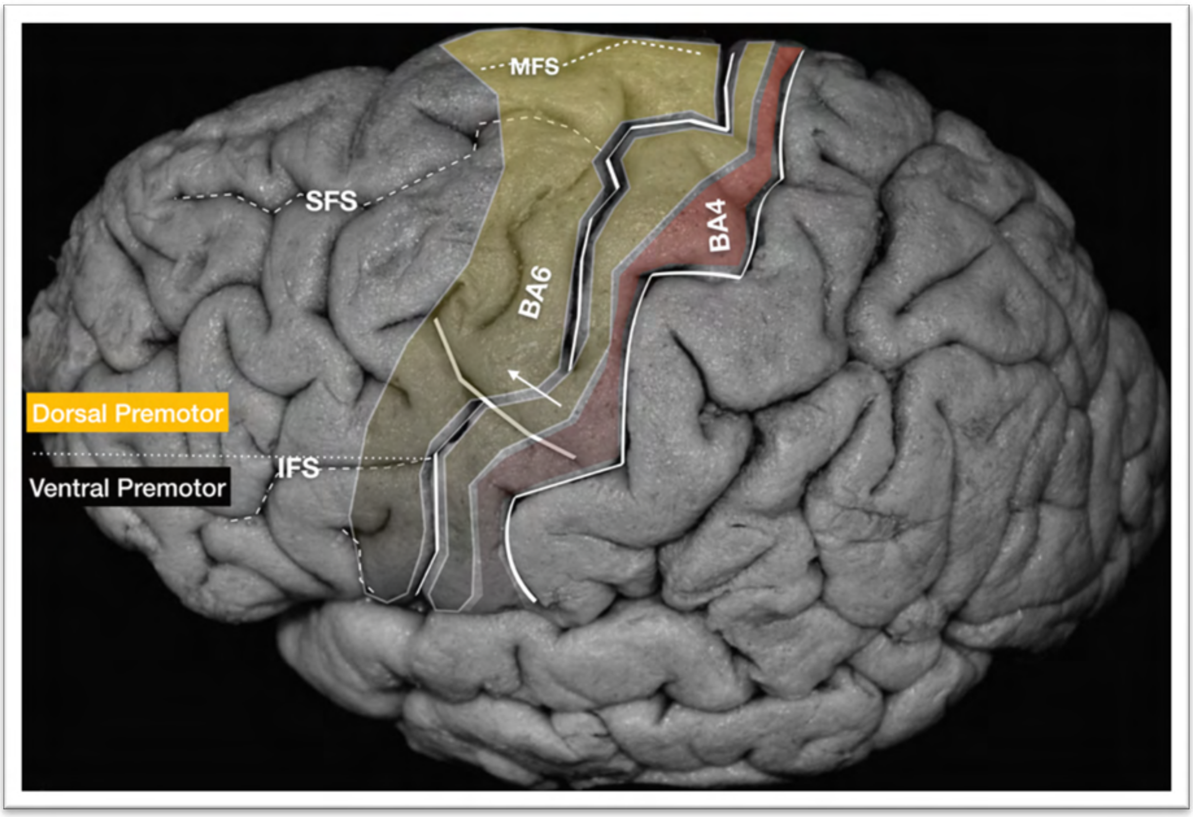


Figure 1.2*. Illustration of the superficial anatomy of the motor and premotor cortex in the lateral aspect of the hemisphere. The precentral gyrus integrates parts of the primary motor and premotor cortices (highlighted in red and yellow color respectively). The premotor cortex also occupies the posterior portion of the superior, middle and inferior frontal gyri. The line passing through the inferior frontal sulcus/precentral sulcus dissection point corresponds to the border between the ventral and dorsal premotor cortex. The central sulcus represents the posterior border of the premotor cortex. The precentral sulcus belongs is part of the premotor cortex. The Superior, Medial and Inferior Frontal Sulci course through the area of the frontal lobe that incorporates the premotor cortex. Usually 1-2 cortical bridges connect the precentral gyrus to the posterior part of the frontal gyri(arrow).*

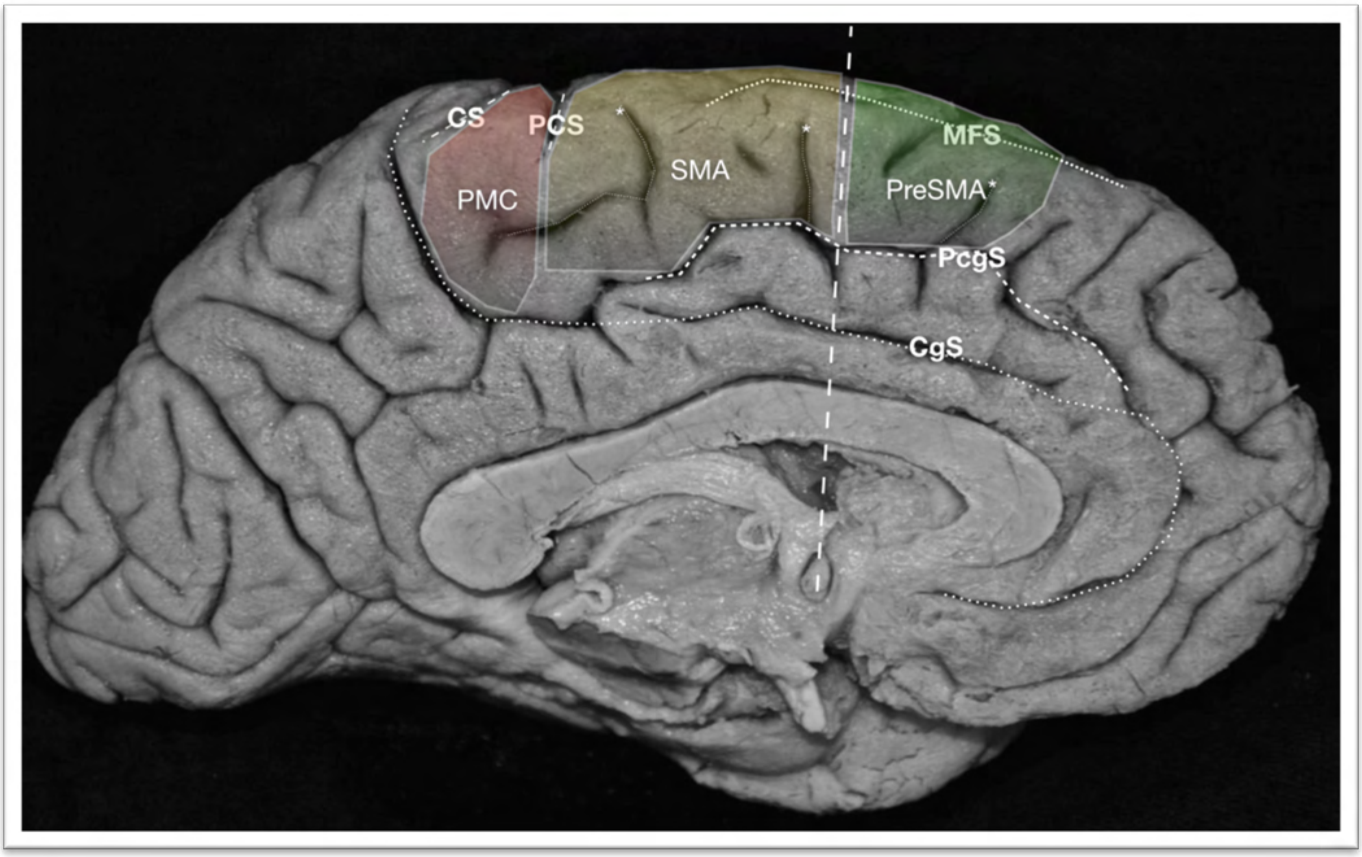


***Figure 1.3**. Medial aspect of the superficial anatomy of the motor and non-primary motor areas. The primary motor cortex is highlighted in red, the SMA is highlighted in yellow and the preSMA in green. The line passing through the anterior commissure corresponds to the transition between the SMA and preSMA. The preSMA extends 2cm anterior to this line. The cingulate or paracingulate (present in 20% of the hemispheres) sulcus, represents the ventral border of the SMA and preSMA*

1.3 INTRODUCING THE DORSAL COMPONENT OF THE SLF: A FIBER TRACT CONNECTING THE SMA & PRE-SMA TO THE PRECUNEUS AND ANTERIOR CINGULATE CORTEX

The Superior Longitudinal Fasciculus (SLF) represents a major association fiber pathway that connects frontal, parietal and temporal areas and is known to be heavily implicated in core cognitive functions such as language, attention, memory and visuospatial skills. Joseph Jules Dejerine and Augusta Dejerine-Klumpke were the first to describe this complex anatomical structure as a part of the language stream in their Atlas “Anatomie des centres Nerveux”.(1) In 1984, Petrides and Pandya introduced the concept of SLF segmentation based on autoradiography studies in non-human primates.(2) Subsequently, Makris and Pandya in 2005 published a DT-MRI study in humans, suggesting the hyper-segmentation of the SLF into four different subcomponents, namely the SLF I, SLF II, SLF III and Arcuate Fasciculus (AF).(3) The anatomical features and neuropsychological correlates of SLF II, SLF III and AF have been studied in detail through laboratory cadaveric white matter dissections, sophisticated neuroimaging techniques and intraoperative direct brain mapping protocols in awake craniotomies.(4-8)

With regard however to the SLF I, current literature derives mainly from DTI studies and lacks detailed descriptions of its topographic anatomy, morphology and architecture.(3, 5, 9-12) Indeed, the SLF I has been thus far depicted as a long association subcortical pathway connecting the superior parietal lobule and precuneus with the dorsal premotor cortex and the SMA complex. Additionally, evidence coming from laboratory white matter dissections is limited, not focused and usually incorporated in more generic studies therefore not highlighting the specific microanatomical characteristics of this fiber tract.(13-16)

Hence our objective was to address this gap by clarifying the topography, trajectory, connectivity and correlative anatomy of the SLF I through focused cadaveric microanatomic dissections. The fiber dissection technique has been proven to be a method of high anatomical accuracy, maintaining the three-dimensional coherence of the white matter tracts, and as such remains the gold standard technique for validating DTI results.(17-20) Data extracted will add on a better and more refined understanding of the brain's connectivity and its structure to function relationship.

1.4 INTRODUCING THE FRONTAL LONGITUDINAL SYSTEM: A FIBER TRACT CONNECTING THE PREMOTOR AND PREFRONTAL AREAS

The hypothesis of an underlying connection between prefrontal and motor-premotor areas has been advocated by various theories that stem from studies in humans and non-human primates. These studies support the notion that specific loci within the premotor cortex –mainly confined in the ventral and rostro-dorsal premotor cortices- are subject to higher order control from prefrontal areas.(21-24) This circuitry allegedly participates in the cognitive aspect of motor behavior such as space perception, action understanding and imitation.(25-31) However, while there is a clear anatomical background regarding the connectivity of primary motor - premotor cortices with the Supplementary Motor Area(32, 33) as well as caudal areas like the parietal, temporal and occipital cortices(6, 12, 34, 35), the structural framework of the prefrontal-premotor circuitry remains vague.

To this end, in a recent anatomo-tractographic study entitled “Short frontal lobe connections of the human brain”, Catani and colleagues identified for the first time in the literature a group of fibers residing in the prefrontal area, which they named “Frontal Longitudinal System (FLS)”.(33) The authors, by applying the fiber dissection technique in one hemisphere and further augmenting their results with tractographic data, revealed that the FLS is a superficial fiber system found to travel within the middle frontal gyrus and to consist of a superior and an inferior frontal chain, radiating up to the frontal pole and essentially resembling an anterior extension of the SLF. This novel finding has indeed offered an initial insight into the structure to function relationship between the precentral gyrus and prefrontal areas but further anatomical evidence validating current knowledge and enhancing understanding of the regional axonal connectivity is currently lacking.

Hence, the purpose of this study was to offer a focused and definitive anatomical proof for the existence, topography, correlative anatomy and connectivity of the Frontal Longitudinal System as an intrinsic frontal pathway, by implementing the Klingler’s white matter dissection technique. This method has been recently proved to be very sensitive and accurate in reflecting the cerebral fiber tract architecture and as such is being currently employed to validate structural data deriving from DTI tractographic studies. With this technique in our armamentarium we attempted to shed light on the subcortical stream sub-serving the prefrontal-premotor cross-talking in the human brain.

1.5 INTRODUCING THE FRONTOCAUDATE TRACT: A FIBER TRACT CONNECTING THE PREMOTOR AND PREFRONTAL AREAS TO THE STRIATUM

The interest on the frontostriatal connectivity is not new. In the 19th century Meynert used the term Corona Radiata of the Caudate nucleus to refer to a system of fibers connecting the frontal lobe with the caudate nucleus in the human brain.(36) Six years later (1893) Muratoff was able to trace a homologous bundle in the canine brain.(37) This time the term subcallosal fasciculus was coined. During the mid-20th century Yakovlev and Locke indicated similar connections between the prefrontal cortex and the caudate nucleus in primates.(38)

Nevertheless, it was not until the late 20th century that significant progress towards a more thorough understanding of the cortico-striatal connectivity was made. The seminal animal studies by Alexander, Crutcher and Webster offered valuable insights into the fundamental principles regulating the functional and structural interconnection between the frontal cortex and the striatum.(39, 40) The presence of a direct and an indirect pathway was advocated, supporting the theory that the corticostriatal circuit should be parcellated into sub-components according to anatomy and function. Indeed, Alexander was able to trace different fronto-striatal loops mediating motor, cognitive and behavioral processes. This theory of a “parallel functional architecture” remains a cornerstone in the perception of basal ganglia anatomy and function to this day.(41)

The interest on the structure to function relationship of the frontostriatal pathways has been revived during the last decades, as various clinical entities ranging from behavioral and psychiatric conditions to movement disorders have been attributed to alterations in the white matter integrity of this subcortical network.(42-47) In this context, understanding the anatomy of the corticostriatal connections in the human brain could be valuable in designing novel treatment strategies for various pathologies. Nevertheless, it is an arduous and challenging process, since the basic techniques implemented in the study of animal brain cannot be applied in humans. Due to this fact, most of the available data on the human fronto-striatal connectivity derives from DTI studies. Yet, the various DWI protocols, although fast and in vivo, present with serious inherent limitations as proven by relevant studies.(18)

Therefore, the amount and quality of direct structural evidence on the anatomy and connectivity of the fronto-striatal pathways is limited. Adding to this point, two further issues arise. First, the terminology used for the fronto-caudate or other fronto-striatal tracts is inconsistent throughout the literature and second the FCT's intrinsic anatomy has been addressed by very few studies. With this in mind we opted to investigate the topography, morphology, connectional anatomy and asymmetry of the fronto-caudate tract. We used fiber dissections since they provide direct anatomical evidence of high sensitivity and are used to validate conflicting DTI results.(18, 48) To the best of our knowledge this is the first focused anatomical study in the English literature addressing this issue.

1.6 INTRODUCING THE CORTICOTEGMENTAL TRACT: AN EXTRAPYRAMIDAL FIBER SYSTEM CONNECTING THE PREMOTOR AND PREFRONTAL AREAS TO THE TEGMENTUM

The word “tegmentum”, derives from the Latin verb “tegere”, which means “to cover”. This term was adopted by early neuroanatomists to describe the part of the midbrain that extends dorsal and therefore “covers” the crus cerebri i.e. the mesencephalic structure that consists of corticospinal and corticobulbar pyramidal fibers. The pivotal topography of the tegmentum-lying between the forebrain and brainstem- underlies its crucial role as a gateway for the non-pyramidal motor routes and the ascending sensory pathways.

The term “extrapyramidal motor system” coined by Johann Prus in 1898, is used to describe a basic and integral component of the human motor network primarily formed by corticofugal fibers that travel through the tegmental area, as opposed to the ventrally allocated pyramidal tracts.(49) The very anatomical organization and functional parcellation of the human extrapyramidal system has attracted interest for over a century. In this vein, Probst, Hoche and Dejerine were among the first to study the extrapyramidal system and succeeded in demonstrating through the Marchi technique the existence of fibers stemming from the frontal area and projecting towards the mesencephalic reticular formation.(50) In a step further and during the second half of the 20th century, cortico-rubro-spinal and cortico-rubro-cerebellar fibers have also been identified as extrapyramidal pathways by a number of studies.(51-55) More recently, the presence of cortico-mesencephalic and cortico-tectal tracts has been well documented in animal studies but has not been as yet demonstrated in the human brain.(56, 57)

In the modern neuroscientific era, the advent of DWI based tractography has indeed blazed new trails in our endeavor to verge towards a more refined understanding of the human connectome. It has further paved the way to combine this fast, in vivo but indirect technique of virtual fiber dissection with the more traditional, direct method of blunt white matter anatomical dissection, with the aim to improve the sensitivity and specificity of data acquisition. However, and in contrast to the thoroughly investigated pyramidal fibers of the corticospinal and corticobulbar tracts, the relevant literature on the intra-hemispheric topography of the descending extrapyramidal fibers within the white matter of the cerebral hemisphere is scarce. With this in mind, we strived to investigate and record the system of fibers that mainly stem from the fronto-parietal cortex and travel within the internal capsule before blending into the tegmental area. The term “Cortico-tegmental Tract” (CTT) is collectively used to include all the fiber pathways that meet these topographic prerequisites and hence stands as an anatomical equivalent of the descending extrapyramidal pathways.

We intentionally opted to use the white matter fiber micro-dissection technique as our stand-alone method of investigation since it has been proven to extrapolate safe results on the anatomy and connectivity of poorly-understood white matter pathways and because it allows for the comprehension and conceptualization of the three-dimensional anatomy in contrast to the two-dimensional perception offered by both histopathological and tractographic studies. While the inherent perplexity of the cortico-tegmental network is given, our overreaching goal is to offer a solid macro-anatomical overview of the cortico-tegmental fiber system for theoretical and clinical use. To our knowledge this is the first white matter dissection study in the relevant literature to focus on the intricate anatomy of the cortico-tegmental pathway as a prominent component within the human extrapyramidal system.

CHAPTER 2: MATERIALS & METHODS

2.1 MATERIALS AND METHODS: GENERAL CONSIDERATIONS

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

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

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

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

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

2.2 DISSECTION TECHNIQUE: DORSAL COMPONENT OF THE SUPERIOR LONGITUDINAL FASCICULUS

After carefully removing the arachnoid membrane and vessels, all hemispheres underwent the Klingler's procedure and were subsequently dissected using the white matter fiber micro-dissection technique.(7, 58)

Given that the SLF I is located in the medial aspect of the hemisphere, we performed medial to lateral fiber dissections, starting from the area of the anterior cingulate cortex and extending posteriorly towards the area of the precuneus, with the parieto-occipital sulcus delineating the posterior limit of our dissections.

Prior to the dissection process, the surface anatomy of the medial cerebral surface was recorded in detail. The cingulate sulcus marked the superior limit of the cingulate gyrus and therefore proved to be a useful superficial landmark that delineated the subcortical boundaries of the superior arm of the cingulum. Special attention was paid to the medial aspect of the superior frontal gyrus as well as to the paracingulate sulcus and gyrus -when present- since the fibers representing what has been described as the SLF I are usually encountered just under the superficial U fibers of this area and therefore can be easily disrupted. In 33% of the studied hemispheres we proceeded with a multi-layered dissection in which a part of the lateral aspect of the frontal lobe and frontoparietal operculum was included in order to understand and demonstrate the correlative anatomy of the SLF I, SLF II and SLF III. It has to be stressed that the medial aspect of the superior frontal gyrus represents a complex area where several subcortical pathways originating from the cingulate gyrus, the SMA complex and paracentral lobule converge, thus rendering the preservation of the structural white matter integrity particularly difficult.

2.3 DISSECTION TECHNIQUE: FRONTAL LONGITUDINAL SYSTEM

Prior to dissection, the most prominent superficial landmarks including the premotor gyrus, the superior, middle and inferior frontal gyri, the precentral, superior, inferior and middle frontal sulci as well as the pars opercularis, pars orbitalis and pars triangularis were identified.

The FLS complex has been recorded by previous studies to reside in the area anterior to the precentral gyrus and to run parallel to the superior and inferior frontal sulci.(33) Therefore, stepwise lateral to medial dissections were employed in all hemispheres. Starting from the frontal lobe, the dissection process gradually extended in the entire fronto-parietal lateral surface with the aim to demonstrate the relationship between the fibers belonging to the SLF and FLS complexes. During the initial steps of the procedure the cortex of areas that represent the anatomical equivalent of the motor and premotor areas(59, 60) i.e. the primary motor (BA *4)*, ventral and dorsal premotor areas (BA 6 and 44), has been spared in order to offer a better perspective of the trajectory and termination pattern of the FLS. In 5 hemispheres, the dissection proceeded up to the level of the Frontal Aslant Tract (FAT) in order to offer a better understanding of the topographic and correlative anatomy of the FLS fibers with regard to the deeper frontal fiber white matter pathways.

2.4 DISSECTION TECHNIQUE: FRONTOCAUDATE FIBERS

Prior to dissection, the surface anatomy of the frontal area was recorded. Focused latero-medial and medio-lateral dissections on the prefrontal/premotor areas were employed in a tandem manner in all specimens to map the fronto-caudate tract and illustrate its spatial relationship with adjacent bundles such as the Frontal Aslant Tract (FAT), anterior limb of the internal capsule (ALIC), anterior thalamic radiations (ATR), corpus callosum (CC) and callosal radiations (CRad). Since most of these tracts converge tightly towards the central core, we were very diligent in differentiating them by mapping and recording their respective trajectory and termination pattern. To elucidate these crucial details, during the final steps of the dissection we detached the central core from the rest of the hemisphere to clearly delineate the different fiber layers and their exact termination areas on the thalamus and caudate nucleus. In five (5) hemispheres, the fibers of the FCT along with their termination zone on the head and body of the caudate nucleus were dissected free from the rest of the hemisphere to illustrate the intrinsic morphology of the tract.

2.5 DISSECTION TECHNIQUE: CORTICOTEGMENTAL FIBERS

Prior to the dissection process the brainstem was dissected at the level of the superior colliculi and was studied later on, separately from the rest of the specimen. At this axial level, the “tegmental entry zone (TEZ)” was defined as the area of entrance of the CTT fibers in the tegmentum.

Given the spatial distribution of the corticotegmental fibers described by previous DTI studies, medial to lateral dissections were initially carried out in all specimens. The dissections followed a meticulous stepwise manner with special attention paid to the structures adjacent to the central core and superior aspect of the tegmentum. During the medial to lateral dissections, the spatial relationship of the cortico-tegmental fibers to the thalamus, caudate nucleus, callosal radiations, anterior thalamic peduncle (ATR) and frontocaudate tract (FCT) was recorded.

Upon completion of the medial to lateral process, all specimens were subsequently dissected in a lateral to medial fashion with the aim to study and record the spatial relationship of the CCT to the Superior Longitudinal Fasciculus (SLF), lentiform nucleus (LN), Internal Capsule(IC) and Corticospinal Tract (CST). In all specimens, the termination pattern of the CTT was carefully traced in the fronto-parietal area and the respective Brodmann’s areas were recorded. In addition, the topography of the corticotegmental fibers was recorded in the TEZ according to their cortical origin.

At the last steps of the procedure, the CTT and CST were progressively dissected free from the rest of the hemisphere and differentiated from each other with the purpose of juxtaposing the pyramidal and extrapyramidal fiber topography and trajectory. In 5 hemispheres, the diencephalic and mesencephalic structures were also dissected free from the specimen to study and illustrate the ventral allocation of the CTT fibers and their relationship with the thalamic, hypothalamic and mesencephalic structures.

At the end of the procedure, the brainstem that was initially removed from the hemisphere at the level of the superior colliculus, was dissected in a lateral to medial fashion and under high-magnification. The fibers of this region were categorized into consecutive layers, starting from superficial to deep, and were subsequently superimposed on the tegmental entry zone.

CHAPTER 3: RESULTS

3.1 RESULTS: SUPERFICIAL ANATOMY

3.1.1 ANATOMY OF THE CENTRAL SULCUS

The depth of the central sulcus represents the posterior border of the primary motor cortex and the border between the latter and the somatosensory cortex. The anatomy of the central sulcus was studied in all studied specimens. The Central or Rolandic Sulcus can be observed as an uninterrupted sulcus with a mean depth of 1.3cm, running from the medial aspect of the hemisphere (paracentral lobule) to the rolandic operculum, a small cortical bridge connecting the precentral to the postcentral gyrus. In 100% of the hemispheres the Central sulcus did not reach the Sylvian Fissure thus creating the aforementioned cortical bridge. The Central Sulcus appears with a number of 4 to 5 turns representing a change of direction and therefore has 5-6 segments with interchanging directions. The superior segment always follows a posterosuperior to anteroinferior direction while the inferior a superoanterior to posteroinferior direction. The central sulcus gives rise to 2-4 small branches rising towards the precentral or postcentral gyrus. Additionally, it connects anteriorly to the area of the posterior frontal lobe throught 1-2 folds that interrupt the precentral gyrus.

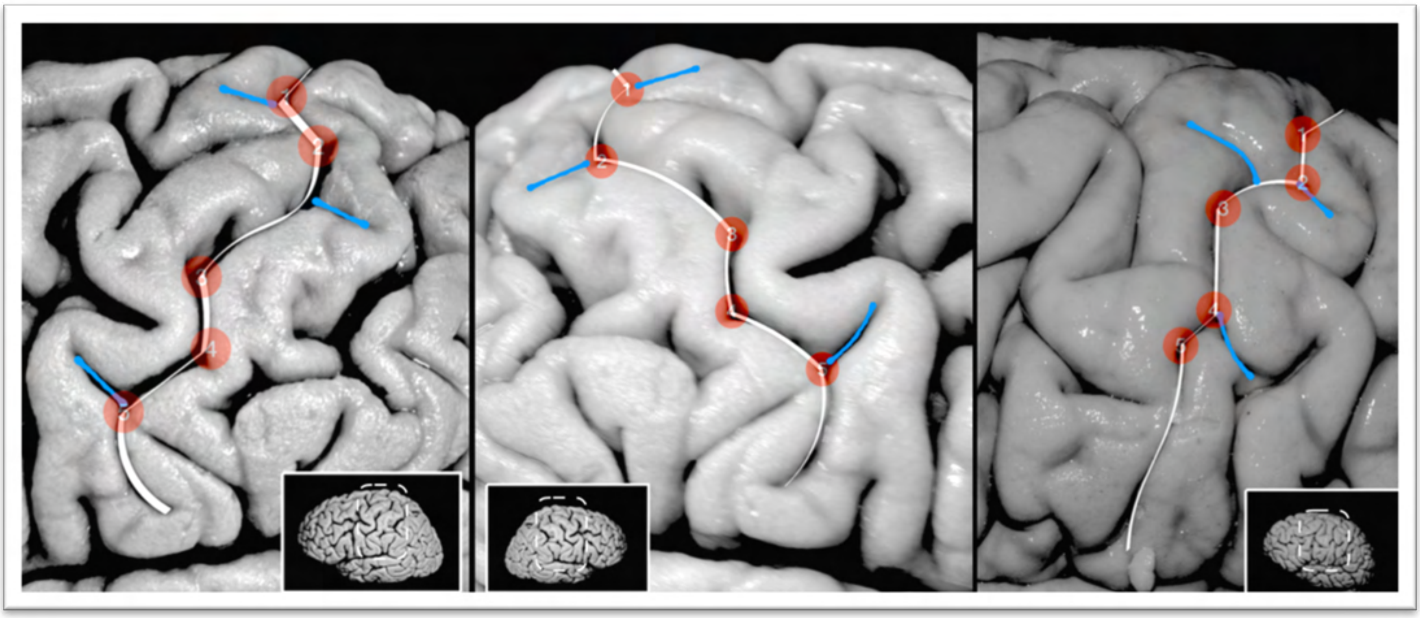
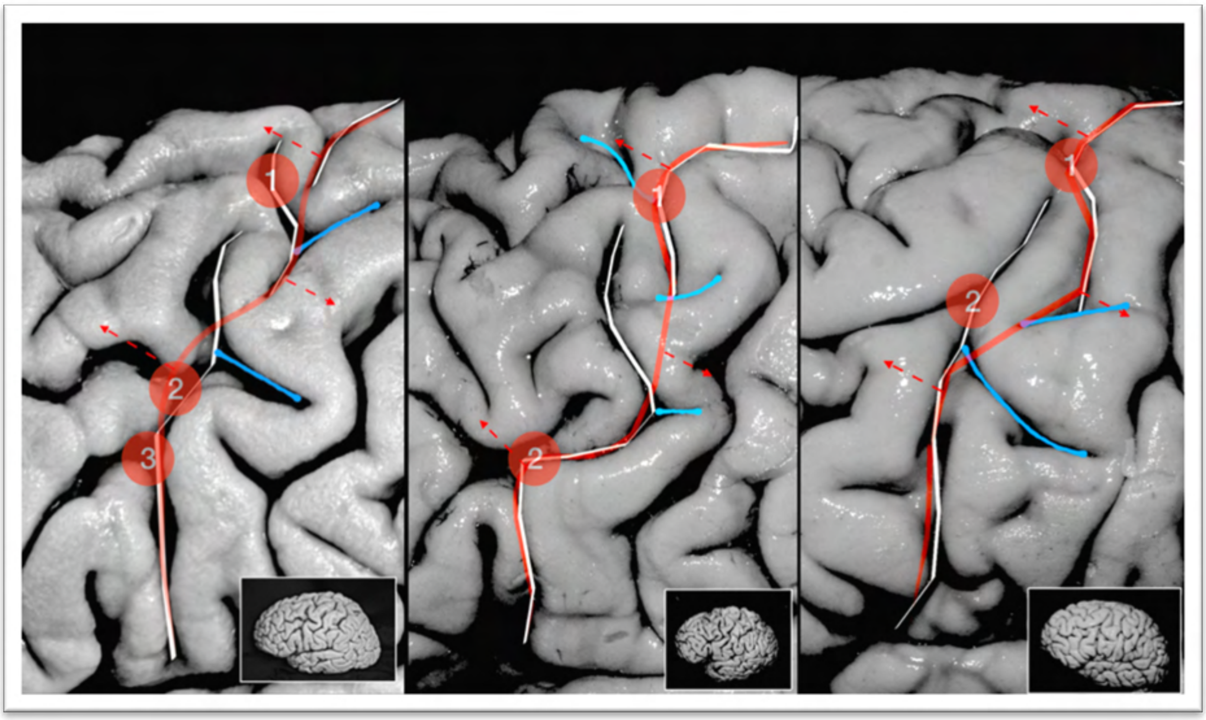


Figure 3.1. Superficial anatomy of the central sulcus. The central sulcus appears with a number of 4-5 points representing a change of direction and therefore 4-5 knees. Two to four branches rise from the central sulcus following a rostral or caudal direction towards the precentral or postcentral gyrus.

3.1.2 ANATOMY OF THE PRECENTRAL SULCUS

The precentral sulcus appears as an interrupted sulcus with a mean depth of 0.8cm. The sulcus usually consists of an inferior segment with a bifid superior ending and a superior segment that is typically intersected by the superior frontal sulcus. A third segment can be observed in 20% of the specimens above the latter as a single small sulcus. By connecting the segments of the precentral sulcus, a continuous silhouette with three knees emerges: a superior and an inferior knee with an anterior convexity and a middle knee with a posterior convexity. A number of 2-4 branches usually rises from the precentral sulcus running towards the precentral gyrus or the posterior part of the superior, middle or inferior frontal gyrus. The precentral sulcus terminates towards the pars opercularis in 100% of the specimens. A number of 2-3 cortical folds connect the precentral gyrus to the posterior part of the frontal lobe.

Figure 3.2. *Superficial anatomy of the precentral sulcus. The precentral sulcus appears as an interrupted sulcus consisting of 2-3 sulci. The silhouette of the precentral sulcus has 3 knees. A superior and an inferior with an anterior convexity and a middle with a posterior convexity. There are 2-3 folds transversing the precentral sulcus and therefore connecting the precentral gyrus to the posterior frontal cortex.*



3.1.3 ANATOMY OF THE PRECENTRAL GYRUS

The precentral gyrus corresponds to part of the primary motor as well as the premotor cortex. It is posteriorly delineated by the central sulcus of Rolando and anteriorly by the precentral sulcus. It is transversed by 3-5 branches of the precentral or central sulcus. In 90% of the specimens an anterior subcentral sulcus divides the inferior portion of the precentral sulcus into two parts. The precentral sulcus connects to the postcentral sulcus through a bridge running below the inferior end of the central sulcus (Broca's inferior pli-de-passage) and to the posterior frontal area through 2-4 bridges that interrupt the precentral sulcus.

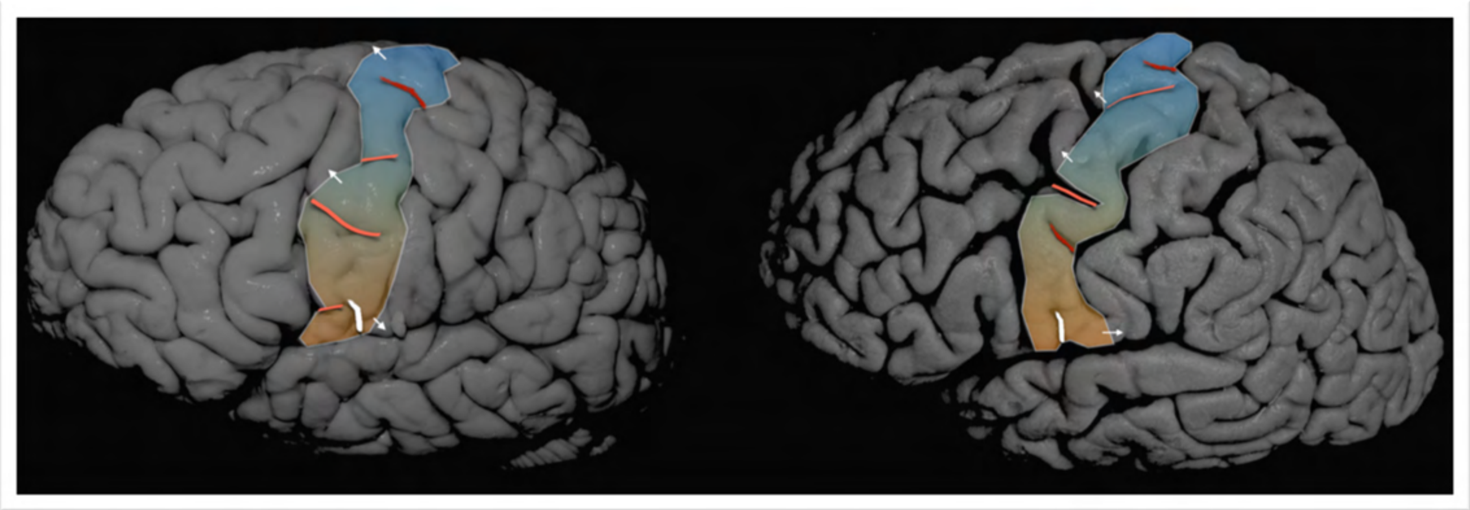


Figure 3.3. *Superficial anatomy and morphology of the precentral gyrus.*

3.1.4 ANATOMY OF THE POSTERIOR FRONTAL AREA

The posterior frontal area, harboring the premotor cortex, is characterized by the presence of the posterior ending of the superior frontal and inferior frontal sulci. Both these sulci intersect the precentral sulcus. The inferior frontal sulcus intersects the precentral sulcus in a point usually found 2-5cm (mean 2.4cm) above the sylvian fissure. In 60% of the hemispheres a middle frontal sulcus can be found running parallel to the superior and inferior frontal sulci. This sulcus intersects the precentral sulcus in 20% of the specimens. A medial frontal sulcus can also be found running within the superior frontal gyrus in 80% of the specimens. This sulcus intersects the superior segment of the precentral sulcus in 10% of the specimens.

3.1.5 ANATOMY OF THE MEDIAL FRONTAL GYRUS AND PARACENTRAL LOBULE

The paracentral lobule represents the medial continuation of the precentral and postcentral gyri as well as the posterior part of the medial frontal gyrus. It is posteriorly delineated by the marginal ramus of the cingulate sulcus and inferiorly by the cingulate sulcus. In 20% of the specimens a paracingulate sulcus running parallel to the latter courses within the paracentral lobule, thus creating an additional gyrus within the latter: the paracingulate gyrus. A number of 2-5 sulci that are either independent or branch from the cingulate or paracingulate sulcus can be often observed in the paracentral lobule and the posterior third of the medial frontal gyrus. The medial continuation of the central sulcus can be observed running for a length of 0.8-1.5cm within the paracentral lobule with an orientation of 45° to the sagittal plane. In this area, the primary motor cortex is delineated from the SMA by the medial continuation of the precentral sulcus while the SMA is delineated from the preSMA by the imaginary line running through the anterior commissure.

3.2 RESULTS: SLF I

3.2.1 SURFACE ANATOMY

The basic and well-known morphological characteristics of the medial part of the superior frontal gyrus, paracentral lobule and precuneus were verified during our study. The anatomical organization, however, of the area adjacent to the anterior cingulate gyrus received special attention due to its apparent variability. Interestingly, we observed that in 80% of the hemispheres included, the anterior cingulate sulcus exhibited a close anatomical proximity to a prominent sulcus known as the paracingulate sulcus.(61-63) This sulcus was found to lie superiorly -at a mean distance of 6mm (range 4-7m) - and parallel with regard to the cingulate sulcus. When present, the paracingulate sulcus delineates inferiorly a gyrus that curves around the anterior part of the cingulate cortex, known as the paracingulate gyrus. The paracingulate gyrus practically divides the medial frontal gyrus from the cingulate gyrus.

3.2.2 MICROANATOMIC DISSECTION

We performed stepwise dissections, starting from the area of the anterior cingulate sulcus and moving posteriorly towards the marginal ramus. After removing the cortical grey matter, the U-fibers of the medial aspect of the hemisphere become apparent. These U-fibers interconnect adjacent gyri and represent the most superficial layer of the white matter encountered. At this point, we placed special attention to the proper and careful dissection of the U-fibers that radiate from the area of the anterior part of the cingulum and curve under the cingulate sulcus towards the area of the paracingulate or medial frontal gyrus. In 20% of the studied specimens where the paracingulate sulcus was not evident, removing these U fibers revealed a longitudinal group of axons running deep to the plane of the cingulate sulcus and dorsal to the superior arm of the cingulum. These fibers correspond to the anterior part of the SLF-I. In the remaining 80% of the hemispheres, this tract was found just under the superficial U-fibers of the paracingulate area, with the paracingulate sulcus and gyrus actually demarcating the silhouette of the anterior part of the SLF-I. Therefore, in all specimens studied, the anterior part of the SLF-I was recorded to lie in a slight supracingulate plane within the white matter of the cingulate or paracingulate gyrus. Attention should be placed on the fact that because the axons of the SLF-I and the overlying U-fibers that radiate from the cingulum, run in overlapping but perpendicular directions, it is easy to remove the fibers of the SLF-I along with the u-fibers of the cingulum. This is, allegedly, the main pitfall for not preserving the SLF-I fibers during standard medial to lateral dissections. In addition, while removing the U fibers that run superior to the plane of the SLF- I, it is important to recognize and preserve the regional cortical terminations. To this end, we observed the anterior portion of the SLF-I to receive a number of fibers originating from the anterior cingulate cortex(BA32), the medial part of the superior frontal gyrus (BA8 and 9), the pre-SMA, SMA proper(BA6) and paracentral lobule(BA1,2,3,4). These fibers converge in an almost perpendicular manner to the SLF-I and form a number of knots that, in our sample, varied from 2 to 4.

During the next dissection stage, we removed the remaining U fibers of the posterior part of the medial aspect of each hemisphere up until the marginal ramus of the cingulate sulcus. At the level of the anterior paracentral lobule, the fibers of the SLF-I were consistently recorded to course in an almost tangential line to the cingulum, following a slight dorsal and lateral trajectory. Due to this tight anatomical proximity, it becomes unclear whether fibers of the SLF-I intermingle with the cingulum. Following the SLF fibers posteriorly, we identified their cortical termination at the area of the anterior precuneus.

3.2.3 MORPHOLOGY AND CONNECTIVITY OF THE SLF I

In our sample, the SLF-I had a mean length of 107mm (range 100-115mm) and was invariably recorded to travel just under the U fibers of the paracingulate or cingulate gyrus, exhibiting an "S-shaped" configuration with two prominent bends: an anterior bend facing upwards and a posterior one facing downwards. These curves represent two distinct segments of the SLF-I: an anterior segment (SLF-Ia) and a posterior segment (SLF-Ip), with the point of their transition lying approximately at the level of the anterior paracentral lobule.

The anterior segment of the SLF-I was always seen to course within the paracingulate gyrus, when this gyrus is present, or within the anterior part of the cingulate gyrus and deep to the cingulate sulcus in any other instance. The mean length of this segment was 45mm (range 43-47mm), while its mean distance from the superior arm of the cingulum was 6mm (range 5-8mm). The SLF-Ia is characterized by the presence of 2-4 knots that represent the fibers terminating at the area of the, medial part of the superior frontal gyrus (BA8 and 9) pre-SMA and SMA proper(medial aspect of BA6), precentral(BA 4) and post-central (BA1,2,3) area. The terminations to the pre-SMA and SMA proper area were invariably present (100% of the studied hemispheres). The terminations towards the medial paracentral lobule (1-2 groups of fibers) where evident in 53% of the hemispheres. In 27% of hemispheres the SLF-Ia terminated towards the medial aspect of BA8(Frontal Eye Fields) and BA9(Medial Prefrontal Cortex). Finally in 40% of the specimens the stem of the SLF-I terminated in the area of the anterior cingulate cortex(BA 32).

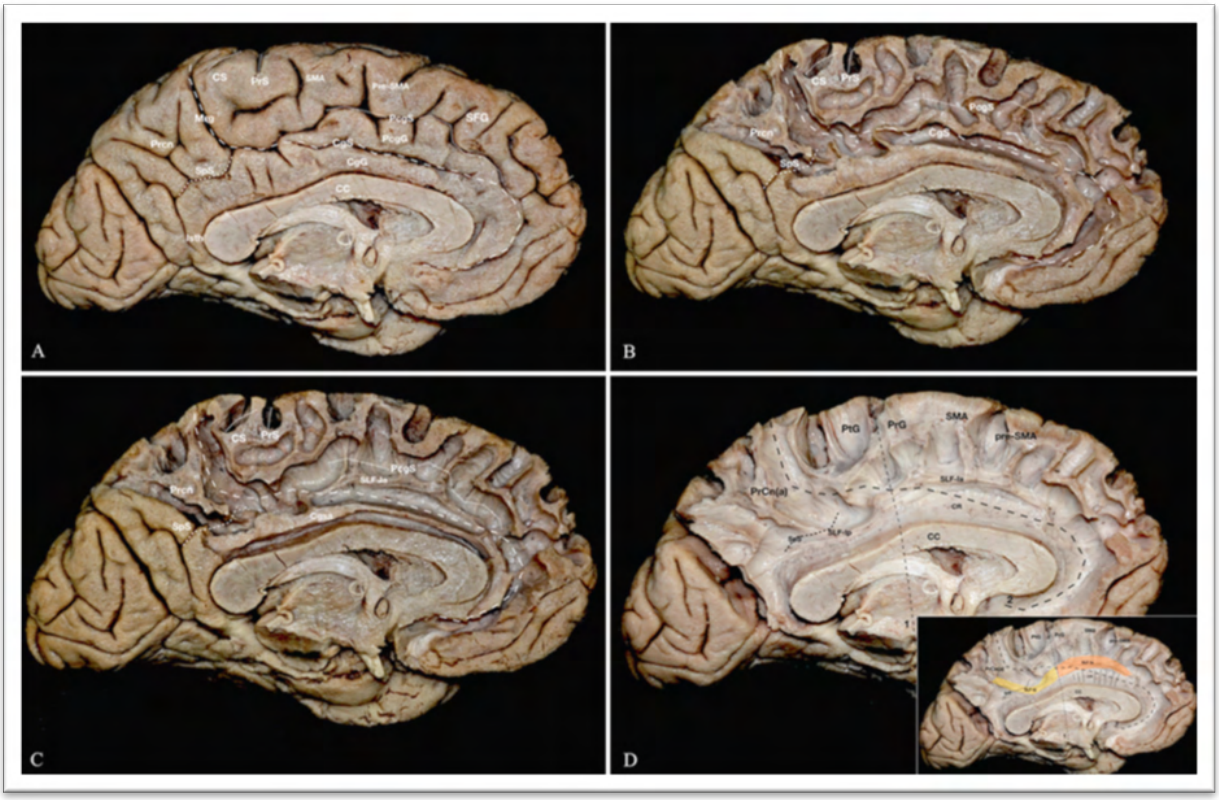


Figure.3.4. Progressive dissection of a left hemisphere illustrating the structural architecture of the SLF-I. (A): The medial surface anatomy is depicted. Note the presence of the paracingulate gyrus and sulcus. (B): the superficial U-fibers are shown after removing the grey matter. The silhouette of the main sulci is marked for better orientation (C): The superficial U-fibers at the area of the paracingulate gyrus are removed revealing a group of longitudinal axons that correspond to the anterior segment of the SLF-I. These fibers lie dorsal to the level of the cingulate sulcus. The superior arm of the cingulum is seen to run parallel to these fibers and inferior to the level of the cingulate sulcus. (D): Progressive dissection reveals the silhouette and terminations of the SLF-I. The two segments of the SLF-I are illustrated with the point of their transition to lie approximately at the level of the anterior paracentral lobule. The anterior segment (SLF-Ia) gives axons to the anterior cingulate cortex, pre-SMA, SMA proper and precentral gyrus while the posterior segment (SLF-Ip) terminates to the postcentral gyrus and precuneus (especially its anterior part). The SLF-Ip crosses the depth of the subparietal sulcus before arching towards the precuneus. (Inset): The SLF is highlighted using orange and yellow color for the anterior and posterior segment respectively. 1= Imaginary line bisecting the paracentral lobule, 2= Cingulate Sulcus, CC= Corpus Callosum, CgG= Cingulate Gyrus, Cgs= Cingulate Sulcus, Cgsa= Cingulum Superior Arm, CR= Callosal Radiations, CS= Central Sulcus, Mrg= Marginal ramus of the cingulate sulcus, PcgG= Paracingulate gyrus, PcgS= Paracingulate sulcus, Prcn= Precuneus, PrCn(a)= Anterior Precuneus, Pre-SMA= Pre-Supplementary Motor Area, PrG= Precentral Gyrus, PrS= Precentral Sulcus, PtG= Postcentral Gyrus, SFG= Superior Frontal Gyrus, SLF-Ia= Superior Longitudinal Fasciculus I – anterior

segment, SLF-Ip= Superior Longitudinal Fasciculus I – posterior segment, SMA= Supplementary Motor Area, SpS= Subparietal sulcus. Reprinted from Komaitis et al by permission of the JNS Publishing Group

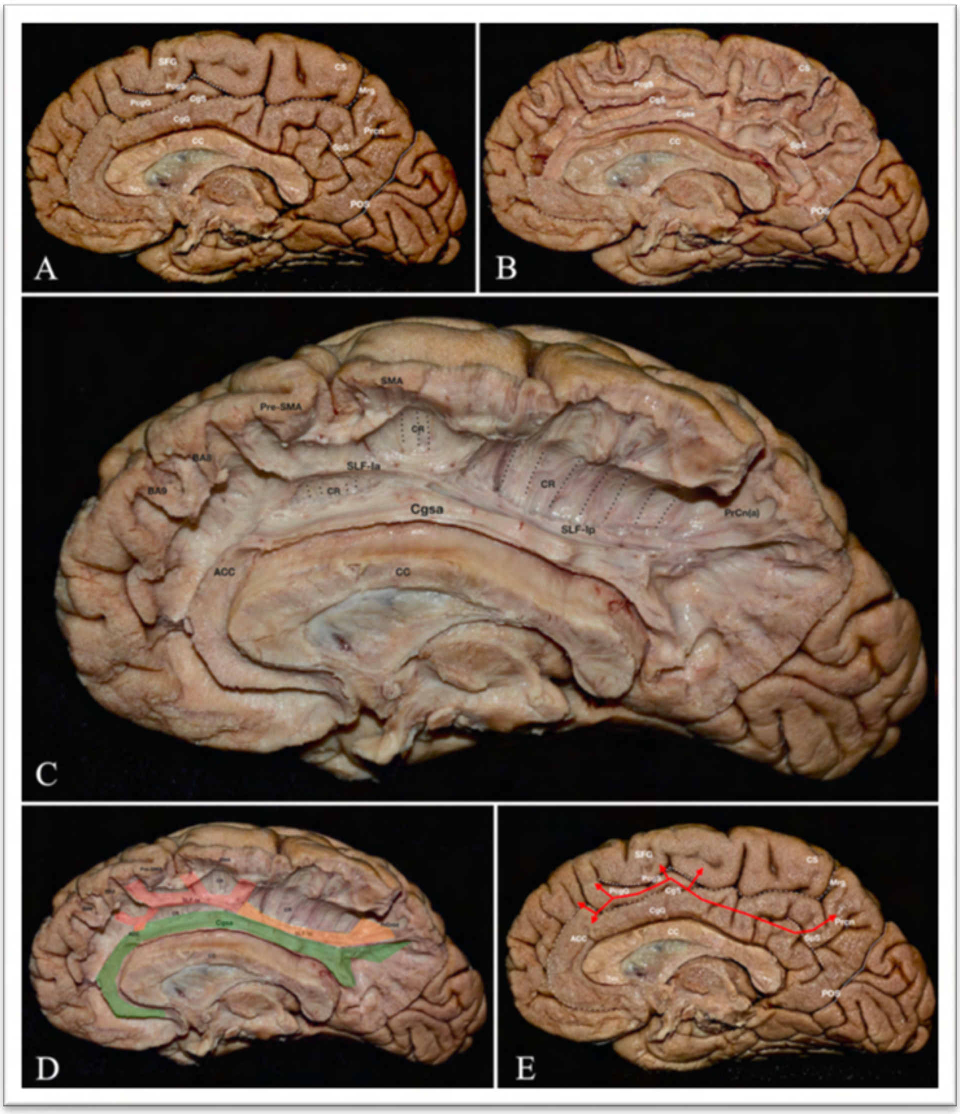


Figure 3.5. Progressive dissection of a right cerebral hemisphere, illustrating the SLF-I and its correlative anatomy to the superior arm of the cingulum. (A): The surface anatomy of the medial cerebral aspect is depicted (B): Grey matter is removed revealing the superficial U-fibers of the medial surface. The silhouette of the main sulci is marked for proper orientation. (C): Dissecting the u-fibers reveals the SLF-I and cingulum, running parallel to each other anteriorly and in a tangential line posteriorly. The fibers of the posterior segment of the SLF-I travel in a lateral and superior trajectory to those of the superior arm of the cingulum and terminate in the area of the anterior precuneus. (D): In order to illustrate the correlative anatomy, the cingulum is highlighted in green colour, the anterior segment of the SLF-I in red and the posterior segment of the SLF-I in orange. (E): Trajectory and terminations of the SLF-I superimposed to the superficial anatomy. ACC= Anterior Cingulate Cortex, BA= Brodmann Area, CC= Corpus Callosum, CgG= Cingulate Gyrus, Cgs= Cingulate Sulcus, Cgsa= Cingulum Superior Arm, CR= Callosal Radiations, CS= Central Sulcus, Mrg= Marginal

ramus of the cingulate sulcus, PcgG= Paracingulate gyrus, PcgS= Paracingulate sulcus, POS= Parieto-occipital sulcus, Prcn= Precuneus, PrCn(a)= Anterior Precuneus, Pre- SMA= Pre-Supplementary Motor Area, SFG= Superior Frontal Gyrus, SLF-Ia= Superior Longitudinal Fasciculus I – anterior segment, SLF- Ip= Superior Longitudinal Fasciculus I – posterior segment, SMA= Supplementary Motor Area, SpS= Subparietal sulcus. *Reprinted from Komaitis et al by permission of the JNS Publishing Group*

The fibers of the posterior segment of the SLF-I in turn were always found to lie within the cingulate gyrus, travelling tangentially to the superior arm of the cingulum – thus exhibiting a paracingulate trajectory- before crossing the plane of the subparietal sulcus to arch towards and consistently terminate at the superior parietal lobule and mainly the anterior part of the precuneus(BA5 and 7). The mean length of SLF-Ip was 57mm (range 55-60mm)

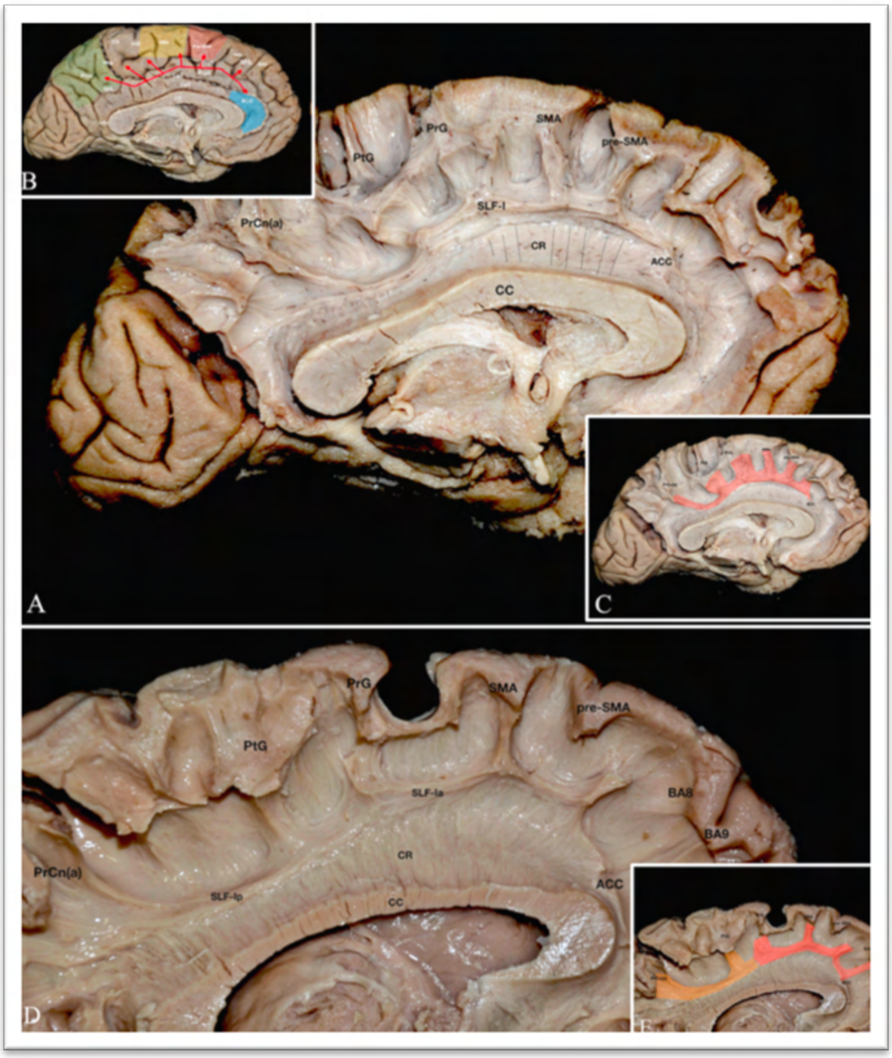


Figure 3.6. Morphology, connectivity and termination pattern of the SLF-I. (A): Left hemisphere. The SLF-I is seen running from the level of dorsomedial frontal gyrus towards the precuneus. Along its course, 6 knots corresponding to 6 sets of terminating fibers can be noticed. Three groups of terminating fibers curve towards the superior frontal gyrus, at the territory of the medial prefrontal cortex, the dorsal premotor cortex, SMA and pre-SMA, two groups of fibers terminate towards the superior and medial aspect of the central lobe, while the basic posterior termination of the SLF-I consists of fibers curving towards the precuneus. Anteriorly the stem of the SLF-I terminates in the area of the anterior cingulate cortex. (B): The trajectory of the SLF-I superimposed on the superficial anatomy of the medial aspect is delineated. The areas corresponding to the anterior cingulate cortex, pre-SMA, SMA proper and precuneus are highlighted in blue, red, yellow and green respectively. (C): The SLF-I with and its terminations are highlighted in red color. (D): A left cerebral hemisphere at the final step of the dissection process. The S-shaped morphology of the SLF-I is illustrated. The anterior segment terminates in the territory of the anterior cingulate cortex, medial frontal gyrus(BA 8 and 9) the pre-SMA, SMA proper and Precentral Gyrus. The posterior segment terminates in the area of the postcentral gyrus and the anterior precuneus. The radiating callosal fibers can be seen running deep to the level of the SLF-I. (E): The anterior and posterior segments of the SLF-I along with terminations are highlighted in red and orange color respectively. ACC= Anterior Cingulate Cortex, BA= Brodmann Area, CC= Corpus Callosum, CR= Corona Radiata, PrCn(a)= Anterior Precuneus, Pre-SMA= Pre- Supplementary Motor Area, PrG= Precentral Gyrus, PtG= Postcentral Gyrus, SLF-I= Superior Longitudinal Fasciculus I, SLF-Ia= Superior Longitudinal Fasciculus I – anterior segment, SLF-Ip= Superior Longitudinal Fasciculus I – posterior segment, SMA= Supplementary Motor Area. Reprinted from Komaitis et al by permission of the JNS Publishing Group

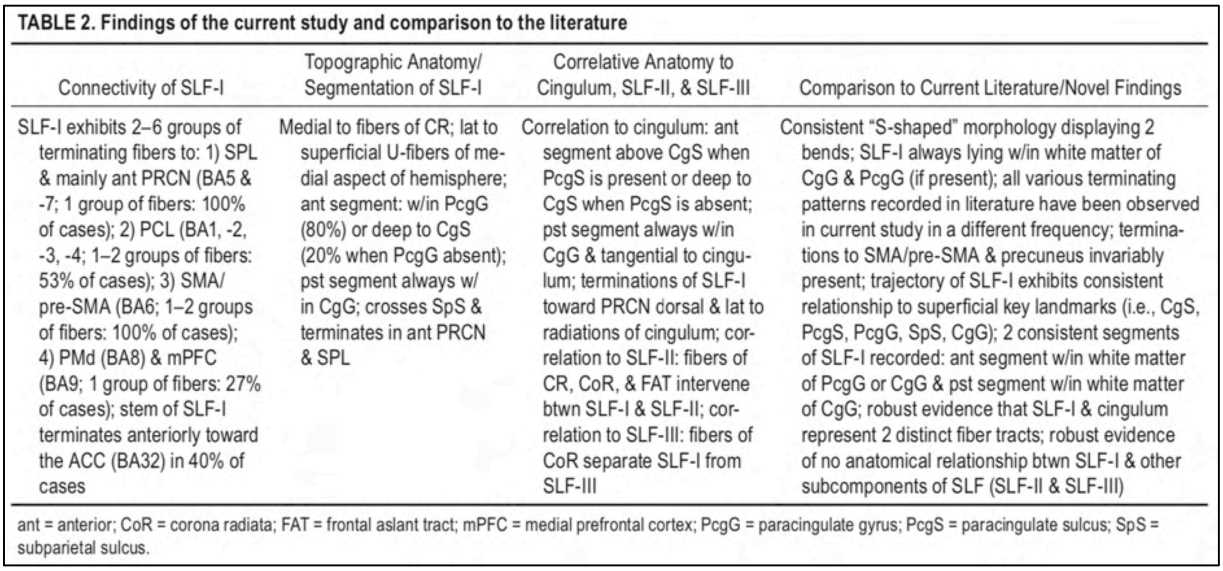


TABLE 2. Findings of the current study and comparison to the literature

Connectivity of SLF-I	Topographic Anatomy/ Segmentation of SLF-I	Correlative Anatomy to Cingulum, SLF-II, & SLF-III	Comparison to Current Literature/Novel Findings
SLF-I exhibits 2–6 groups of terminating fibers to: 1) SPL & mainly ant PRCN (BA5 & -7; 1 group of fibers: 100% of cases); 2) PCL (BA1, -2, -3, -4; 1–2 groups of fibers: 53% of cases); 3) SMA/ pre-SMA (BA6; 1–2 groups of fibers: 100% of cases); 4) PMd (BA8) & mPFC (BA9; 1 group of fibers: 27% of cases); stem of SLF-I terminates anteriorly toward the ACC (BA32) in 40% of cases	Medial to fibers of CR; lat to superficial U-fibers of medial aspect of hemisphere; ant segment: w/in PcgG (80%) or deep to CgS (20% when PcgG absent); pst segment always w/ in CgG; crosses SpS & terminates in ant PRCN & SPL	Correlation to cingulum: ant segment above CgS when PcgS is present or deep to CgS when PcgS is absent; pst segment always w/in CgG & tangential to cingulum; terminations of SLF-I toward PRCN dorsal & lat to radiations of cingulum; correlation to SLF-II: fibers of CR, CoR, & FAT intervene btwn SLF-I & SLF-II; correlation to SLF-III: fibers of CoR separate SLF-I from SLF-III	Consistent “S-shaped” morphology displaying 2 bends; SLF-I always lying w/in white matter of CgG & PcgG (if present); all various terminating patterns recorded in literature have been observed in current study in a different frequency; terminations to SMA/pre-SMA & precuneus invariably present; trajectory of SLF-I exhibits consistent relationship to superficial key landmarks (i.e., CgS, PcgS, PcgG, SpS, CgG); 2 consistent segments of SLF-I recorded: ant segment w/in white matter of PcgG or CgG & pst segment w/in white matter of CgG; robust evidence that SLF-I & cingulum represent 2 distinct fiber tracts; robust evidence of no anatomical relationship btwn SLF-I & other subcomponents of SLF (SLF-II & SLF-III)

ant = anterior; CoR = corona radiata; FAT = frontal aslant tract; mPFC = medial prefrontal cortex; PcgG = paracingulate gyrus; PcgS = paracingulate sulcus; SpS = subparietal sulcus.

3.2.4 CORRELATIVE ANATOMY

SLF-I and Cingulum

During the microanatomic dissections, we identified the SLF-I and the superior arm of the cingulum as two almost parallel, longitudinal fiber tracts that exhibit a distinct boundary up to the level of the anterior paracentral lobule. In this area, the SLF-I dives towards the cingulum, coursing in a tight and seemingly indiscrete anatomical trajectory to it, before bending again upwards to terminate to the precuneus. Aiming to define whether a cleavage plane between these white matter pathways in the region of the anterior paracentral lobule exists, we attempted to dissect apart the fibers of the cingulum from those of the SLF-I, focusing on the preservation of their anatomical integrity. Indeed and despite their proximity, we were able to distinguish a clear dissection plane between these two tracts in all studied specimens proving that they are discrete anatomical entities.

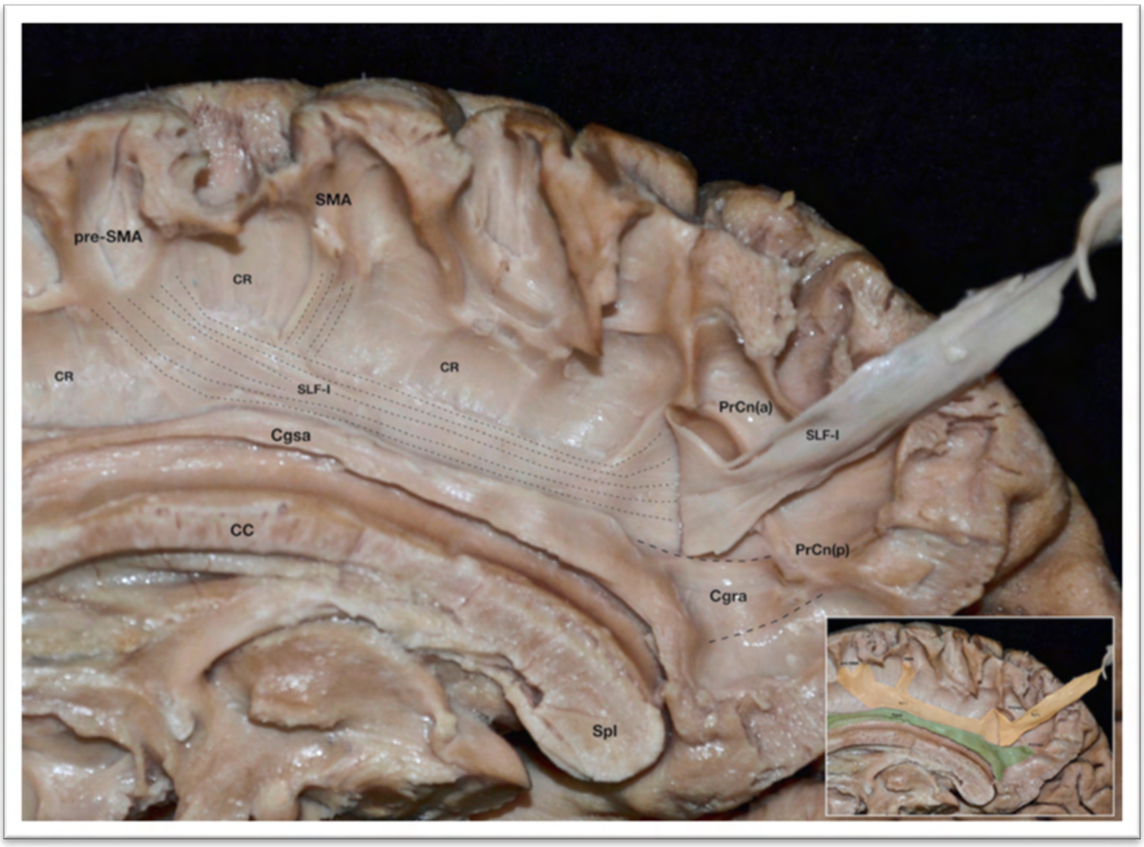


Figure.3.7. SLF-I and Cingulum.Medial view of a right cerebral hemisphere illustrating the superior arm of the cingulum and SLF-I. The fibers of the SLF-I are followed posteriorly along their course I.e. from the SMA towards the precuneus. In this way, the different trajectories of these discrete fiber pathways can be appreciated. The fibers of the SLF-I can be adequately removed under the microscope without interrupting the integrity of the superior arm of the cingulum at any point during its course. (inset): The SLF-I and superior arm of the cingulum highlighted in yellow and green respectively. Cgra= Radiations of the cingulum towards the precuneus, Cgsa= Superior arm of the cingulum, CR= Callosal Radiations, PrCn(a)= Anterior Precuneus, PrCn(p)= Posterior Precuneus, SLF-I= Superior Longitudinal Fasciculus I, SMA= Supplementary Motor Area. Reprinted from Komaitis et al by permission of the JNS Publishing Group

Relationship between the SLF-I and SLF-II.

In order to investigate the anatomical relationship between the SLF-I and SLF-II and given that the SLF-II lies in the white matter of the lateral aspect of the cerebral hemisphere, we further shifted our direction of dissection on the lateral cerebral aspect in three (3) hemispheres. After removing the gray matter and U fibers of the frontal lobe up to the level of the precentral sulcus, we encountered the axons of the SLF-II coursing superficial to the Corona Radiata (CR), at the level of the Middle Frontal Gyrus (M2). Focusing our dissection on the white matter intervening between these two tracts, we revealed a 4-6mm layer of fibers coursing in a vertical trajectory and stemming from the Callosal Radiations and Corona Radiata. These fibers were consistently recorded to run in a perpendicular direction to the fibers of the SLF II and SLF I without intermingling with them at any point. Therefore, our results support the argument that the SLF-I and SLF-II are two long association fibers tracts that run parallel to each other without maintaining any anatomical connection and should be deemed as discrete anatomical entities.

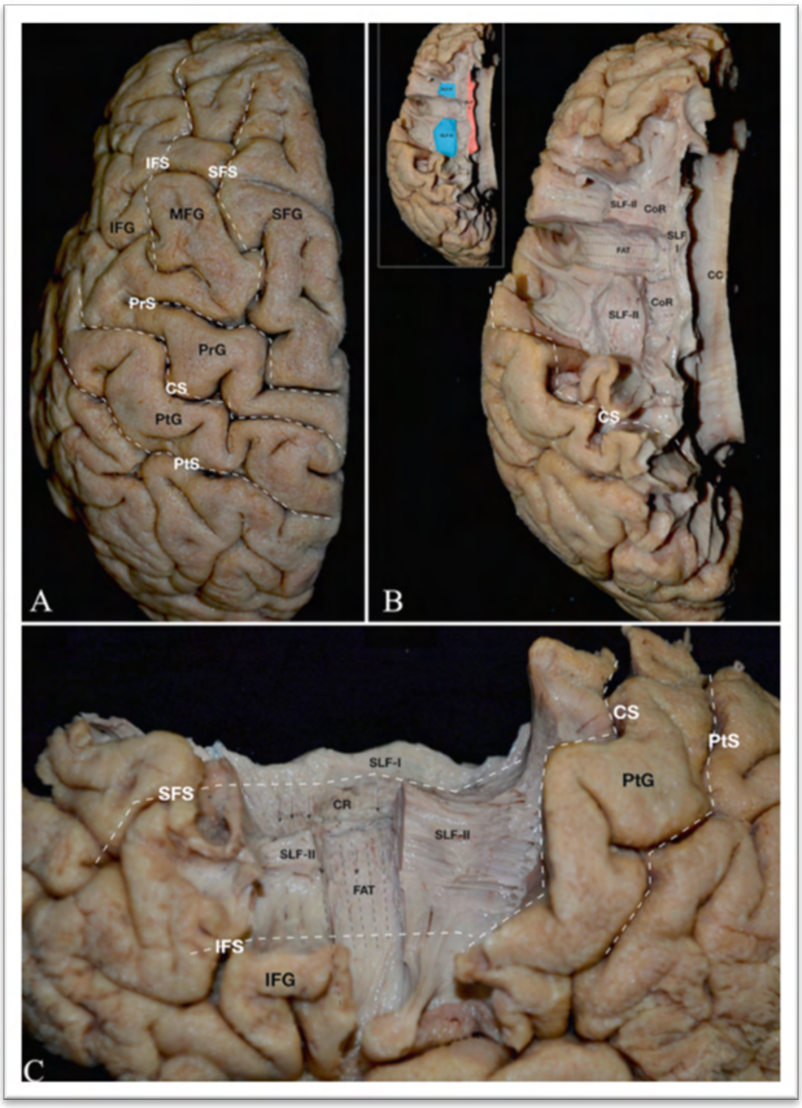


Figure 3.8. Superior and lateral views of a left hemisphere showing the relationship between the SLF-I and the SLF-II. (A): Superior view illustrating the surface anatomy. (B): Same hemisphere after a standard medio-lateral dissection which was further extended on the lateral cerebral surface by removing the u-fibers of the superior, middle and inferior frontal gyri. The SLF-I and SLF-II are demonstrated. Progressive meticulous dissection reveals the fibers of the Frontal Aslant Tract, travelling from the SMA to the inferior frontal gyrus, along with the projecting fibers of the corona radiata, both of which are seen to intervene between the SLF-I and SLF-II. (inset): The SLF-I and SLF-II in red and blue color respectively. (C): lateral view of the correlative anatomy in the same hemisphere. CC= Corpus Callosum, CoR= Corona Radiata, CS= Central Sulcus, FAT= Frontal Aslant Tract, IFG= Inferior Frontal Gyrus, IFS= Inferior Frontal Sulcus, MFG= Middle Frontal Gyrus, PrG= Precentral Gyrus, PrS= Precentral Sulcus, PtG= Postcentral Gyrus, PtS= Postcentral Sulcus, SFG= Superior Frontal Gyrus, SFS= Superior Frontal Sulcus, SLF-I= Superior Longitudinal Fasciculus I, SLF-II= Superior Longitudinal Fasciculus II Reprinted from Komaitis et al by permission of the JNS Publishing Group

Relationship between the SLF I and SLF III

In two specimens, we employed the same procedure as above but further focused our dissections on the inferior frontal and supramarginal gyri, in order to demonstrate the relationship between the SLF-I and SLF-III. We additionally removed the middle and superior frontal gyri to illustrate the regional correlative anatomy. Again, a 14-17mm vertical layer of fibers stemming from the Corona Radiata -just above its transition area to the internal capsule - and the Callosal Radiations was observed to separate the two subcomponents of the SLF system. Neither the SLF-I nor the SLF-III mix or intermingle with these fibers at any point during their course. As previously seen with regard to the SLF-II, the SLF-I and SLF-III run in parallel directions and do not exhibit any direct anatomical connection, therefore constituting two discrete anatomical entities.

Figure 3.9. Superior and medial views of a dissected left hemisphere depicting the relationship between the SLF-I and the SLF-III. (Left): Superior view of a left hemisphere after a standard medial to lateral dissection process, which we further extended over the lateral aspect of the central lobe, parietal lobe and part of the central core. The areas of the rolandic operculum and frontoparietal operculum were dissected in order to reveal the ventral component of the SLF, namely the SLF-III. Progressive dissection of the fibers of the corona radiata up to the central core allowed a clear view of the anatomical relationship between the SLF-I and SLF-III. This white matter layer of Corona Radiata fibers clearly separates the two components of the Superior Longitudinal Fasciculus. (inset): Fiber tracts highlighted in different colors: Superior arm of the cingulum(green color), SLF-I(red color), Corona Radiata(blue color), SLF-III(yellow color). (Right): Medial view of the same hemisphere. CC= Corpus Callosum, CdN= Caudate Nucleus (body), Cgsa= Superior arm of the cingulum, CoR= Corona Radiata , CR= Callosal Radiations, Fpo= Frontoparietal Operculum, IntCps= Internal Capsule, SLF-I= Superior Longitudinal Fasciculus I, SLF- III= Superior Longitudinal Fasciculus III, Th= Thalamus Reprinted from Komaitis et al by permission of the JNS Publishing Group

3.3 RESULTS: FLS & FAT

3.3.1 MORPHOLOGY, FIBER ALLOCATION AND CONNECTIVITY OF THE FLS

The Frontal Longitudinal fiber system was identified and recorded in all studied hemispheres. In 80% of cases, where a prominent middle frontal sulcus was present, the FLS was encountered just under the most superficial U fibers at the depth of the sulcus. In the remaining 20% of cases, where the middle frontal sulcus was absent, the FLS was seen to lie just medial to the superficial U-fibers of the middle frontal gyrus. (It was further found to consist of a superficial layer of fibers, which closely resembled the U-fibers and interconnected adjacent areas within the precentral, middle, superior and inferior frontal gyri and of a deeper layer of longer fibers connecting more remote areas in the premotor and prefrontal cortex.

In addition, the fibers of the FLS were observed to travel in two discrete levels i.e. a superior and an inferior level, therefore resembling a superior and inferior longitudinal chain of fibers (as described by Catani et al). In 2 hemispheres, the superior and inferior longitudinal chains represented two completely separate groups of fibers with a clear cleavage plane between them. In this case the superior chain was seen to run from the dorsal premotor cortex towards the middle part of the superior frontal gyrus (BA 9) while the inferior chain to connect the ventral premotor cortex, that is the ventral precentral gyrus and pars opercularis (BA 44) with the pars triangularis (BA 45), pars orbitalis (BA 11), middle frontal gyrus (BA 46) and frontal pole. In the rest of the hemispheres the superior and inferior longitudinal chains were recorded to converge and form a single stem with no evident dissection plane between them.

The termination pattern of the FLS was relatively consistent. Posteriorly, the fibers of the FLS were always observed to terminate to the ventral and dorsal premotor cortex. Terminations towards the precentral gyrus were also encountered in 67% of the cases. The dorsolateral prefrontal cortex (BA 46), pars triangularis (BA 45) and frontal pole (BA 10) received fibers in all of the studied hemispheres (100%) while in 47% hemispheres the FLS also exhibited connections with the pars orbitalis (BA 47). Finally, fibers of the inferior frontal longitudinal chain were recorded to terminate towards Brodmann's Area 9 in 60% of the specimens. No variability or asymmetry between the right and left side concerning the morphology, topography or termination pattern of the FLS was recorded.

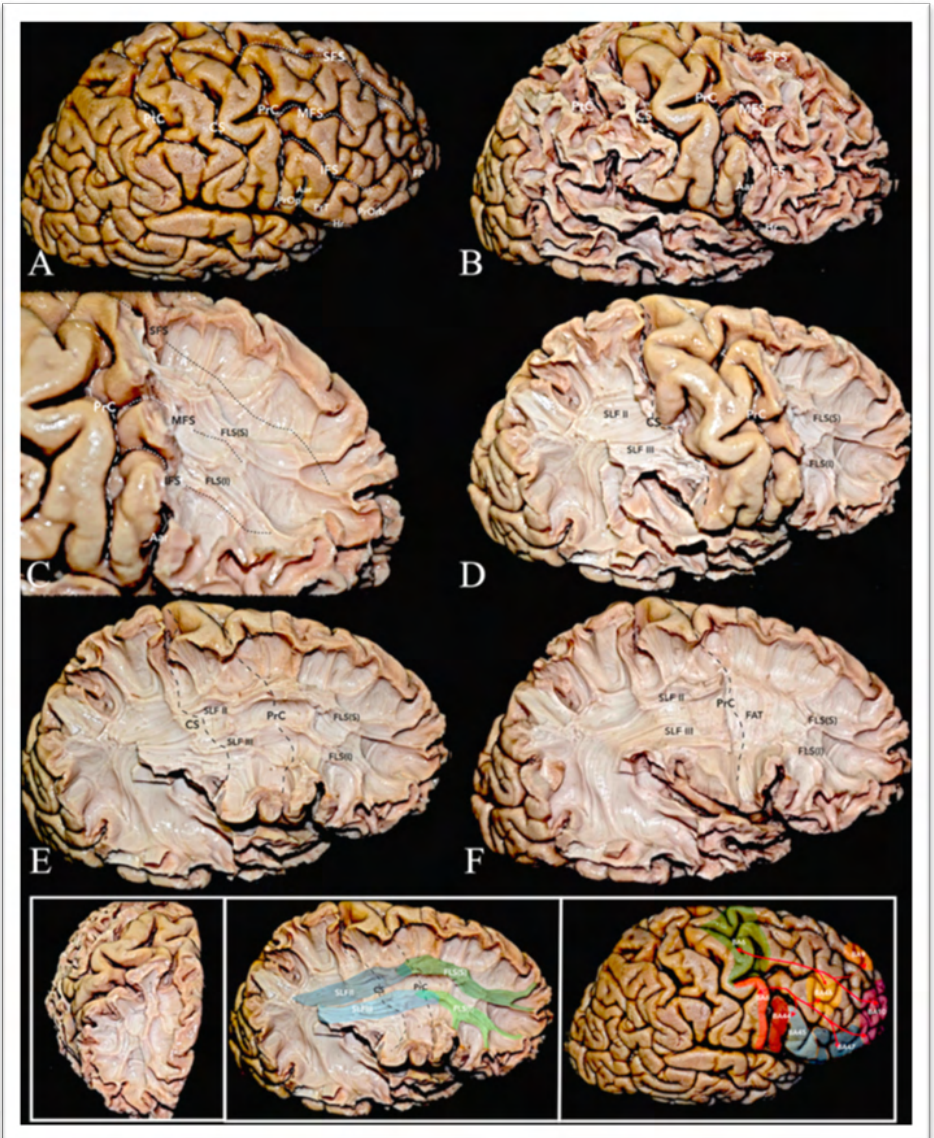


Figure.3.10. Progressive dissection of a right hemisphere illustrating the structural morphology and correlative anatomy of the FSL. A: The lateral surface anatomy is illustrated. Note the presence and location of the Middle Frontal Sulcus. B: After removing the cortical grey matter the superficial U-fibers become evident. The cortex of the area of the precentral gyrus and posterior frontal gyri (corresponding to the motor and premotor areas) has been spared. The contours of the main sulci are illustrated. C: A focused illustration of the frontal area after removing the U-fibers. The FLS is apparent as a superior and an inferior longitudinal system of fibers running parallel to the superior and inferior frontal sulci respectively. Note that a clear plane between the two fiber systems is evident. D: Next step with the U-fibers removed at the temporo-parietal areas and revealing the SLF complex. SLF-II and SLF-III tracts are illustrated. E: The cortex and U-fibers in the precentral/posterior-frontal area are removed revealing the relationship of the fibers of the SLF and FLS. In this specimen, the two fiber tracts appear continuous, with the SLF-II merging with the superior chain and the SLF-III merging with the inferior chain of the FLS. Note that the fibers of SLF and FLS exhibit major terminations in the precentral area. We were not able to trace fibers of the FLS posterior to this level. F: The posterior part of the FLS has been removed revealing the FAT interconnecting the Superior and Inferior Frontal Gyri. Inset: Left: Antero-superior view of the FLS. Middle: Relationship between the FLS and SLF. The SLF-II and SLF-III are highlighted in dark and light blue respectively. The FLS(S) and FLS(I) are highlighted in dark and light green respectively. Right: Trajectory and connectivity of the FLS superimposed on the superficial anatomy. The different anatomo-functional areas are highlighted in different colors: Green: Dorsal Premotor Cortex

(BA6), Red: Ventral Premotor Cortex (BA6), Dark red: Ventral Premotor Cortex/Pars Opercularis (BA44), Yellow: Dorsolateral Prefrontal Cortex (BA 46), Orange: Dorsolateral Prefrontal Cortex (BA 9), Light Blue: Ventrolateral Prefrontal Cortex/Pars Triangularis (BA 45), Dark Blue: Ventrolateral Prefrontal Cortex/Pars Orbitalis (BA 47), Magenta: Rostrolateral Prefrontal Cortex/Frontal Pole (BA 10). (The anatomical boundaries of the premotor area have been defined according to findings of previous studies.[28,35]). Aar= Anterior ascending ramus of the Sylvian Fissure, BA= Brodmann's Area, CS= Central Sulcus, FAT= Frontal Aslant Tract, FLS(I)= Frontal Longitudinal System: Superior frontal longitudinal chain, FLS(S)= Frontal Longitudinal System: Inferior frontal longitudinal chain, FP= Frontal Pole, Hr= Horizontal ramus of the Sylvian Fissure, IFS= Inferior Frontal Sulcus, MFS= Middle Frontal Sulcus, PrC= Precentral Sulcus, PrOp= Pars Opercularis, PrOrb= Pars Orbitalis, PrT= Pars Triangularis, PtC= Postcentral Sulcus, SFS= Superior Frontal Sulcus, SLF-II= Superior Longitudinal Fasciculus II, SLF-III= Superior Longitudinal Fasciculus III Reprinted from Komaitis et al by permission of the JNS Publishing Group

3.3.2 CORRELATIVE ANATOMY

Relationship between the FLS and SLF

During the dissections, the FLS was seen to exhibit a variable relationship with the fibers of the SLF system. This relationship was highly depended on the termination pattern of the two fiber groups in the area of the posterior frontal lobe. In 20% of the studied hemispheres the SLF and FLS were recorded as two completely distinct tracts with the former terminating in the area of the precentral gyrus anteriorly while the latter terminating in the posterior part of the superior, middle and inferior frontal gyri posteriorly. In the majority (80 %) of cases we macroscopically identified the FLS as the anterior extension of the SLF fiber system. Specifically, the SLF-III, was observed to blend with the fibers of the inferior chain of the FLS in the area of the ventral precentral gyrus and pars opercularis therefore exhibiting an anatomical continuity. The same applies for the middle component of the SLF complex, namely the SLF-II, which was recorded to intermingle with fibers of the superior chain of the FLS in the area of the dorsal part of the precentral gyrus and posterior part of the middle and superior frontal gyri. Nonetheless, the FLS exhibits a different architecture compared to the SLF. First, the uppermost fibers recorded to belong to the FLS reside in a more superficial plane than the relevant fibers of the SLF. Second, the fibers of the FLS follow a significantly shorter trajectory compared to those of the SLF, in order to connect adjacent frontal areas. It has to be highlighted that we did not identify and isolate any of the FLS fibers beyond the level of the precentral gyrus.

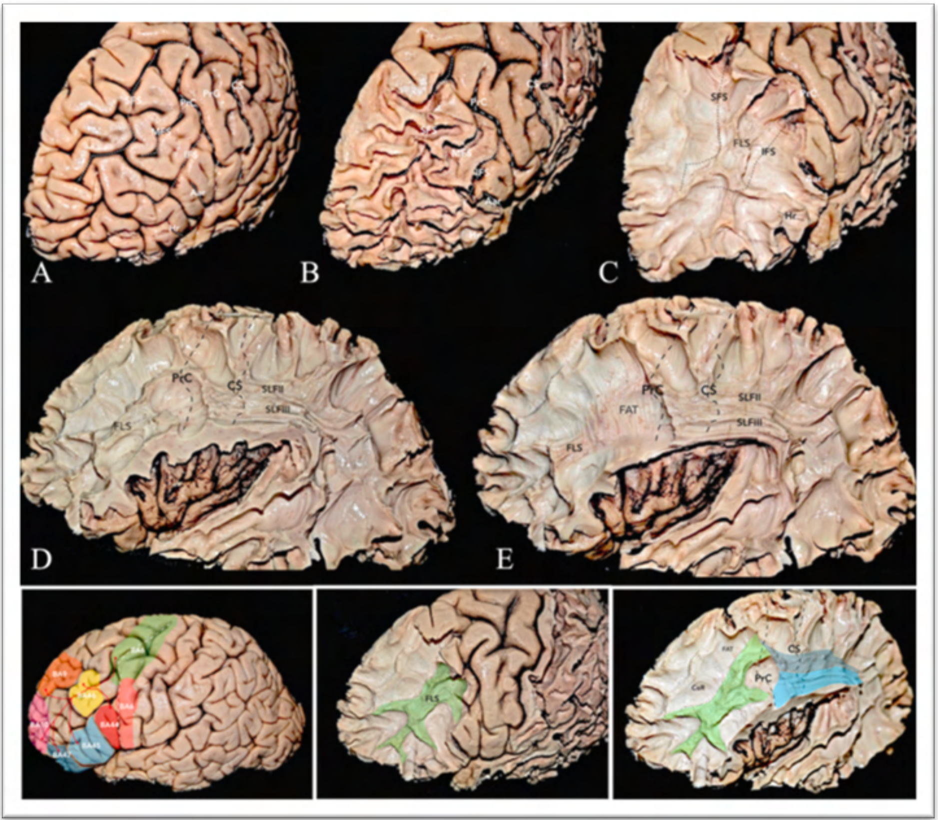


Figure.3.11: Progressive dissection of a left hemisphere illustrating the morphology, correlative anatomy and connectivity of the FLS. A: Antero-Superior view and surface anatomy of a left lateral cerebral surface. B: Superficial U-fibers and the contour of the main frontal sulci is illustrated. C: The FLS is revealed as a single stem of fibers traveling as far as the area of the frontal pole. The superior fibers of the FLS can be seen terminating towards the superior frontal gyrus, frontal pole and posterior part of the middle frontal gyrus. The inferior fibers of the FLS terminate in the pars opercularis, pars triangularis, pars orbitalis and frontal pole. D: Lateral view. The U-fibers of the lateral aspect of the hemisphere have been removed to show the relationship between the fibers of the FLS and SLF. In this case the SLF terminates abruptly in the area of the precentral gyrus. The superior fibers of the FLS terminate posteriorly in the same area while the inferior fibers terminate in the pars opercularis. No anatomical continuity between the fibers of the two systems is documented in this specimen. Insets: Superior: Cortical terminations and trajectory of the FLS superimposed on the superficial anatomy. The different anatomo-functional areas are highlighted in different colors: Green: Dorsal Premotor Cortex (BA6), Red: Ventral Premotor Cortex (BA6), Dark red: Ventral Premotor Cortex/Pars Opercularis (BA44), Yellow: Dorsolateral Prefrontal Cortex (BA 46), Orange: Dorsolateral Prefrontal Cortex (BA 9), Light Blue: Ventrolateral Prefrontal Cortex/Pars Triangularis (BA 45), Dark Blue: Ventrolateral

Prefrontal Cortex/Pars Orbitalis (BA 47), Magenta: Rostrolateral Prefrontal Cortex/Frontal Pole (BA 10). (The anatomical boundaries of the premotor area have been defined according to findings of previous studies.[28,35]) Middle: Morphology of the FLS highlighted in green color. Inferior: The correlative anatomy and termination plane of the FLS and SLF is illustrated. The SLF-II and SLF-III are highlighted in dark and light blue respectively while the FLS is highlighted in green color. The level of the precentral and central gyri is also illustrated. Note the different termination plane of the two fibers tracts. Aar= Anterior ascending ramus of the Sylvian Fissure, AF= Arcuate Fasciculus, BA= Brodmann's Area, CoR= Corona Radiata, CS= Central Sulcus, FAT= Frontal Aslant Tract, FLS= Frontal Longitudinal System, Hr= Horizontal ramus of the Sylvian Fissure, IFS= Inferior Frontal Sulcus, MFS= Middle Frontal Sulcus, PrC= Precentral Sulcus, PrG = Precentral Gyrus, PrOp= Pars Opercularis, PrOrb= Pars Orbitalis, PrT= Pars Triangularis, PtC= Postcentral Sulcus, SFS = Superior Frontal Sulcus, SLF-II= Superior Longitudinal Fasciculus II, SLF-III= Superior Longitudinal Fasciculus III Reprinted from Komaitis et al by permission of the JNS Publishing Group

Although the FLS displays a similar trajectory to the SLF, resembling its anterior continuation, it certainly exhibits significant morphological differences and therefore these tracts should be considered as two discrete anatomical entities.

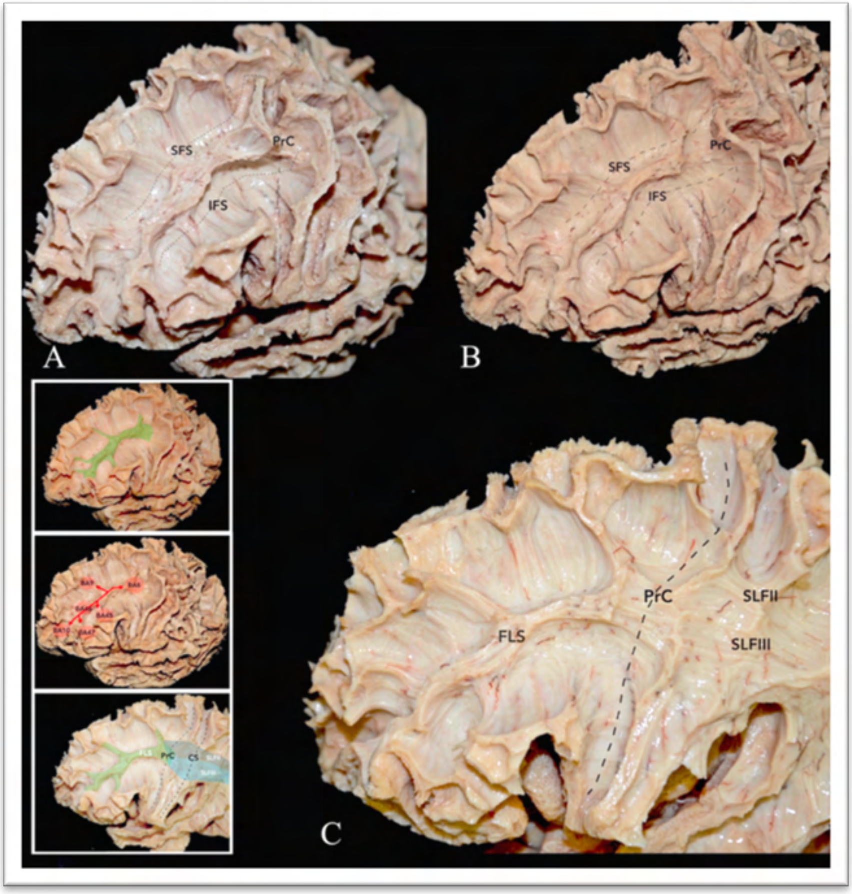


Figure.3.12: Antero-superior views of a dissected left hemisphere. Allocation of fibers within the FLS and relationship between the FLS and SLF fibers. A: After the most superficial U-fibers of the frontal area have been removed, the superficial fiber layer of the FLS is revealed. This layer blends with the deep U-fibers of the middle frontal gyrus to interconnect adjacent areas of the Middle, Superior and Inferior Frontal Gyri. B: Removing the superficial layer of the FLS reveals the deeper fibers contributing to this system. These fibers follow a longer trajectory compared to the fibers of the superficial layer and connect more remote areas in the frontal lobe. C: In the same specimen, the FLS appears as an anterior extension of the SLF system. Insets: Left: Morphology of the FLS highlighted in green color. Middle: Connectivity and trajectory of the FLS. Right: Relationship between the FLS and SLF fibers. The FLS is highlighted in green while the SLF-II and SLF-III are highlighted in dark and light blue respectively. In this case, these two fiber systems appear macroscopically continuous.BA= Brodmann's Area, CS= Central Sulcus, FLS= Frontal Longitudinal System, IFS= Inferior Frontal Sulcus, PrC= Precentral Sulcus, SFS= Superior Frontal Sulcus, SLF-II= Superior Longitudinal Fasciculus II, SLF-III= Superior Longitudinal Fasciculus II Reprinted from Komaitis et al by permission of the JNS Publishing Group

3.4 RESULTS: FCT

3.4.1 SURFACE ANATOMY AND STEPWISE DISSECTIONS

Surface landmarks on the lateral and medial cerebral aspect were recorded to act as reference points for future dissections. Hence, the superior and inferior frontal sulci, the precentral, central and postcentral sulci, the superior, middle and inferior frontal gyri, the precentral and postcentral gyri, the cingulate sulcus and gyrus, the medial aspect of the superior frontal gyrus, the corpus callosum and the anterior commissure were all identified.

Lateral to medial dissections

Upon removing the cortical grey matter and the underlying u-fibers, we expose the SLF/AF complex. Dissecting away the longitudinal fibers of the SLF/AF complex helps to uncover the continuous fibers of the Centrum Semiovale (CS - running above the level of the ventricular system) and Corona Radiata (CR - running at the level of the lateral ventricles). In this step, the Frontal Aslant Tract (FAT) is also identified as a distinct group of fibers running from the SMA towards the posterior part of the inferior frontal gyrus. In the region of the insula, upon dissecting the fibers of the extreme capsule and claustrum, one encounters the grey substance of the putamen. The putamen is removed along with the part of the globus pallidus that overlies the thalamus. In addition, the projecting fibers of the CS/CR are gradually dissected until their deepest layer that resides in the subventricular zone is reached. At this stage, a meticulous dissection technique is required to preserve the integrity of the very thin white matter that comprises the fronto-caudate and fronto-thalamic projections. At the end of this step, the ventral segment of the fronto-caudate tract (FCTv) is identified and seen to terminate on the head of the caudate nucleus. The FCTv exhibits a lazy S shaped configuration, with its fibers initially observed to travel in a relatively straight direction and then seen to curve to adapt to the silhouette of the head of the caudate nucleus before terminating at this area. While the FCTv is nicely exposed at this stage, the dorsal component of the tract (FCTd) is covered by fibers of the anterior thalamic radiation (ATR), which are seen to pass slightly lateral to the caudate nucleus in order to terminate to the thalamus. These fronto-thalamic fibers are carefully removed during the medial to lateral dissections to reveal the underlying fibers of the FCTd. In the last step, the frontal horn is entered and the spatial relationship of the FCT with the intraventricular structures and the Corpus Callosum is demonstrated.

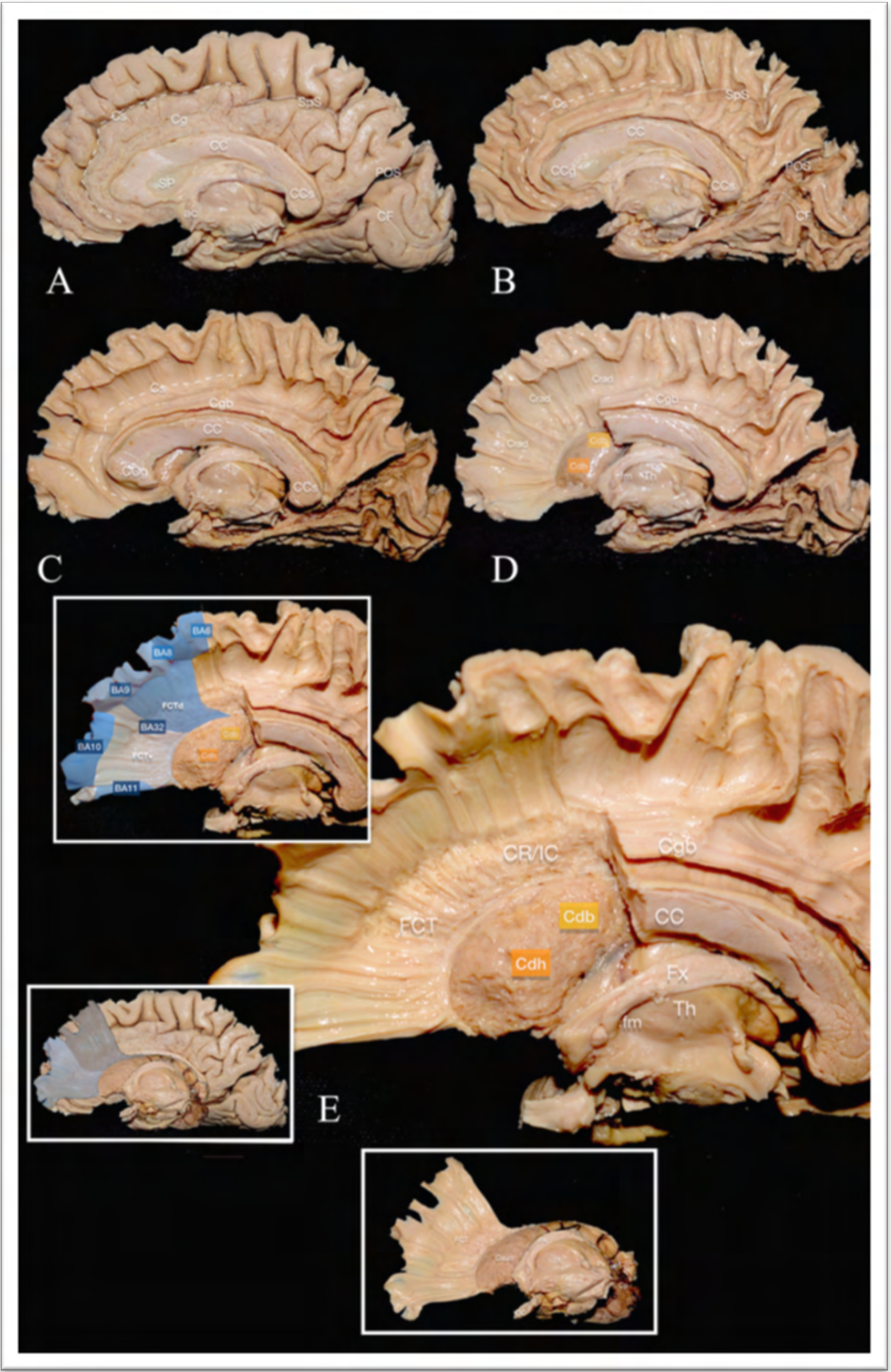


Figure.3.13. Stepwise medial to lateral dissection of a right hemisphere.

A: The relevant superficial anatomy is marked with dotted lines.

B: The Superficial U-fibers are exposed. The silhouette of the main sulci is superimposed on the specimen for orientation purposes.

C: The superficial U-fibers of the frontal area are removed. The superior arm of the cingulum is evident.

D: The rostrum, genu and anterior part of the bod of the corpus callosum as well as the superior arm of the cingulum are dissected away. The intraventricular part of the caudate nucleus and the callosal radiations are illustrated.

E: The ependymal layer covering the caudate nucleus is carefully removed. The callosal radiations are dissected in a superior to inferior direction to reveal the fibers of the FCT and their termination zone on the caudate nucleus. Inset (upper): The FCTv and FCTd are highlighted in light blue and dark blue respectively, with the first terminating on the head of the caudate and the second on the body of the caudate nucleus. The relevant Brodmann areas to which the tract terminate are highlighted. Inset (middle): The silhouette of the FCT superimposed on the surface of the same specimen. Inset (lower): Advanced stage of a medio-lateral dissection of a right hemisphere. The FCT along with its termination zone on the caudate nucleus and the structures of the limbic lobe and diencephalon are dissected free from the rest of the hemisphere. The morphology of the tract is demonstrated

ac = Anterior Commissure , BA = Brodmann's Area, CC = Corpus Callosum , CCg = Genu of the Corpus Callosum, CCs = Splenium of the Corpus Callosum , Cdb = Body of the caudate nucleus, Cdh = Head of the caudate nucleus, CF = Calcarine Fissure, Cg =Cingulate Gyrus, Cgb = Body of the Corpus Callosum, CR = Corona Radiata, Crad = Callosal Radiations , Cs = Cingulate Sulcus, FCTd = Dorsal component of the Fronto-caudate Tract, FCTv = Ventral component of the Fronto-caudate Tract, fm = Foramen of Monro, Fx = Fornix, IC = Internal Capsule, POS = Parieto-occipital Sulcus, SP = Septum Pellucidum , SpS = Subparietal Sulcus, Th = Thalamus Reprinted from Komaitis et al by permission of the JNS Publishing Group

Medial to lateral dissections

Medial to lateral dissections were carried out in a tandem manner in all specimens in order to accurately understand the morphology and topography of the FCT. After removing the cortex and superficial u-fibers up to the level of the marginal ramus of the cingulate sulcus, we encounter the superior arm of the cingulum. Then, the anterior part of the cingulum and corpus callosum are dissected away and the anatomy of the frontal horn and caudate nucleus is appreciated. At this stage, the callosal radiations are also apparent. Upon removing the callosal radiations we reveal the fibers of the FCT seen to radiate from the head and body of the caudate nucleus towards the frontal area. At this last step of the entire dissection process the fibers of the FCT are the only fibers preserved in the frontal area. The FCT and its respective termination zone on the caudate nucleus can be dissected free from the rest of the hemisphere.

3.4.2 SEGMENTATION AND CONNECTIVITY PATTERN OF THE FCT

Segmentation and connectivity pattern of the FCT

We consistently identified two discrete segments of the FCT. The ventral segment (FCTv) is formed from fibers recorded to originate from the frontal pole (BA10), fronto-orbital region (BA11), ventrolateral prefrontal cortex (BA47) and ventral part of the anterior cingulate cortex (BA32) and terminate on the head of the caudate nucleus (100% of the specimens). The dorsal segment (FCTd) receives fibers from the anterior part of the pre-SMA (BA6), dorsolateral and dorsomedial prefrontal cortex (BA8 & BA9) and dorsal anterior cingulate cortex (BA32), travels medial to the fibers of the ATR and terminates to the body of the caudate nucleus. The transition zone of the FCTv to FCTd corresponds to the transition area of the head to the body of the caudate, which is located at the level of the foramen of Monro. Further, the FCTv was consistently seen to be thicker and bulkier than the FCTd.

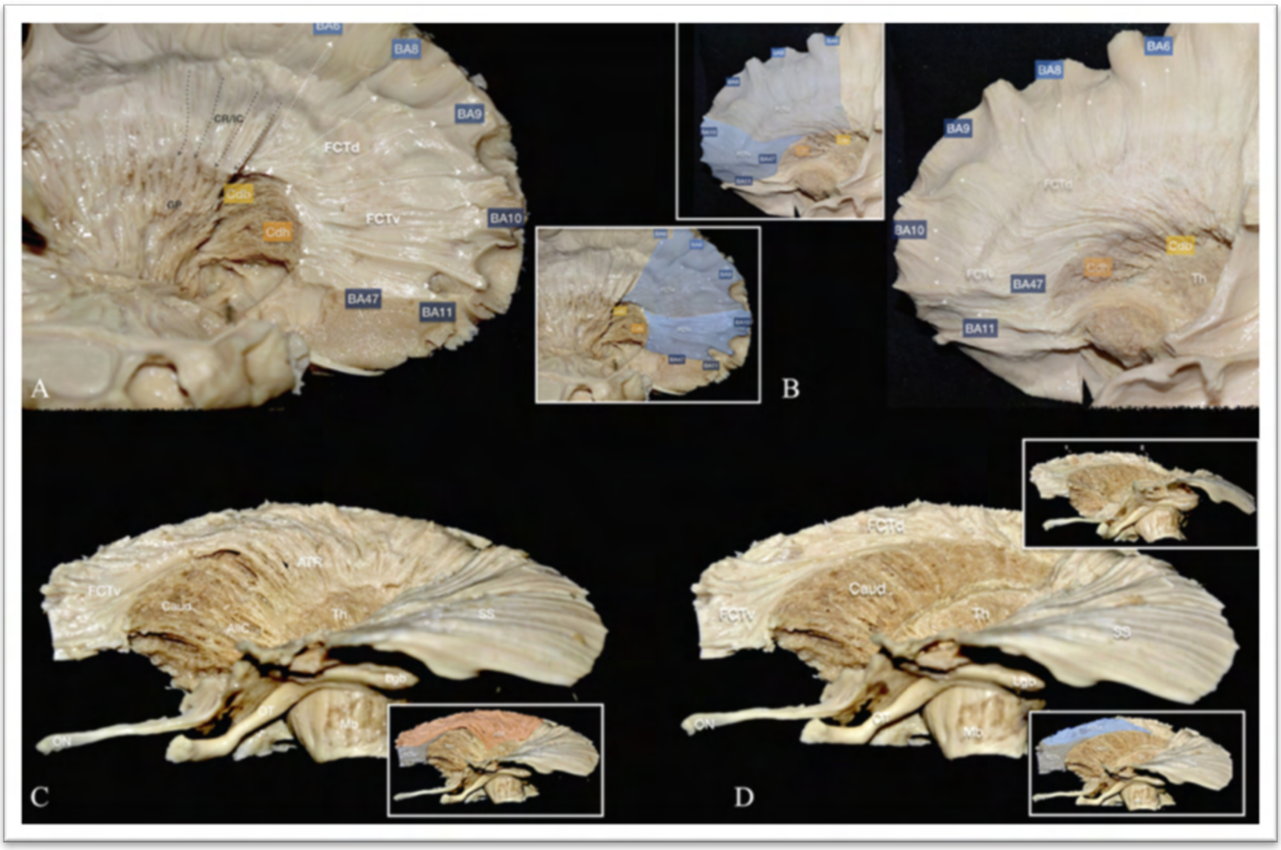


Figure.3.14 Dorsal and Ventral connectivity of the FCT.

A: Advanced stage of a latero-medial dissection of a right hemisphere. The morphology of the dorsal terminations of the FCT is illustrated. Inset: The fibers of the FCTd (dark blue) arising from the body of the caudate nucleus can be seen radiating towards Brodmann's areas 8 and 9 (anterior pre-SMA and DLPFC). The fibers of the FCTv (light blue) arising from the head of the caudate can be seen terminating towards BA 10 and BA 11. The boundary between the head and body of the caudate nucleus is marked with a dashed line.

B: Advanced stage of a latero-medial dissection of a left hemisphere. The dorsal connectivity of the FCT is again illustrated. Inset: Appreciate the FCTd (dark blue) connecting the body of the caudate with the anterior pre-SMA (BA8) and DLPFC(BA9) and the FCTv (light blue) radiating from the head of the caudate towards the frontal pole (BA10) and orbitofrontal cortex(BA 11).

C: Ventral connectivity of the FCT and its relationship to the ATR. Oblique views of advanced stages of a latero-medial dissection of a left hemisphere. The central core of the hemisphere along with the diencephalic and mesencephalic structures are dissected free from the rest of the hemisphere. The termination fibers of the FCT on the head and body of the caudate have been preserved. At this step, the FCTv is seen to terminate to the head of the caudate nucleus while the FCTd is covered by the fibers of the ATR that pass lateral to reach the thalamus. Inset: The FCTv and ATR are highlighted with dark blue and red respectively.

D: Ventral connectivity of the FCT. Oblique views of advanced stages of a latero-medial dissection of a left hemisphere. The fibers of the ATR have been removed and the fibers of the FCTd are nicely illustrated to terminate to the body of the caudate nucleus. Inset(lower): The FCTv and FCTd are highlighted in dark and light blue respectively. Inset (upper): An arbitrary line passing through the anterior border of the anterior perforated substance demarcates the transition between the FCTv and FCTd. A second line passing through the lateral geniculate body defines the posterior limit of the FCTd and thus the posterior limit of the entire FCT. These lines were consistently recorded to delineate the aforementioned boundaries in all studied specimens.

ALIC = Anterior Limb of the Internal Capsule, APS = Anterior Perforated Substance, ATR = Anterior Thalamic Radiation, BA = Brodmann's Area, Caud = Caudate Nucleus, Cdb = Body of the Caudate Nucleus, Cdh = Head of the Caudate Nucleus, CR = Corona Radiata, FCTd = Dorsal component of the Fronto-caudate Tract, FCTd = Dorsal component of the Fronto-caudate Tract, FCTdtz = Dorsal component of the Fronto-caudate Tract termination zone, FCTv = Ventral component of the Fronto-caudate Tract, FCTv = Ventral component of the Fronto-caudate Tract, FCTvtz = Ventral component of the Fronto-caudate Tract termination zone, GP = Globus Pallidus, IC = Internal Capsule, Lgb = Lateral Geniculate Body, Mb = Midbrain, ON = Olfactory Nerve, OT = Optic Tract, SS = Sagittal Stratum, Th = Thalamus Reprinted from Komaitis et al by permission of the JNS Publishing Group

3.4.3 SPATIAL RELATIONSHIPS OF THE FCT

The FCT is a deep-seated group of fibers that lies in the subventricular zone of the frontal horn, which is located medial with respect to the CS/CR and lateral to the callosal radiations. At the level of the superior frontal gyrus the fibers of the FCT travel medial in relation to the fibers of the FAT. As mentioned, the FCT is documented to terminate on the superolateral margin of the caudate nucleus at the level of the CR/ALIC transition. Therefore, the differentiation between fibers of FCT and ALIC is accurate and reliable because in contrast to the FCT, the fibers of the anterior limb bypass the basal ganglia and course between the head of the caudate and the globus pallidus. Finally, as already stated, the ATR lies just lateral to the FCTd.

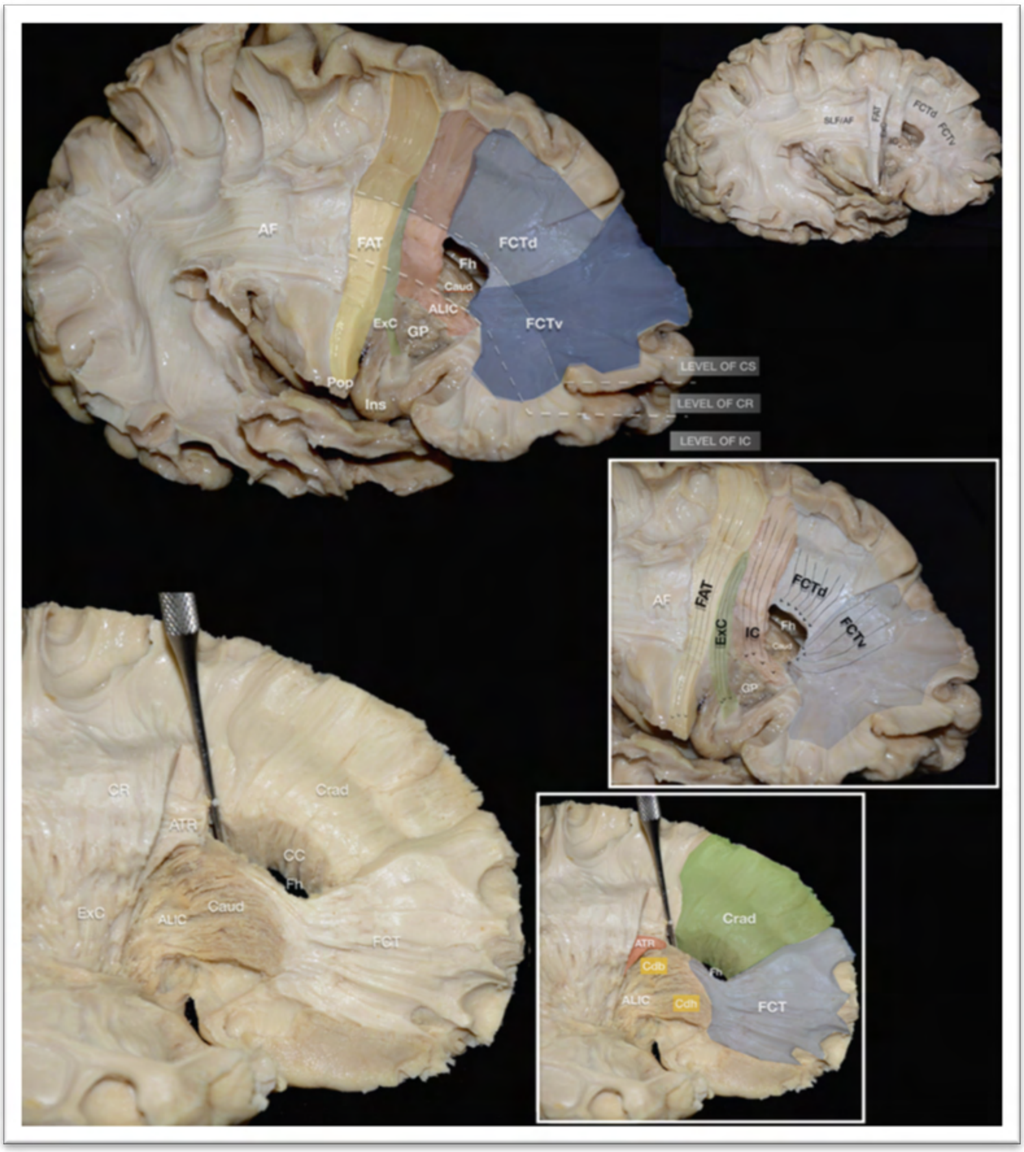


Figure.3.15. Spatial relationship of the FCT with adjacent structures. Progressive latero-medial dissection of a right hemisphere.

Superior view: The different fiber layers of the frontal white matter can be appreciated. The respective plane of the Centrum Semiovale (CS) (above the level of the lateral ventricle), Corona Radiata (CR) (at the level of the lateral ventricle) and Internal Capsule (IC) (below the level of the lateral ventricle) are marked with dashed lines. At the level of the CS and CR the different fiber pathways cannot be differentiated. Below the level of the lateral ventricle, the different tracts can be distinguished based on their termination area. Different colors are used for the various bundles: Yellow color for the FAT, green color for the external capsule, red color for the internal capsule and blue color for the FCT. The frontal horn is entered to give a perspective of depth to the reader. The FCT forms the inner layer of the CS/CR white matter before entering the ventricle. Inset(upper): Lateral view of the same hemisphere without colored highlights. Inset(middle): Close-up of the frontal area. Arrows are used to indicate the relative trajectory of the different tracts within the frontal white matter.

Inferior view: The relationship of the FCT with respect to the corpus callosum and callosal radiations is illustrated. The dorsal segment of the FCT has been removed and the frontal horn is entered. The FCT lies lateral to the fibers of the callosal radiations and medial to the fibers of the ATR and ALIC. Inset(lower): The corpus callosum and callosal radiations are highlighted in green, the FCT in blue and the ATR in red.

AF = Arcuate Fasciculus, ALIC = Anterior Limb of the Internal Capsule, ATR = Anterior Thalamic Radiation, Caud = Caudate Nucleus, CC = Corpus Callosum, Cdb = Body of the Caudate Nucleus, Cdh = Head of the Caudate Nucleus, CR = Corona Radiata, Crad = Callosal Radiations, CS = Centrum Semiovale , ExC = External Capsule, FAT = Frontal Aslant Tract, FCTd = Dorsal component of the Fronto-caudate Tract, FCTv = Ventral component of the Fronto-caudate Tract, Fh = Frontal Horn, GP = Globus Pallidus, IC = Internal Capsule, Ins = Insula, Pop = Pars Opercularis Reprinted from Komaitis et al by permission of the JNS Publishing Group

3.5 RESULTS: CTT

3.5.1 STEPWISE DISSECTIONS

Medial to Lateral Dissections

Upon removing the cortical grey matter, we reveal the superficial u-fibers along with the cingulum bundle. Progressive dissection of the U-fibers, superior arm of the cingulum and corpus callosum exposes the anatomy of the lateral ventricle in a way that the callosal radiations can be appreciated. The caudate nucleus is evident and its thin ependymal covering is removed. The grey matter of the caudate must be meticulously dissected to identify a thin layer of fibers that lies in the white matter just lateral to the nucleus and is formed by the thalamic radiations and the fronto-caudate tract. Following the careful removal of this white matter layer, we gradually reveal the cortico-tegmental fibers. We follow these fibers in their dorsal direction up to their termination area that is recorded to extend from the posteromedial part of the superior frontal gyrus to the superior aspect of the postcentral gyrus. Following these fibers in their ventral direction we see them entering the tegmentum posterior to the substantia nigra, in what we define as the tegmental entry zone (TEZ).

Along their course and trajectory, the corticotegmental fibers are seen to travel in the white matter of the genu and posterior limb of the internal capsule with no fibers traced in the anterior limb of the internal capsule (ALIC). The fibers of the ALIC lie anterior to the CTT and substantia nigra when entering the cerebral peduncle. The CTT's entry zone to the tegmentum was consistently located at the lateral half of this area. Interestingly, during the dissections a cortico-topic distribution of the CTT was revealed. More specifically, the majority of the CTT fibers stemming from BA8 were recorded to reside to the anterior part of the TEZ, the majority of CTT fibers arising from BA4&BA6 to the middle part and the fibers from BA1/2/3 to the posterior part of the TEZ.

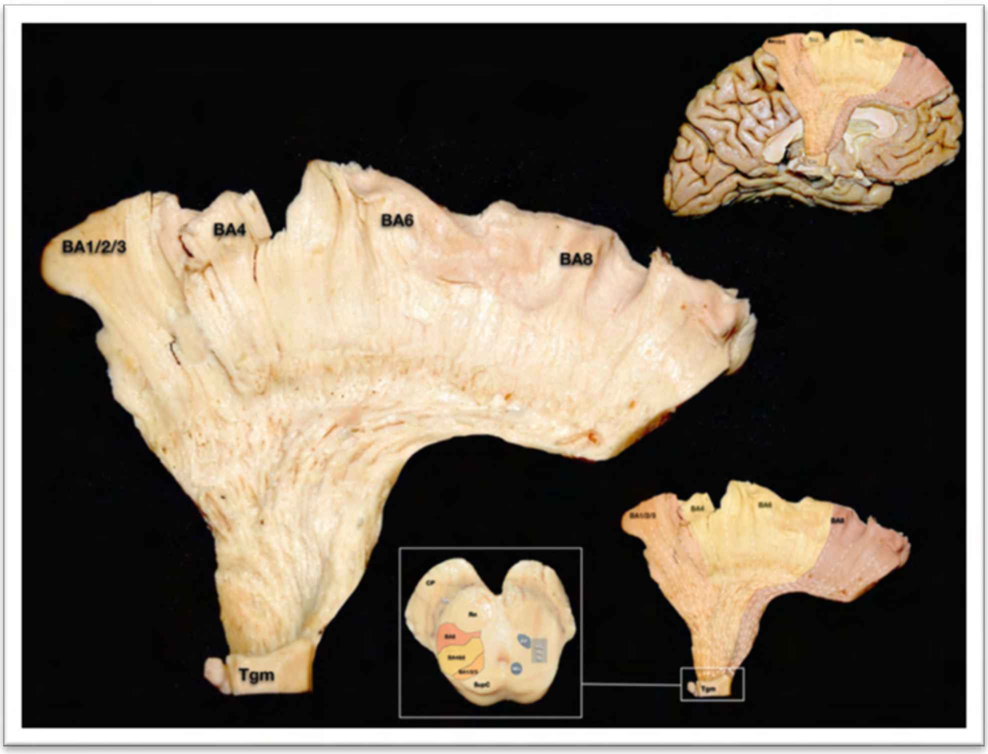


Figure.3.16 Medial views of a left hemisphere showing the morphology, cortical terminations and distribution pattern of CTT fibers in the Tegmental Entry Zone.

CTT fibers originate from the middle and posterior aspect of the superior frontal gyrus (BA6&8), precentral gyrus (BA4), postcentral gyrus (BA1/2/3) and paracentral lobule (BA4&BA1/2/3) and exhibit an oblique fan-shaped configuration.

Lower right Inset: Segmentation of the CTT according to cortical origins: anterior segment (red color) originates from BA8 (preSMA, DPFC, FEF), middle segment (yellow color) stems from BA4&BA6 (DPMC and MC) and posterior segment (orange color) starts from BA1/2/3(SC). The trajectory of each component is marked with interrupted lines.

Superior Inset: The silhouette of CTT is superimposed on the medial surface anatomy.

Lower left Inset: The Tegmental Entry Zone is illustrated. Different colors are used to highlight the distribution of fibers according to their cortical origin. The location of the mesencephalic reticular formation, medial lemniscus, spinal and trigeminal lemniscus and mesencephalic nucleus are also illustrated.

BA= Brodmann's Area, CP= Cerebral Peduncle, mL= Medial lemniscus, Mn= Mesencephalic Nucleus, RF= Reticular Formation, Rn= Red Nucleus, sL= Spinal lemniscus, Sn= Substantia Nigra, Tgm= Tegmentum, tL= Trigeminal lemniscus. Reprinted from Komaitis et al by permission of Neurosurgical Review - Springer Nature Publishing Group

Lateral to Medial Dissections

We included latero-medial dissections to give a complete anatomical perspective of the CTT. Upon removing the cortical grey matter and superficial U-fibers of the frontoparietal area, we expose the fibers of SLF. At the level of the insula and following progressive dissection of the extreme/external capsules and claustrum, we reveal the silhouette of the lentiform nucleus. The posterior part of the lentiform nucleus is removed to gain access to the genu of the internal capsule that comprises the corticospinal tract (CST) as its most superficial layer. The fibers of the CST are seen to project towards the cerebral peduncle, lying anterior to the substantia nigra. These fibers are meticulously removed to reveal the fibers of the CTT that course in a different trajectory, traveling in a plane posterior to the substantia nigra when entering the tegmental area.

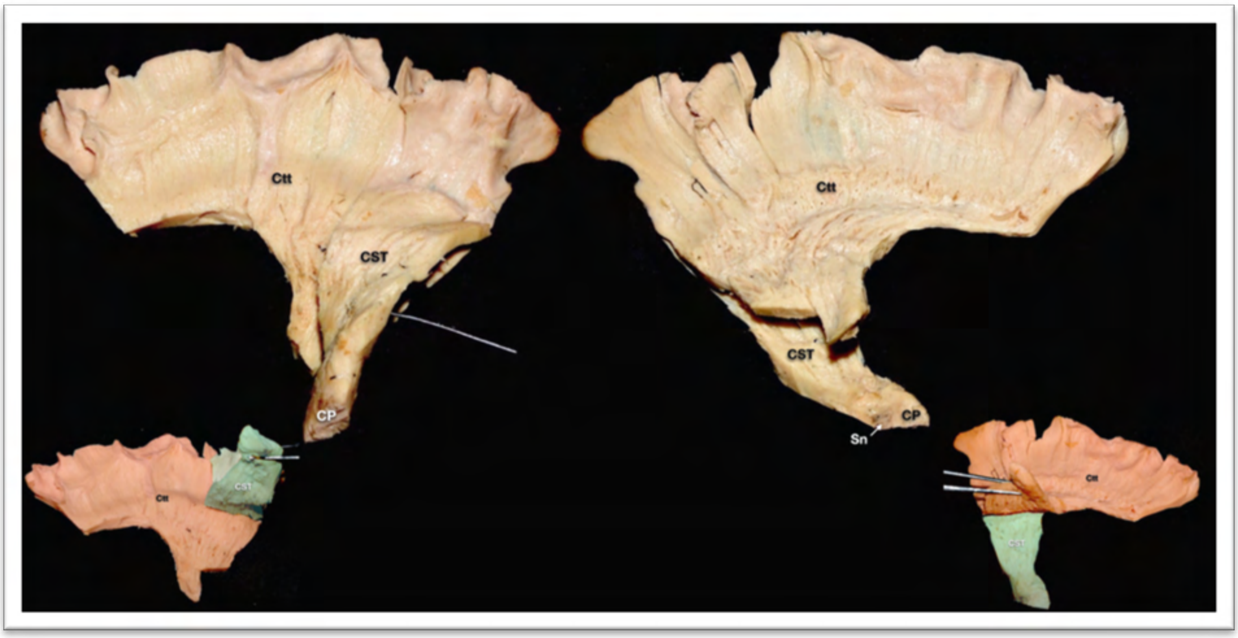


Figure.3.17. Lateral (left side of the photo) and medial views (right side of the photo) of an advanced dissection stage of a left sided specimen. The spatial relationships of the CTT and CST are shown. CTT incorporates fibers originating from a wider cortical area compared to the CST. CST travels anterior to the substantia nigra in contrast to CTT fibers that follow a more posterior trajectory. The different orientation of the two fiber systems can be appreciated. These two fibers tracts can be adequately dissected and differentiated in all studied hemispheres.

CP= Cerebral Peduncle, CST= Corticospinal Tract, Ctt= Corticotegmental Tract, Sn= Substantia Nigra Reprinted from Komaitis et al by permission of Neurosurgical Review - Springer Nature Publishing Group

3.5.2 MORPHOLOGY OF THE CTT AND ITS SPATIAL RELATIONSHIP TO ADJACENT FIBER TRACTS

As previously demonstrated, CTT fibers reside in the white matter of the genu and posterior limb of the internal capsule. The CTT can be traced medial to the fibers of the CST and lateral to the fibers of the thalamic radiations. While the fibers of the CST maintain a postero-superior to antero-inferior trajectory, radiating from the precentral gyrus to the cerebral peduncle, the trajectory of the CTT varies in the rostro-caudal axis. The caudal fibers exhibit a straight superior to inferior configuration while the rostral fibers adopt a lazy-S morphology, bending caudally and then inferiorly before entering the tegmentum. Additionally, the rostral aspect of the CTT was always bulkier in comparison to the caudal one.

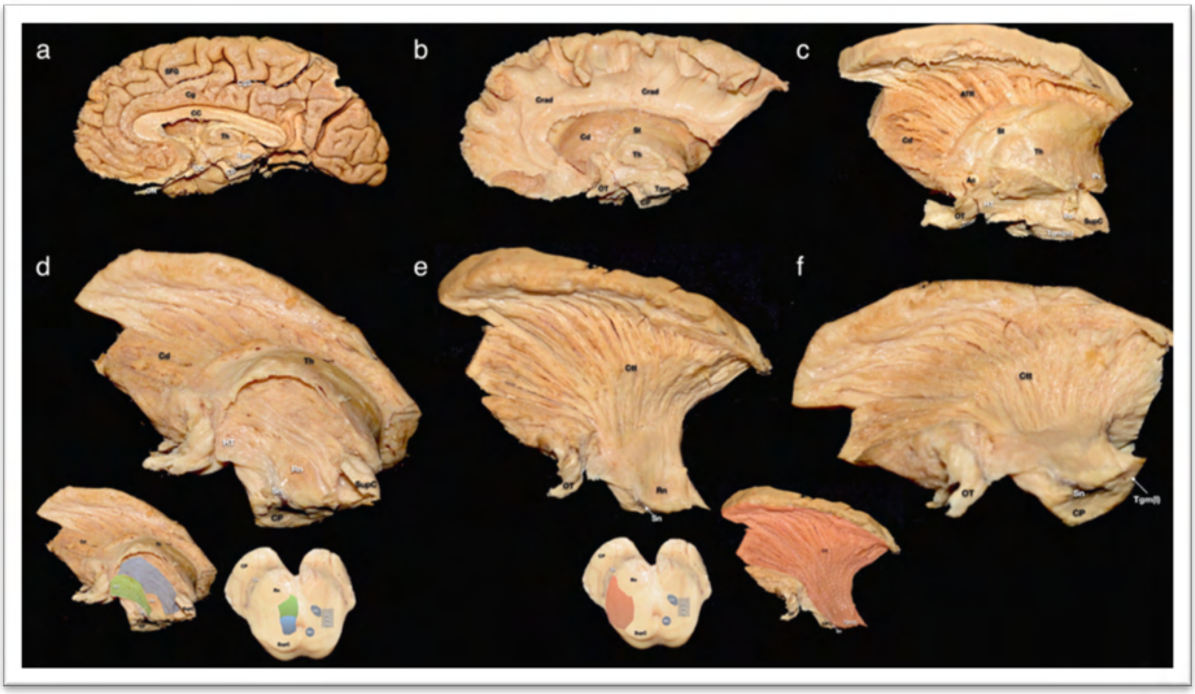


Figure.3.18. Medial views of a progressive nuanced dissection of a right hemisphere. The ventral allocation of CTT fibers and their relationships to diencephalic structures, thalamic radiations and thalamo/hypothalamotegmental fibers are shown.

A: Medial aspect of the hemisphere and corresponding surface anatomy.

B: The cortical grey matter, superficial U-fibers and superior arm of the cingulum have been removed exposing the callosal radiations.

C: The central core and mesencephalon are dissected free from the rest of the hemisphere. Removing the grey matter of the caudate nucleus reveals the anterior thalamic radiation (ATR). ATR fibers are seen to bypass the caudate and reach the thalamus at the area of the stria terminalis. Gradual dissection of the ATR exposes the fronto-caudate tract (FCT) as it terminates in the superolateral aspect of the caudate nucleus.

D: The medial aspect of the thalamus and hypothalamus is dissected to reveal the thalamo- and hypothalamo-tegmental fibers that project towards the medial aspect of the tegmentum. Inset (left): The thalamo-tegmental and hypothalamo-tegmental fibers are highlighted in blue and green color respectively.

Inset (right): The entry zone of the thalamo-tegmental and hypothalamo-tegmental fibers at the superior tegmentum (level of the superior colliculi) is highlighted in blue and green respectively.

E: Dissecting away the fibers of the ATR and the grey matter of the caudate nucleus uncovers the CTT. Its fibers travel posterior to the substantia nigra and enter the lateral aspect of the tegmentum.

Inset (left): The TEZ of the CTT is highlighted in red color.

Inset (right): CTT is highlighted in red color.

F: Inferomedial view of the same specimen. CTT fibers can be seen reaching the tegmentum at its lateral half.

Ac= Anterior Commissure, ATR= Anterior Thalamic Radiation, CC= Corpus Callosum, Cd= Caudate Nucleus, Cg= Cingulate Gyrus, CgS= Cingulate Sulcus, CP= Cerebral Peduncle, Crad= Callosal Radiations, HT= Hypothalamus, mL= Medial Lemniscus, Mn= Mesencephalic Nucleus, OC= Optic Chiasm, ON= Optic Nerve, OT= Optic Tract, Pc= Posterior Commissure, Pv= Pulvinar, RF= Reticular Formation, Rn= Red Nucleus, SFG= Superior Frontal Gyrus, sL= Spinal Lemniscus, Sn= Substantia Nigra, St= Stria Terminalis, Tgm(l)= Lateral Tegmental Area, Tgm(m)= Medial Tegmental Area, Tgm= Tegmentum, Tgm= Tegmentum, Th= Thalamus, tL= Trigeminal Lemniscus Reprinted from Komaitis et al by permission of Neurosurgical Review - Springer Nature Publishing Group

3.5.3 CORTICAL TERMINATION AREAS OF THE CTT

The fibers of the CTT could be traced in the middle and posterior part of the superior frontal gyrus (BA8 and BA6 respectively) in 100% of the studied specimens. These areas correspond to the dorsal premotor cortex, SMA, pre-SMA and frontal eye field (FEF). Consistent terminations (100% of the specimens) were also evident in the superior part of the precentral gyrus and supero-anterior part of the paracentral lobule (BA 4) i.e. the primary motor cortex. In 65% of cases, fibers of the CTT were tracked in the superior part of the postcentral gyrus and the supero-posterior part of the paracentral lobule (BA 1/2/3), areas that functionally correspond to the somatosensory cortex.

Interestingly, we did not observe hemispheric asymmetries regarding the CTT's morphology, topography or connectivity.

3.5.4 INTRODUCING THE "TEGMENTAL ENTRY ZONE(TEZ)" AND TRACKING THE INFRA-TEGMENTAL DISTRIBUTION OF CTT FIBERS

In all cases, the CTT reached the superior aspect of the tegmentum (level of the superior colliculi) in its lateral half, in contrast to the thalamo/hypothalamic-tegmental fibers that enter this area mainly (but not solely) in its medial half. CTT fibers stemming from BA8 were located anteriorly in this lateral tegmental zone, whereas fibers from BA4&BA6 and BA1/2/3 in the middle and posterior parts respectively. The term Tegmental Entry Zone (TEZ) was coined for this area and is used to stress the fact that this region does not represent the termination area of the CTT.

By dissecting the brainstem in a lateral to medial direction we were able to differentiate and classify four layers of white matter fibers. The first and most superficial layer consists of fibers projecting towards the superior cerebellar peduncle and lateral aspect of the floor of the fourth ventricle. These fibers were recorded to travel in 45° angle. The second layer is formed by fibers radiating towards the superior/inferior colliculi complex and superior aspect of the floor of the fourth ventricle (area of the locus coeruleus). These fibers share an orientation of 30 °. The third layer includes longitudinal projecting fibers running in a supero-inferior trajectory, from the tegmental area towards the lateral funiculus. Finally, the fourth and deepest layer exhibits fibers coming from the superior cerebellar peduncle and decussating towards the contralateral tegmental area, in the ventral tegmental decussation. By superimposing these four layers into the TEZ area we were able to put together a table showing the origin and projection of fibers categorized in 11 distinct zones.

Figure.3.19 Lateral to medial dissection of the brainstem below the level of the superior colliculi. A: Lateral view. In the first and most superficial layer the bulk of the fibers projects towards the superior cerebellar peduncle and the lateral part of the 4th ventricle floor. These fibers maintain an orientation of approximately 45°.

Inset: Fibers projecting to the superior cerebellar peduncle and to lateral aspect of the floor of the 4th ventricle are highlighted in light and dark pink respectively. The distribution of these fibers at the level of the TEZ is highlighted in pink in the axial plane.

B: Lateral view. The second consecutive layer of fibers can be seen to project towards the tectal area (superior and inferior colliculus) and the superior part of the 4th ventricular floor (area of the locus coeruleus). These fibers exhibit a more horizontal configuration of approximately 30-40°.

Inset: Fibers projecting to the tectal area and superior aspect of the floor of the 4th ventricle are highlighted in light and dark magenta respectively. The distribution of these fibers at the level of the TEZ in the axial plane is highlighted in magenta.

C: The 3rd consecutive layer mainly consists of longitudinal descending fibers that project in a 90° angle towards the lateral and anterior funiculus. These fibers travel at the same plane but posterior to the pyramidal fibers.

Inset: The longitudinal fibers projecting to the lower brainstem and spinal cord are highlighted in red color. The distribution of these fibers at the level of the TEZ in the axial plane is highlighted in red.

D: The 4th and deepest fiber layer can be seen to project from the superior cerebellar peduncle and red nucleus and contributes to the ventral tegmental decussation. These fibers take a 45° orientation towards the contralateral tegmental area.

Inset (lower): Fibers projecting towards the ventral tegmental decussation are highlighted in green. The distribution of these fibers at the level of the TEZ is highlighted in green.

Inset (upper): Postero-lateral view of a different specimen. The fibers originating from the superior cerebellar peduncle can be followed towards the ventral tegmental decussation. The more superficial fibers projecting to the tectum and locus coeruleus can be also appreciated.

E: Axial cut of the tegmentum at the level of the superior colliculi. Left side. The aforementioned layers are superimposed on the TEZ. In this way a diagram matching the respective cortical origins of the CTT fibers to possible projection areas below the level of the superior colliculus is created. This diagram includes 11 different zones that are summarized in TABLE 2. The same corresponding colors are used to illustrate the four subsequent layers of infrategmental fibers with respect to their cortical projection from Brodmann's Areas 1,2,3,4,6 and 8.

CP= Cerebral Peduncle, CST= Corticospinal tract, FVF(l)= Lateral aspect of the 4th ventricle floor, FVF(m)= Medial aspect of the 4th ventricle floor, FVF= Floor of the 4th ventricle, IC= Inferior Colliculus, Lc= Locus Coeruleus, MCP= Middle Cerebellar Peduncle, Rn= Red Nucleus, SC= Superior Colliculus, SCP= Superior Cerebellar Peduncle, Sn= Substantia Nigra, TST= Tegmentospinal tracts Reprinted from Komaitis et al by permission of Neurosurgical Review - Springer Nature Publishing Group

CHAPTER 4: DISCUSSION

4.1 THE DORSAL COMPONENT OF THE SLF

Since its first description in non-human primates by Petrides and Pandya in 1984, the SLF-I remains an equivocal, ill-defined anatomical structure, with unclear characteristics. Most of the recent evidence related to this fiber pathway derives from DTI studies and provides vague information regarding its microanatomical structure. Indeed, in 2005, Makris and colleagues, published for the first time tractographic evidence supporting the presence of the SLF-I as a distinct fiber tract in the human brain, interconnecting the superior parietal lobule, precuneus, central lobe, posterior part of the superior frontal gyrus and SMA complex. According to the authors, the SLF-I was found to lie in the dorsomedial part of the superior frontal gyrus.(3) Eight years later, Jang and Hong also recruited tractographic data to confirm the presence of the SLF-I as an association fiber tract connecting the same cortical areas.(10) Kamali and colleagues moved forward and published a DTI analysis describing the different subcomponents within the SLF system, namely the SLF-I, SLF-II and SLF-III. According to them, the SLF-I originates in the superior and medial parietal cortex, running within the cingulate gyrus and adjacent to the cingulum, before terminating in the dorsal and medial aspect of the frontal cortex.(5) In 2014, Hecht and colleagues studied the SLF-I both in humans and in non-human primates. They defined the SLF-I as a fiber tract connecting the superior frontal gyrus to the superior parietal lobule and further found a wider pattern of cortical terminations than before and a tendency of right lateralisation in non-human primates.(11) In a thorough tractographic analysis published in 2015, Wang and colleagues recorded the presence of the SLF-I as a distinct bundle interconnecting the aforementioned areas in 60% of the patients enrolled. In the cases where the SLF-I was identified, it was encountered medial to the corona radiata and in proximity to the cingulum within or superior to the white matter of the cingulate gyrus.(12) To date, tractographic studies have offered a rough anatomical understanding of this fiber tract with fluctuating however, variability on the extracted evidence and therefore no definite conclusions can be drawn on its intrinsic architecture and microanatomical characteristics.

Blunt dissection studies, in turn, addressing the morphology and architecture of the SLF-I are limited in the literature. In this context, a recent laboratory investigation entitled "Fiber tracts of the dorsal language stream in the human brain" by Yagmurlu and colleagues, advocated the presence of the SLF-I as a long association tract running parallel to the cingulum and above the level of the cingulate sulcus.(15) In the same vein, Baydin and colleagues published a paper on the white matter architecture of the inferior and medial aspects of the cerebrum in 2017, demonstrating this tract to course above the cingulate sulcus and medially to the callosal fibers, connecting the anterior cingulate gyrus to the medial frontal gyrus and precuneus.(16) Bozgurt et al, in an almost synchronous study focusing on the axonal connectivity of the SMA, confirmed these results.(13) Further, Monroy-Sossa et al, in their recently published paper regarding the microsurgical anatomy of the vertical rami of the SLF-II, reportedly encountered the SLF-I as a distinct bundle connecting the superior frontal gyrus to the precuneus. They also draw attention on the fact that the cingulate radiations at the level of the precuneus are located inferior and lateral to the SLF-I.(64) Evidently, these anatomic descriptions of the SLF-I provide a general concept about the tract's morphological characteristics and are neither focused nor detailed due to the more generic objective of the aforementioned studies. Furthermore, anatomic and tractographic data do not show a high degree of correspondence thus resulting in misinterpretations or misconceptions about the tract's architecture and axonal connectivity.

This discrepancy among anatomo-tractographic evidence has raised doubts over the existence of the SLF-I in the human brain, paving the way for the argument that this fiber tract has no anatomical integrity and actually represents a part of the cingulum. Indeed, Maldonado and colleagues published in 2012 a study in which their anatomic dissections did not confirm the existence of a discrete long association fiber tract running within the white matter of upper and middle portion of the medial frontal gyrus, paracentral lobule and precuneus. According to the authors, the presence of adjacent short association fibers (U-fibers) curving under the depth of the vertical sulci of the supero-medial cerebral aspect may give the false impression of a long association tract both in DTI and in cadaveric studies.(65) In 2016, Wang et al, supported that the SLF-I stems from the cingulum and is not related to the SLF-II and SLF-III fiber tracts.(12) In the same line, Wu and colleagues, while exploring the subdivisions of the cingulum through the fiber dissection technique, revealed a group of axons arising from the cingulum and arching between the precuneus and the SMA. They named these fibers the CBIV bundle of the cingulum and argued that this fiber group actually represents what has been incorrectly identified in previous studies as the SLF-I. (14) Table 1 provides a summary of the current literature on the dorsal component of the SLF.

Given the aforementioned diversity of findings, we aimed to shed light on the very existence and potential morphological characteristics of the SLF-I through a focused white matter dissection method since this is proven to be an approach of high anatomical accuracy and is regarded as the gold standard technique for validating data arising from DTI studies. Our results document that the SLF-I represents a distinct white matter tract, travelling always under the superficial U fibers of the cingulate or paracingulate gyrus, and connecting the cortical hubs of the medial cerebral hemisphere i.e. the anterior cingulate cortex (BA 32), the medial frontal gyrus (medial aspect of BA6,8,9), the paracentral lobule(BA1,2,3,4) and the superior parietal lobule and precuneus (BA5 and 7). In contrast to previous studies, we placed particular attention on the variability of the regional surface anatomy and recorded the paracingulate sulcus and gyrus as additional landmarks in 80% of cases. In our view, the presence and proper identification of this "paracingulate cortical pattern" is crucial. When a paracingulate gyrus is evident, then the SLF-I should always be encountered in this area and never within the white matter of the superior frontal gyrus. Dissecting only the medial aspect of the superior frontal gyrus in quest of the SLF-I can lead to the conclusion that this fiber tract is absent, as seen in the study by Maldonado and colleagues. Additionally, the paracingulate sulcus can be misinterpreted as the cingulate sulcus particularly in hemispheres with a non-prominent morphology of the anterior cingulate area. In this event, looking for the SLF-I above the superior bank of the misinterpreted "cingulate" sulcus will lead to false negative results. Thus, the presence of this "paracingulate cortical pattern" may add perplexity and confusion during data extraction and in our opinion, is the main reason for the inconsistency and ambiguity encountered across the relevant literature.

In all specimens, we further observed two discrete subcomponents with regard to the tract's trajectory to the cingulum: an anterior segment (SLF-Ia) and a posterior segment (SLF-Ip), with the point of their transition recorded approximately at the level of the anterior paracentral lobule. With respect to the relationship of SLF-I to the cingulum, we were able to develop a clear cleavage plane between the two adjacent tracts thus proving their anatomical integrity and independence and further validating the DTI results of Kamali et al. Interestingly, we failed to identify a direct anatomical relationship between the SLF-I and the SLF-II/ SLF-III complex whereas the pattern of its cortical connectivity is in line with current literature.

Since interconnecting regions such as the anterior cingulate cortex, pre-SMA, SMA proper, paracentral and precuneal lobule, the SLF-I is believed to participate in the neural circuit involved in the regulation of higher motor functions.(66) In fact, functional studies advocate the role of the pre-SMA in modifying learned motor behaviors based on environmental stimuli. In this regard, a pre-planned motor response could be amended according to the circumstances.(67, 68) The SMA in turn is heavily involved in processes like motor initiation, task-sequence control and speech. Many studies document that this region subserves bilateral initiation, sequencing and execution of motor patterns and is allegedly regarded as a “supramotor” hub.(69-74) Additionally, the precuneus is considered to be a high order cerebral area involved in self-perception based on visual and proprioceptive parameters. As part of the functional core of the Default Network, it integrates visuospatial information critical for self-perception and awareness.(75-81) According to Filimon and colleagues, the precuneus is parcellated into an anterior part processing visual input and a posterior part related mostly to non-visual proprioceptive afferent pathways.(75)

A recent analysis by Parlatini and colleagues, which combined tractographic with meta-analytic data, enriched our knowledge concerning the functional role of the three sub-components of the SLF. The results further confirm the role of the SLF-I in the spatial/motor circuitry. (82) The anatomical integrity and morphology of the SLF-I, as documented in our study, offer valuable insights on the structural connectivity of the aforementioned high order paralimbic areas, raising awareness about this tract's anatomo-functional significance. Future studies however are necessary to elucidate its precise role in normal and pathological conditions.

4.2 THE FRONTAL LONGITUDINAL SYSTEM

The motor - premotor areas have been constantly in the epicenter of various anatomical and functional endeavors both in human and non-human primates. Since the era of Penfield, Jasper and Rasmussen, data stemming from micro-stimulation, cytoarchitectonic, neurophysiologic and functional studies have paved the way towards a better and more comprehensive understanding of the organization and connectivity of the motor/premotor circuitry. The initial conceptualization of these regions as discrete units underpinning the pure execution of motor actions has been overshadowed during the last decades. Various field researchers nowadays support the notion that specific motor and cognitive functions interact and share common anatomo-functional substrates(26, 28, 83-85). Thus, the emerging hypothesis which strongly advocates the premotor cortex to act as an intermediate hub between prefrontal and primary motor areas has been gaining ground.(21, 22, 24) In this vein, the term "cognitive aspects of motor function" was recently coined in order to denote motor behaviors such as withholding and releasing of motor task responses, mental rotation, imagery, prediction of sequential motor, visual and auditory patterns and motor mimicking(26).

Adding to this concept, previous studies have considered the rostral part of the premotor cortex –primarily the rostro-dorsal premotor cortex- as an area believed to sub-serve mixed cognitive-motor functions.(25, 86) The dorsolateral prefrontal cortex in turn including BA 9 and 46, which is documented to mediate core cognitive high order executive functions such as working memory, cognitive flexibility and planning, has been documented to maintain a tight functional relationship with the premotor hub.(21) Studies in both non-human primates and humans support the hypothesis of an alleged circuitry serving the connectivity between the aforementioned areas.

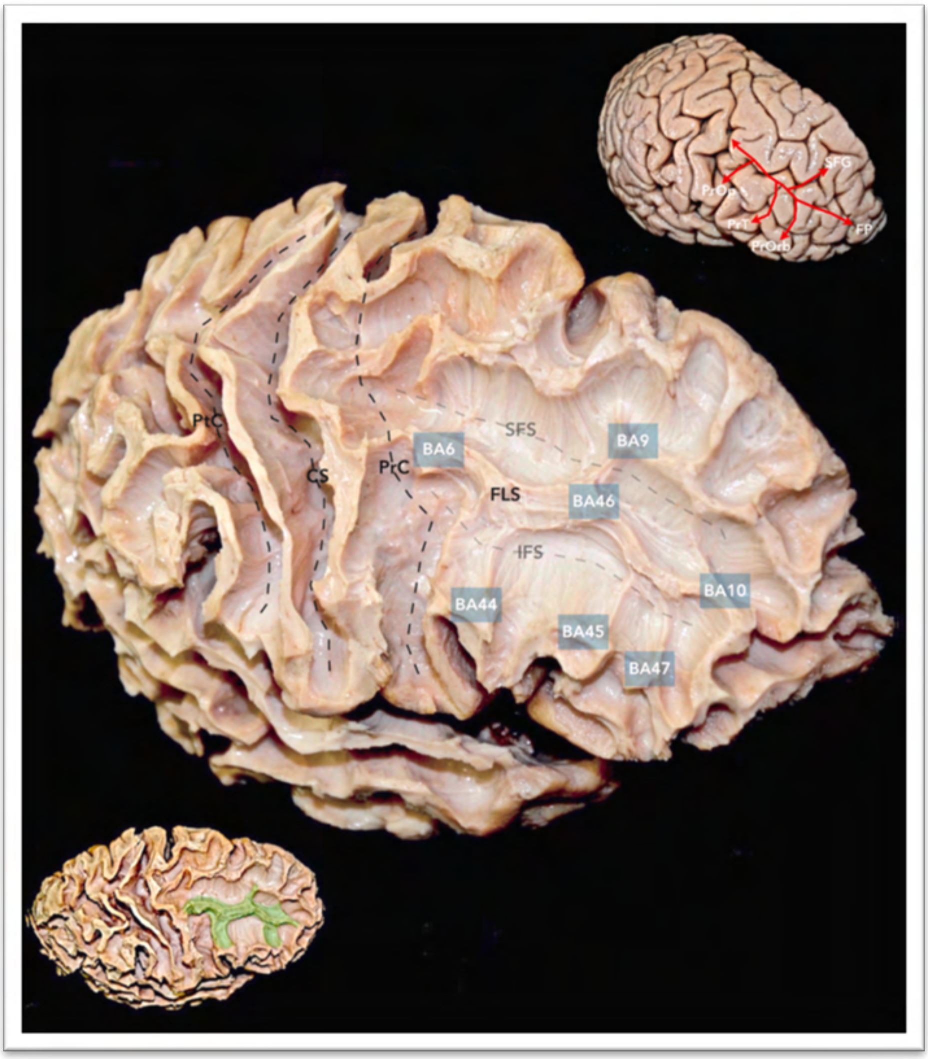


Figure.4.1: Morphology and connectivity of the FLS. Antero-Superior view of a dissected right hemisphere. The FLS fibers are evident at the level of the middle frontal gyrus, traveling anteriorly as far as the frontal pole. The interconnected Brodmann areas are highlighted in blue boxes. Inset: Upper-Right: Trajectory and terminations of the FLS superimposed on the superficial anatomy. Lower-Left: Morphology of the FLS highlighted in green color. BA= Brodmann's Area, CS= Central Sulcus, FLS= Frontal Longitudinal System, FP= Frontal Pole, IFS= Inferior Frontal Sulcus, PrC= Precentral Sulcus, PrG = Precentral Gyrus, PrOp= Pars Opercularis, PrOrb= Pars Orbitalis, PrT= Pars Triangularis, PtC= Postcentral Sulcus, SFG= Superior Frontal Gyrus, SFS= Superior Frontal Sulcus, PrOrb= Pars Orbitalis, PrT= Pars Triangularis, PtC= Postcentral Sulcus, SFG= Superior Frontal Gyrus, SFS= Superior Frontal Sulcus Reprinted from Komaitis et al by permission of the JNS Publishing Group

However, little anatomical evidence exists to support this notion in the human cerebrum. In this context, recently Catani and colleagues focused on the short connections of the human frontal lobe and provided for the first time in the literature structural evidence supporting the presence of a fiber system that could potentially underpin a prefrontal/premotor circuitry. The authors revealed, through limited anatomical dissections in one cadaveric hemisphere further enhanced by a tailored tractographic protocol, a white matter pathway, which they named "Frontal Longitudinal System, consisting of short and long fibers travelling in the middle frontal gyrus and connecting the dorsolateral aspects of premotor and prefrontal regions.(33) According to them, the FLS comprised two segments, a superior and an inferior longitudinal chain of fibers, with the first running from the precentral gyrus to the middle and superior frontal gyri and the latter from the precentral gyrus to the middle and inferior frontal gyri. They also observed that these fiber chains consistently converged towards the frontal pole. This axonal connectivity pattern lends support to a prefrontal-premotor circuitry in the human brain. Nonetheless, since this first description, there has been no additional structural evidence validating the existence of the FLS and further unveiling its morphology, topography and inherent subcortical architecture. Our aim was therefore to address this gap and shed light into the exact anatomical characteristics of this tract by using the white matter fiber dissection technique as our main method of investigation. This resurgent anatomical procedure, which entails the so called "freeze-thaw" preparation of cadaveric specimens, has been microscopically proved to preserve the structural integrity of the white matter axons and therefore the results obtained are of high anatomical accuracy and reliability.(20) On the contrary, although the DTI-tractographic method is a fast, non-invasive and in vivo technique for exploring the cerebral white matter architecture, it is however prone to anatomical inaccuracies, which can lead even to the reconstruction of “erroneous fiber tracts”, mainly due to the “crossing”, ‘kissing” and “bending” fiber effects and because of the differences observed in the post processing and acquisition parameters. As a consequence, DTI findings particularly regarding previously unrecognized or under-studied white matter tracts have to be fully validated and confirmed by the more robust and anatomically accurate white matter dissection technique. (See study strength and limitations section).(18, 87, 88)

Indeed, by using the fiber micro-dissection technique we were able to consistently encounter a fiber system with the same gross anatomical characteristics as described by Catani and colleagues. According to our findings the FLS represents a system that comprises short superficial fibers connecting adjacent areas of the precentral, superior, middle, inferior frontal gyri and the frontal pole as well as deeper fibers with longer configuration which connect more distant loci of the same areas. The FLS was found to reside within the white matter of the middle frontal gyrus, running parallel to the superior and inferior frontal sulci as previously described. We could effectively distinguish two distinct fiber systems, representing the superior and inferior longitudinal chains in only 13% of

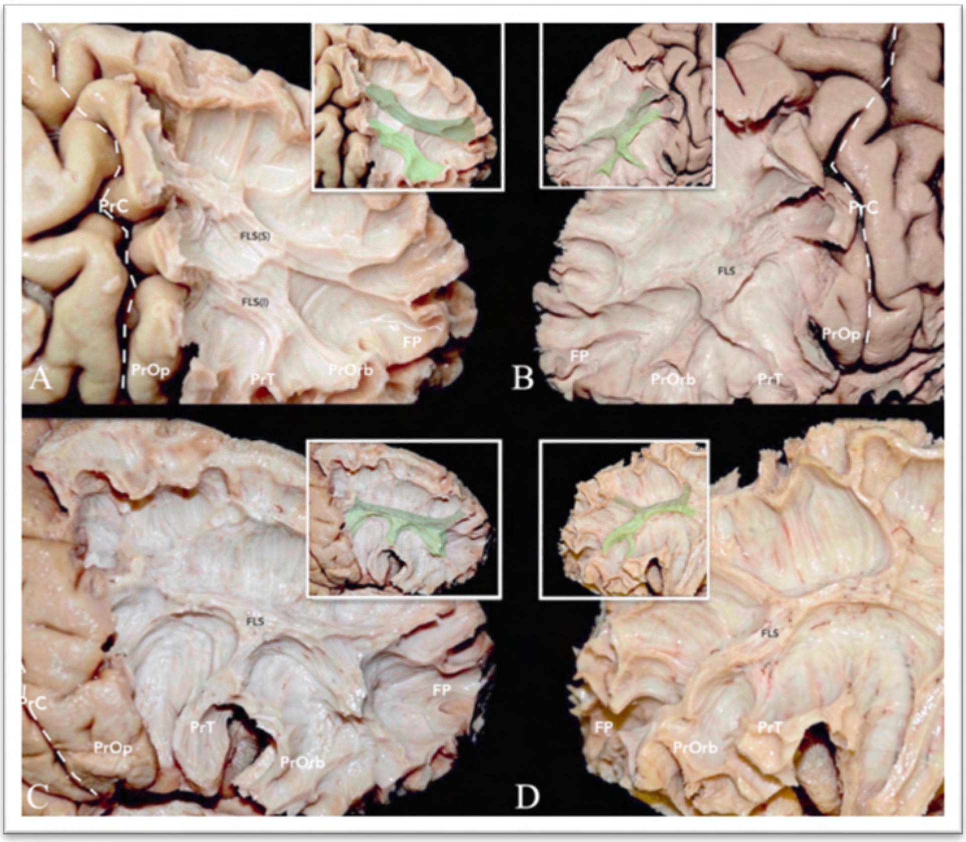


Figure.4.2: Different morphological patterns of the FLS in two left and two right hemispheres. A: Right hemisphere. The FLS consists of two discreet fiber systems: a superior and an inferior frontal longitudinal chain. Inset: The superior and inferior frontal longitudinal fibers are highlighted in dark and light green respectively. B: Left hemisphere. The superior and inferior fibers of the FLS converge into a single stem with no clear cleavage plane between them. Inset: The superior and inferior fibers are highlighted in dark and light green respectively. C: Right hemisphere. Again, the fibers of the FLS form a single stem and travel as far as the frontal pole. Inset: The superior and inferior aspect of the FLS are highlighted again in dark and light green respectively D: Right hemisphere. The fibers of the FLS form a single stem. Inset: Again the superior fibers are highlighted in dark green while the inferior fibers are highlighted in light green. FLS(I)= Frontal Longitudinal System: Inferior frontal longitudinal chain, FLS(S)= Frontal Longitudinal System: Superior frontal longitudinal chain, FLS= Frontal Longitudinal System, FP= Frontal Pole, PrC= Precentral Sulcus, PrOp= Pars Opercularis, PrOrb= Pars Orbitalis, PrT= Pars Triangularis Reprinted from Komaitis et al by permission of the JNS Publishing Group

the studied hemispheres. In the majority of the dissected specimens the superior and inferior fibers of the FLS converged to form a single stem that was recorded to reach the area of the frontal pole.

In addition, the termination pattern of the FLS was meticulously studied and recorded. Interestingly, the most consistent cortical terminations of the FLS were those found towards the posterior part of the middle and superior frontal gyri, which anatomically correspond to the rostral part of the dorsal premotor cortex [BA6]), and those on the middle frontal gyrus as well as the anterior part of the superior frontal gyrus, corresponding to the DLPFC (BA 46 and 9). This pattern of axonal connectivity is in line with data stemming from functional studies and documenting that the dorsolateral prefrontal cortex and the rostral aspect of the dorsal premotor cortex hold a close functional relationship and represent the major hubs of the prefrontal-premotor cross-talking system.(25)

During our dissections, special attention was given to the relationship between the frontal fibers assigned to the FLS and the fibers classically described as the Superior Longitudinal Fasciculus. The SLF has been recorded in the majority of previous DTI and fiber dissection studies to terminate in the area of the precentral gyrus (BA 4 & 6) and posterior part of the middle (BA 6) and inferior frontal gyri (BA 44).(3, 6, 12, 35) Terminations extending as far as the dorsolateral prefrontal cortex (BA 46& 9) have been also described by some authors.(5, 15, 89) In a further step, Yagmurlu and colleagues identified and recorded possible terminations of the SLF II in the area of the frontal pole(BA 10) in 28% of the studied specimens.(15) Additionally, in the extended 2018 tractographic study entitled “A Connectomic Atlas of the Human Cerebrum”, Sughrue and colleagues advocate that the SLF complex extends as far as the posterior part of the middle and inferior frontal gyri as well as to a part of the dorsolateral prefrontal cortex.(90, 91) These authors further support the local functional and white matter connectivity between adjacent frontal areas including the premotor cortex, the dorsolateral and rostrolateral prefrontal cortices and the frontal pole.(91)

We therefore aimed at defining the relationship between the SLF and the group of longitudinal fibers encountered in the frontal area, described by Catani and his colleagues to compose the FLS. Our data support the notion that the FLS macroscopically resembles an anterior extension of the SLF fibers. Indeed, in the majority of the studied specimens we observed the two fiber pathways to exhibit structural continuity. The concept of hyper-segmentation of the SLF has been advocated by previous authors.(3, 34) In our view, the FLS should be treated as a separate segment within the superior longitudinal fiber system for two reasons. First, we recorded cases where the FLS and SLF terminate in different areas and therefore constitute two distinct systems. Second, the FLS exhibits an intrinsic configuration and architecture that is different to this of the SLF, as its fibers seem to be confined and terminate exclusively in the area of the frontal lobe in contrast to the fibers of the SLF complex. In any case, these fiber pathways possibly share a pivotal role in the connectivity of the motor/premotor areas, with the SLF allegedly sub-serving its caudal connectivity and the FLS its rostral connectivity.

To our knowledge this is the first focused and dedicated anatomical study which sheds light into the exact anatomical and morphological characteristics of this frontal fiber system. Our data could offer valuable insights into the connectivity of the premotor area and further act as a sound anatomical basis for the tight functional relationship revealed between the prefrontal and premotor areas.

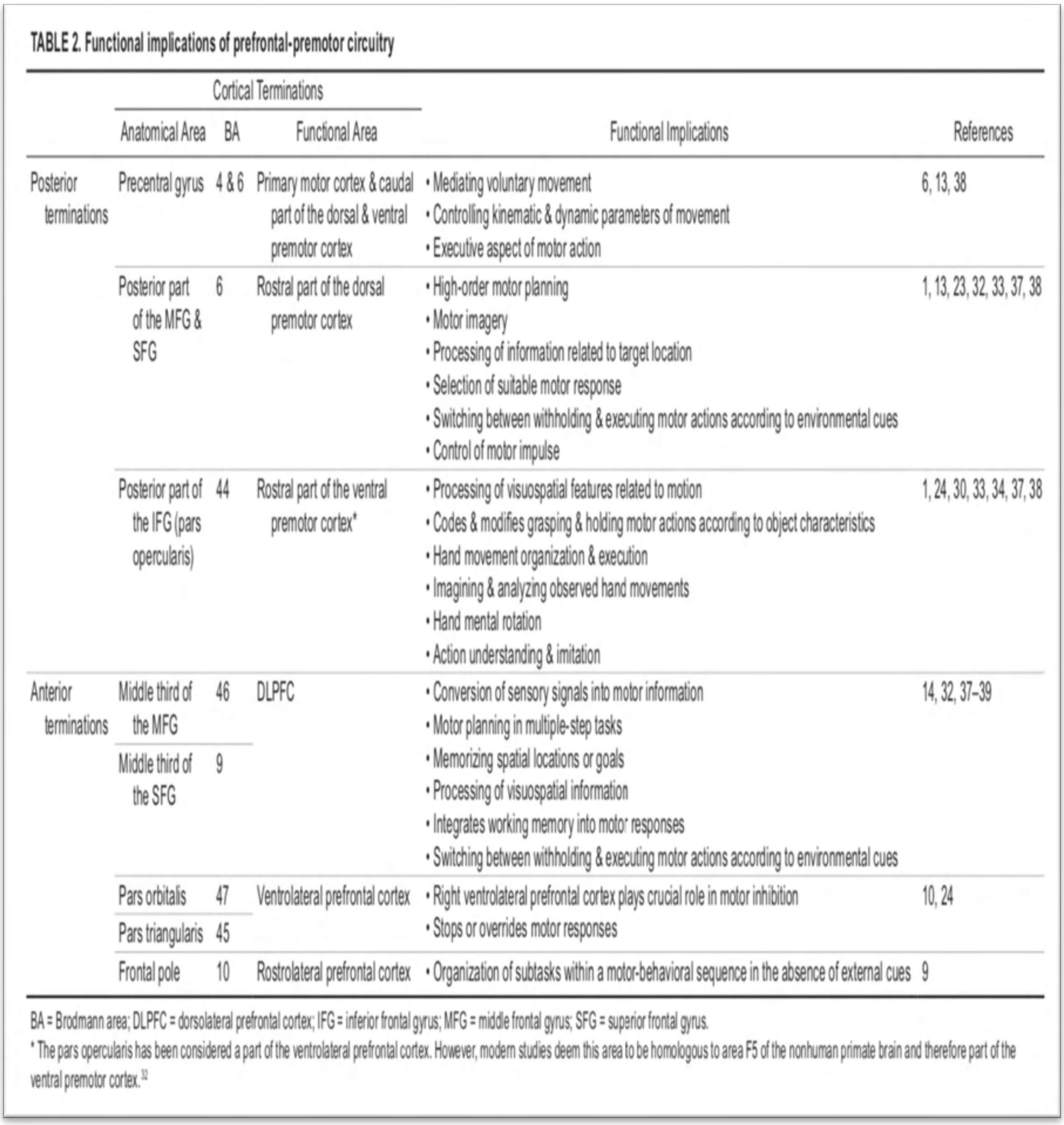


TABLE 2. Functional implications of prefrontal-premotor circuitry

	Cortical Terminations				
	Anatomical Area	BA	Functional Area	Functional Implications	References
Posterior terminations	Precentral gyrus	4 & 6	Primary motor cortex & caudal part of the dorsal & ventral premotor cortex	• Mediating voluntary movement • Controlling kinematic & dynamic parameters of movement • Executive aspect of motor action	6, 13, 38
	Posterior part of the MFG & SFG	6	Rostral part of the dorsal premotor cortex	• High-order motor planning • Motor imagery • Processing of information related to target location • Selection of suitable motor response • Switching between withholding & executing motor actions according to environmental cues • Control of motor impulse	1, 13, 23, 32, 33, 37, 38
	Posterior part of the IFG (pars opercularis)	44	Rostral part of the ventral premotor cortex*	• Processing of visuospatial features related to motion • Codes & modifies grasping & holding motor actions according to object characteristics • Hand movement organization & execution • Imagining & analyzing observed hand movements • Hand mental rotation • Action understanding & imitation	1, 24, 30, 33, 34, 37, 38
Anterior terminations	Middle third of the MFG	46	DLPFC	• Conversion of sensory signals into motor information • Motor planning in multiple-step tasks • Memorizing spatial locations or goals • Processing of visuospatial information • Integrates working memory into motor responses • Switching between withholding & executing motor actions according to environmental cues	14, 32, 37–39
	Middle third of the SFG	9			
	Pars orbitalis	47	Ventrolateral prefrontal cortex	• Right ventrolateral prefrontal cortex plays crucial role in motor inhibition • Stops or overrides motor responses	10, 24
	Pars triangularis	45			
	Frontal pole	10	Rostrolateral prefrontal cortex	• Organization of subtasks within a motor-behavioral sequence in the absence of external cues	9

BA = Brodmann area; DLPFC = dorsolateral prefrontal cortex; IFG = inferior frontal gyrus; MFG = middle frontal gyrus; SFG = superior frontal gyrus.

* The pars opercularis has been considered a part of the ventrolateral prefrontal cortex. However, modern studies deem this area to be homologous to area F5 of the nonhuman primate brain and therefore part of the ventral premotor cortex.[32]

4.3 THE FRONTOCAUDATE TRACT

In the neuroscientific literature, the existence of a wide fronto-striatal circuitry and its implication in higher motor and cognitive processes have been well appreciated. The caudate nucleus and putamen represent the main input of the basal ganglia and have been proven to exhibit strong connections with the prefrontal area both in animals and humans. Particularly, the head of the caudate constitutes the main target of afferent fibers stemming from both prefrontal and frontopolar cortices. (39, 40, 92-97) Many animal and human studies have paved the way towards a more comprehensive understanding of this fronto-striatal complex and have offered valuable insights into the topography and morphology of its different subcomponents. However, most of the existing data in humans derives from sophisticated DWI protocols while there seems to be a paucity of direct structural evidence much needed to shape a more accurate understanding of these pathways. In addition, the nomenclature used to describe the subcomponents of this network is inconstant, thus adding further perplexity.

Indeed, in Table 2 we provide a review of the literature focusing on the structural evidence of the fronto-caudate connectivity. More specifically, in a DTI study *Lehericy* and colleagues aimed to elucidate the SMA and pre-SMA connections to the human striatum.(98) The authors advocate that the caudate nucleus holds strong connectivity with the pre-SMA while the putamen is functionally relevant to the SMA and motor cortices. This pre-SMA/caudate stream is further implicated by the authors to subserve motor preparation and sequencing. Later, *Kamali* and colleagues coined the term “Prefronto-caudate pathway” to describe a group of fibers seen to arise from the prefrontal cortex and to curve around the head of the caudate nucleus before terminating to the thalamus.(93) The authors found the so called prefronto-caudate tract to travel medial in relation to the Anterior Thalamic Radiation (ATR) and postulated its functional implication in a broad spectrum of disorders including schizophrenia, Parkinson's and Huntington's disease. One of the very few studies providing direct structural evidence was that by *Rigoard* and colleagues.(96) The authors employed focused fiber dissections to explore the anatomy of the human accumbofrontal fasciculus and proposed three types of connections between the orbitofrontal cortex (OFC) and the striatum: the accumbofrontal fasciculus connecting the medial OFC with the nucleus accumbens and the intermediate and the lateral fasciculi connecting the medial and lateral OFC respectively with the head of the caudate nucleus. In an elegant study, *Kinoshita* and colleagues combined evidence from DTI and awake subcortical mapping and provided useful insights on the structural morphology, connectivity and function of the pre-SMA/caudate pathway.(99) The term "frontostriatal tract" was used to describe a group of fibers seen to lie medial to the Frontal Aslant Tract and to connect the pre-SMA with the anterior part of the caudate nucleus. The authors further advocated that this pathway was an integral part of a wider "negative motor network" since its stimulation elicited inhibition of motor initiation in both hemispheres and verbal fluency deficits in the dominant hemisphere. The topography of the FST proposed in the paper by *Kinoshita et al* was further supported by *Bozgurt* and colleagues in a DTI and fiber dissection study.(13) Again, the FST was identified as a fiber bundle connecting the pre-SMA with the caudate nucleus. However, in contrast to this anatomo-functional framework, recent DTI studies support the notion that the frontocaudate pathway extends to a wider termination area than previously thought, including the dorsolateral, orbitofrontal and ventrolateral prefrontal cortices.(100-102) Similarly, accumulating evidence advocates the theory that the fronto-caudate tract is also heavily implicated in behavioral symptoms including apathy in patients with ADHD.

It is therefore evident that the nomenclature used across studies is variable since some authors use the term frontocaudate or frontostriatal tract to describe the connectivity between the pre-SMA(13, 98, 99) and caudate while others use the same term to include additional fibers originating from the frontal pole and the dorsolateral, ventrolateral and orbitofrontal cortices.(33, 96, 100-102) This lack of consistent terminology paired with the diverse structural data met among different research groups adds confusion on the anatomy and functional significance of the fronto-caudate tract.

In an effort to elucidate this controversial issue, we used focused fiber dissections with the aim to offer sound evidence on the anatomy and essential characteristics of the FCT. We intentionally employed the white matter dissection technique as our basic method of investigation since it is documented to yield direct structural data of high accuracy and as such is currently used as one of the “gold standards” for validating DWI results. It needs to be stressed that although the DWI tractographic technique is a fast and non-invasive method that allows for real time fiber dissections, it is unfortunately prone to erroneous results mainly due to the effect of noisy peaks and ambiguous crossing-kissing fiber populations. Therefore, it has been repeatedly emphasized that even in ideal conditions the accuracy of such an indirect method like the DWI is inherently limited and further validation is necessary.(18, 103)

Hence, by using fiber dissections we were able to consistently identify a deep-seated fiber tract seen to connect a wide area of the prefrontal cortex with the head and anterior part of the body of the caudate nucleus. This tract, for which we use the name “fronto-caudate tract” after its connectivity pattern, exhibits a fan-shaped configuration with wide axonal terminations recorded towards the DLPFC, VLPFC, pre-SMA, OPPFC and OFC. We were also able to parcellate and differentiate the fibers radiating from the pre-SMA and dorsolateral prefrontal cortex from those coming from the frontopolar, orbitofrontal and ventrolateral prefrontal cortices. The former group of fibers was invariably observed to end posterior to the point marked by the transition of the head to the body of the caudate nucleus i.e. a point that corresponds to the foramen of Monro, while the latter group terminated anterior to this point. In this way, we could divide the tract into two distinct segments i.e. a dorsal one (FCTd) connecting the pre-SMA and DLPFC with the anterior part of the body of the caudate, and a ventral one (FCTv) connecting the OFPFC, OPPFC and VLPFC with the head of the caudate nucleus. This structural segmentation pattern is in agreement with previous studies advocating a functional distinction between a limbic and a cognitive fronto-striatal stream.

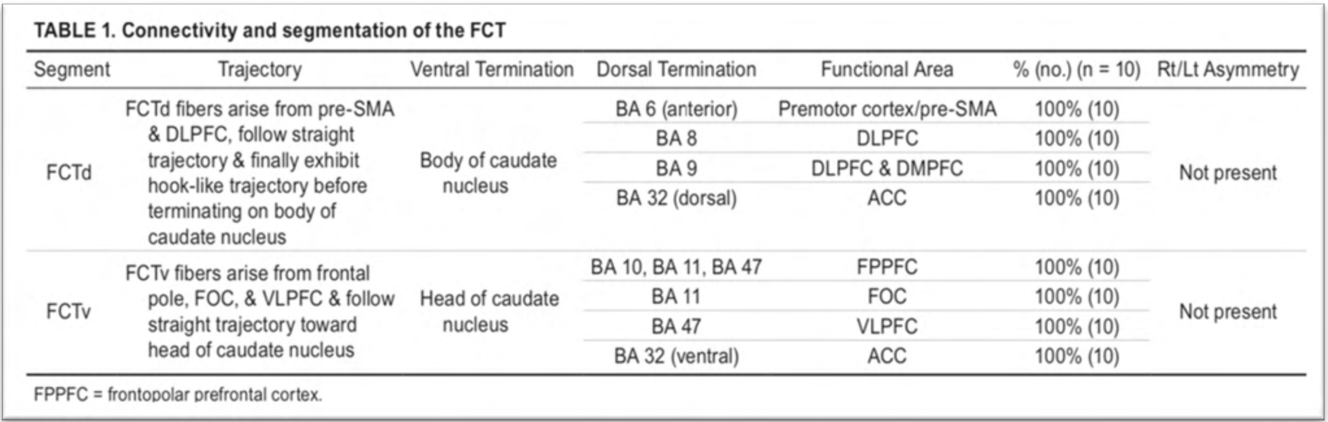


TABLE 1. Connectivity and segmentation of the FCT

Segment	Trajectory	Ventral Termination	Dorsal Termination	Functional Area	% (no.) (n = 10)	Rt/Lt Asymmetry
FCTd	FCTd fibers arise from pre-SMA & DLPFC, follow straight trajectory & finally exhibit hook-like trajectory before terminating on body of caudate nucleus	Body of caudate nucleus	BA 6 (anterior)	Premotor cortex/pre-SMA	100% (10)	Not present
			BA 8	DLPFC	100% (10)	
			BA 9	DLPFC & DMPFC	100% (10)	
			BA 32 (dorsal)	ACC	100% (10)	
FCTv	FCTv fibers arise from frontal pole, FOC, & VLPFC & follow straight trajectory toward head of caudate nucleus	Head of caudate nucleus	BA 10, BA 11, BA 47	FPPFC	100% (10)	Not present
			BA 11	FOC	100% (10)	
			BA 47	VLPFC	100% (10)	
			BA 32 (ventral)	ACC	100% (10)	

FPPFC = frontopolar prefrontal cortex.

Further, our findings on the topography and spatial relationships of the FCT are in line with the relevant literature. The FCT was always encountered to reside lateral to the callosal radiations and medial to the fibers of the Corona Radiata/Internal Capsule. Interestingly, the FCTv was seen to lie medial to the anterior limb of the internal capsule while the FCTd was encountered medial to the fibers of the anterior thalamic radiation that bypass the caudate nucleus to reach the thalamus. Left – right asymmetries were not observed but instead we recorded an asymmetry within the FCT itself, with the ventral segment being always thicker and bulkier than the dorsal. One can therefore hypothesize that the caudate nucleus exhibits stronger connectivity with the frontopolar and orbitofrontal cortices than with the pre-SMA and dorsolateral prefrontal cortex.

Functional Role of the FCT.

The results of the current study lend support to traditional theories on the functional significance of the prefrontocaudate connectivity. Alexander describes three discrete fronto-striatal circuits: a sensorimotor circuit processing information related to somato-motor and oculomotor function, an association (or cognitive) circuit connecting the pre-SMA and DLPFC to the striatum and a limbic circuit connecting the orbitofrontal cortex to the striatum.(39) The association circuit is believed to orchestrate cognitive motor functions, such as visuo-motor association, sequencing and motor learning. Awake stimulation evidence also supports the notion that the association circuit is heavily involved in motor initiation and verbal fluency.(99) The limbic circuit in turn is implicated in behavioral inhibition, decision-making and motivation. In this framework, the fronto-striatal loop has been linked with a wide spectrum of motor and behavioral clinical entities like autism, Parkinson and Huntington disease, schizophrenia and ADHD.(42, 43, 47, 104) Indeed, our proposed connectivity and segmentation pattern offers sound structural basis for Alexander's functional paradigm. In that respect, the dorsal FCT seems to equal the association stream while the ventral FCT is homologous to the limbic stream.

Overall, the Fronto-caudate tract is documented to participate in the functional connectivity of the caudate nucleus with premotor and prefrontal areas. Hence, it can be conceptualized as a pathway bridging cognitive and motor behaviors. The caudate nucleus has been advocated to participate in a plethora of motor and non-motor processes such as procedural and associative learning and motor initiation and/or inhibition.(97) Likewise, the premotor cortex, orchestrates motor planning, sequencing and modification by integrating internal cognitive and external sensory cues.(84) The SMA/pre-SMA complex in turn, controls motor sequencing, internal generated movement, locomotion and postural stability and also plays a key-role in motor ignition during volitional movement.(71) Finally, the dorsal prefrontal, orbitofrontal and frontal pole cortices are linked to a wide spectrum of cognitive and behavioral functions including execution, attention, decision making, complex behavioral planning and social control.(105) Since one way to infer the function of subcortical pathways is to map their axonal connectivity, it can be postulated that the FCT is implicated in integrating high order behaviors such as motor and speech initiation, inhibition and sequencing, postural and gait stability, locomotion, attention preservation and shift, reward/reinforcement processes, planning and motivation. It is clear however that more clinical data is needed for a thorough understanding of the tract's anatomo-functional significance.

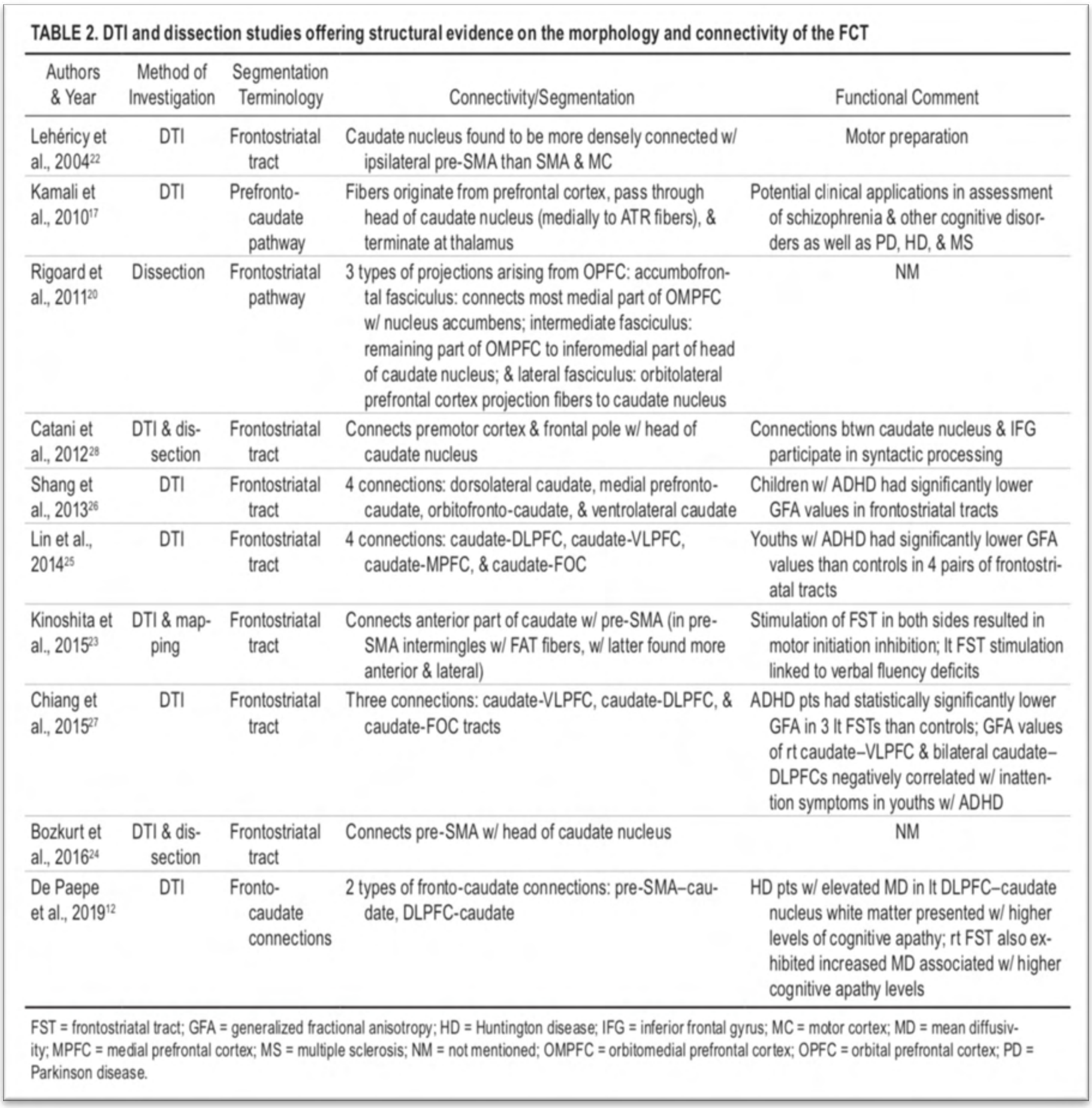


TABLE 2. DTI and dissection studies offering structural evidence on the morphology and connectivity of the FCT

Authors & Year	Method of Investigation	Segmentation Terminology	Connectivity/Segmentation	Functional Comment
Lehéricy et al., 2004[22]	DTI	Frontostriatal tract	Caudate nucleus found to be more densely connected w/ ipsilateral pre-SMA than SMA & MC	Motor preparation
Kamali et al., 2010[17]	DTI	Prefronto-caudate pathway	Fibers originate from prefrontal cortex, pass through head of caudate nucleus (medially to ATR fibers), & terminate at thalamus	Potential clinical applications in assessment of schizophrenia & other cognitive disorders as well as PD, HD, & MS
Rigoard et al., 2011[20]	Dissection	Frontostriatal pathway	3 types of projections arising from OPFC: accumbofrontal fasciculus: connects most medial part of OMPFC w/ nucleus accumbens; intermediate fasciculus: remaining part of OMPFC to inferomedial part of head of caudate nucleus; & lateral fasciculus: orbitolateral prefrontal cortex projection fibers to caudate nucleus	NM
Catani et al., 2012[28]	DTI & dissection	Frontostriatal tract	Connects premotor cortex & frontal pole w/ head of caudate nucleus	Connections btwn caudate nucleus & IFG participate in syntactic processing
Shang et al., 2013[26]	DTI	Frontostriatal tract	4 connections: dorsolateral caudate, medial prefronto-caudate, orbitofronto-caudate, & ventrolateral caudate	Children w/ ADHD had significantly lower GFA values in frontostriatal tracts
Lin et al., 2014[25]	DTI	Frontostriatal tract	4 connections: caudate-DLPFC, caudate-VLPFC, caudate-MPFC, & caudate-FOC	Youths w/ ADHD had significantly lower GFA values than controls in 4 pairs of frontostriatal tracts
Kinoshita et al., 2015[23]	DTI & mapping	Frontostriatal tract	Connects anterior part of caudate w/ pre-SMA (in pre-SMA intermingles w/ FAT fibers, w/ latter found more anterior & lateral)	Stimulation of FST in both sides resulted in motor initiation inhibition; lt FST stimulation linked to verbal fluency deficits
Chiang et al., 2015[27]	DTI	Frontostriatal tract	Three connections: caudate-VLPFC, caudate-DLPFC, & caudate-FOC tracts	ADHD pts had statistically significantly lower GFA in 3 lt FSTs than controls; GFA values of rt caudate–VLPFC & bilateral caudate–DLPFCs negatively correlated w/ inattention symptoms in youths w/ ADHD
Bozkurt et al., 2016[24]	DTI & dissection	Frontostriatal tract	Connects pre-SMA w/ head of caudate nucleus	NM
De Paepe et al., 2019[12]	DTI	Fronto-caudate connections	2 types of fronto-caudate connections: pre-SMA–caudate, DLPFC-caudate	HD pts w/ elevated MD in lt DLPFC–caudate nucleus white matter presented w/ higher levels of cognitive apathy; rt FST also exhibited increased MD associated w/ higher cognitive apathy levels

FST = frontostriatal tract; GFA = generalized fractional anisotropy; HD = Huntington disease; IFG = inferior frontal gyrus; MC = motor cortex; MD = mean diffusivity; MPFC = medial prefrontal cortex; MS = multiple sclerosis; NM = not mentioned; OMPFC = orbitomedial prefrontal cortex; OPFC = orbital prefrontal cortex; PD = Parkinson disease.

The role of the FCT in modern Neurosurgery

The role of the Ventral Internal Capsule/Ventral Striatum (VCVS) as an effective and feasible target for DBS in patients with depressive and OCD related conditions has been thoroughly addressed by recent well-designed clinical studies.(106-108) This surgical application arises from the hypothesis that DBS may act indirectly on the cortex, by intervening with the underlying white matter.(109) Because of the wide cortical distribution pattern of fiber pathways, stimulating a confined area of white matter can putatively affect multiple cortical territories. In this regard, by stimulating the VCVS one could modify the activity of the orbitofrontal and medial prefrontal cortices, which are believed to participate in cognitive processes such as that of behavioral shaping driven by environmental cues. Hence, a better understanding of the spatial distribution of frontal fibers and their respective termination areas could contribute to a more effective and sophisticated DBS planning. In this framework, the confined area that the Frontocaudate Tract converges either to the head of the caudate as the ventral FCT or to the transition of the caudate head and body as the dorsal FCT may potentially offer novel DBS targets for motor or psychiatric disorders. This also hold true for the newly introduced stereotactic ablative procedures used in modern functional neurosurgery.

In modern glioma surgery, awareness should be raised with regard to the implication of the FCT in what is known as the “negative motor modulatory network”.(110) Evidence from awake brain mapping studies has linked the stimulation of the frontostriatal circuitry with intraoperative unilateral or bilateral movement disorders for both hemispheres and verbal fluency deficits for the dominant one.(99) Eventhough, the risk of a permanent and complete SMA syndrome (contralateral akinesia and mutism) is not high when resecting or transgressing negative motor areas, indeed deficits in the control of fine motor behaviors, bimanual coordination and dexterity may be present and should be carefully balanced in the preoperative planning and decision making.(111, 112) A tailored approach to achieve the optimal onco-functional balance for a given patient taking into consideration oncological, functional, occupational and quality of life characteristics along with the patient's personal will and consent is the mainstay of modern neuro-oncological treatment.(113) This becomes even more relevant with regard to the emerging concept of "supratotal resections" applied both in low and high-grade lesions to extent progression free and overall survival, where a very balanced decision should be carefully made along the aforementioned lines.

4.4 THE CORTICOTEGMENTAL TRACT

The extrapyramidal system is typically divided in a cortical-basal ganglia-cortical loop and a descending corticofugal component.(50, 114, 115) The corticofugal part is further subdivided into components that are categorized according to their connectivity pattern. To this end, cortico-rubro-spinal, cortico-rubro-cerebellar, cortico-reticulo-spinal, cortico-tecto-spinal and cortico-vestibulo-spinal pathways have been identified as distinct functional units within the extrapyramidal mosaic.(50, 56, 57, 115-119) With regard to their macroscopic anatomy, it has been advocated by previous tractographic studies that the main bulk of the human descending extrapyramidal fibers converge towards a confined anatomical area within the internal capsule and form a wide cortico-tegmental system before reaching the brainstem.(117, 118, 120, 121) This fiber system can be therefore perceived as an extensive cortico-subcortical river that receives various extrapyramidal tributaries. A key anatomical observation in support of the structural relationship of the CTT to the extrapyramidal circuitry is that the fibers of this bundle were consistently recorded to connect the cortex with the tegmental area and cannot be allocated to any of the major sensory pathways passing through the tegmental area since these typically synapse in the thalamus. (122, 123)

Among the most well studied cortico-tegmental subcomponents is the cortico-reticular tract (CRT). This pathway that allegedly participates in postural control and locomotor function has attracted special attention during the last decade. More specifically, Yeo and colleagues published the first DTI study which provides structural evidence on the anatomy of the human cortico-reticular tract.(124) The authors succeeded in consistently identifying the CRT as a fascicle initially stemming from the premotor cortex (BA6) and precentral gyrus (BA4), projecting then medially and anterior to the CST and entering the tegmental area before terminating in the mesencephalic and pontine reticular formation. In a recent paper Jang and Seo explored the cortical distribution of the CRT.(125) According to the authors the tract was seen to originate predominantly from the primary motor and premotor cortex (100% of the hemispheres), with axons traced in the somatosensory cortex in 76.2% of cases. Later on, the same authors validated the subcortical distribution of the CRT in agreement with the pattern proposed by Yeo and colleagues.(118)

The cortico-rubral projections in turn have been repeatedly investigated in the non-human primate brain. According to the seminal studies of Humphrey, Gold and Reed, the red nucleus receives direct cortical input from areas BA4, BA6, BA8 and BA 5.(54, 55) Nevertheless, very limited evidence exists on the related anatomy and connectivity of this tract in the human brain. Recent DTI studies support the existence of a cortico-rubral pathway connecting the superior frontal gyrus, superior aspect of the precentral and postcentral gyri and paracentral lobule to the red nucleus.(53, 121, 126) According to these reports the cortico-rubral fibers travel within the internal capsule before reaching their target. Below the level of the red nucleus, the cortico-rubral fibers seem to be distributed along two descending pathways: the rubro-cerebellar pathway projecting to the ipsilateral and contralateral cerebellar hemisphere through the superior cerebellar peduncle and the rubro-spinal entering the lateral funiculus.

While the direct connectivity between the cortex, reticular formation and red nucleus has been more or less documented, cortical projections to the tectum and oculomotor nuclei have only been advocated by studies in non-human primates. The term cortico-mesencephalic tract has been used by Levin in 1936 to describe projections from BA8 to the tegmental area. Forty years later, Astruc and colleagues validated the presence of relevant fibers that originate from BA8 and travel within the internal capsule towards the tegmental area, again in the brain of non-human primates.(127) However, the presence of a cortico-tectal or cortico-mesencephalic pathway involved in oculomotor function has not been adequately supported by relevant structural evidence in humans.

It can be well argued that tractographic studies have offered a crucial yet generic anatomical perspective of the various fiber tracts that contribute to the corticotegmental connectivity and therefore it is difficult to draw definite conclusions on the topography and architecture of the fibers of this system. It is for this reason that we opted to explore the structural characteristics of the descending extrapyramidal pathway through a direct anatomical method like the white matter fiber dissection technique, which as meticulously proven provides data of high accuracy. Hence, our results reveal that the CTT can be consistently traced as a distinct white matter pathway traveling in the deep layer of the genu and posterior limb of the internal capsule. It is always located medial to the CST and exhibits a different fiber orientation, maintaining a clear but tight cleavage plane from the CST, which aids in their proper differentiation. In addition, we were able to systematically map the cortical termination pattern of the CTT. This area includes the superior aspect of motor, premotor, dorsal prefrontal and somatosensory cortices and coincides with the cortical origin of the various extrapyramidal tracts as illustrated by previous tractographic studies.

We further went on and tried to parcellate these fibers according to their corresponding cortical -and therefore functional- origin. As analyzed in the Results section, the fibers originating from BA8, BA4/6 and BA1/2/3 share an antero-posterior spatial orientation. Hence, the CTT can be perceived as a fiber tract composed of 3 distinct anatomo-functional segments: an anterior segment stemming from the pre-SMA/FEF/DPMC, a middle segment descending from the DPMC and PMC and a posterior segment carrying fibers from the SC. In a step further, we meticulously defined the infra-tegmental distribution of these fibers among various descending pathways projecting to the tectal area (cortico-tectal pathway, cortico-mesencephalic pathway), superior cerebellar peduncle (cortico-rubro-cerebellar pathway), floor of the fourth ventricle (projections to locus coeruleus, vestibular nuclei and oculomotor nuclei) and tegmento-spinal connections towards the anterior(anterior reticulo-spinal) and lateral (lateral reticulo-spinal and rubro-spinal tracts) funiculus.

The results of this study lend support to the hypothesis that the CTT serves primarily as an extrapyramidal "conduit", although it cannot be excluded that fibers conveying different functions are also included. As such the CTT allegedly represents a carrier of multimodal cues related to locomotion, postural control, tone adjustment, motor inhibition, organization of complex movements and reflex control.

Towards a dynamic, hodotopical and delocalized model for motor behavior: Anatomo-functional substrates and clinical repercussions.

In neuroscience, the corticospinal and corticobulbar tracts have attracted special interest and have been extensively studied as key-components for the preservation of motor function. In this vein and mainly driven by the advent of awake brain mapping techniques, numerous studies have offered important online data with regard to the function and neural correlates of the pyramidal circuitry by means of MEPs, direct cortical stimulation of the primary motor cortex and subcortical stimulation of the corticospinal fibers.(128-133) Further and in the same context, tractographic representations of the CST's topography have also been used in intraoperative neuronavigation systems during image guided neurosurgical procedures as a method to preserve the primary motor circuit and to correlate anatomical, functional and radiological data.(134-137) Nonetheless, the same spirit did not apply for the extrapyramidal component of the human motor network mainly because its structural architecture was for a long period ill defined.

However, a paradigm-shift is emerging. Our perception of the neural correlates of fine motor behaviors has significantly changed primarily due to the results of awake brain mapping studies in combination with novel structural data stemming from white matter dissection and tractographic techniques.(110, 113, 138) In essence, the role and relationship of the human pyramidal and extrapyramidal systems in motor organization and execution have been reassessed in the light of converging anatomo-functional evidence focusing on extrapyramidal pathways like the fronto-caudate tract, the frontostriatal pathway, the frontal aslant tract, the frontal longitudinal system etc. and pave the way towards a parallel, delocalized and dynamic model for motor behavior.(48, 99, 139, 140)

To this end, clarifying the anatomical architecture of the extrapyramidal system is crucial to the development of methods to map and further appreciate the role of this network in programming and execution of movement. The present endeavor is one of the limited studies offering sound structural evidence on the morphological characteristics of the descending human extrapyramidal pathway that could be employed intraoperatively to assess its function and clinical significance. Future studies are definitely needed to further link the spatial structural distribution with the functional sub-specialization of the human extrapyramidal pathways.

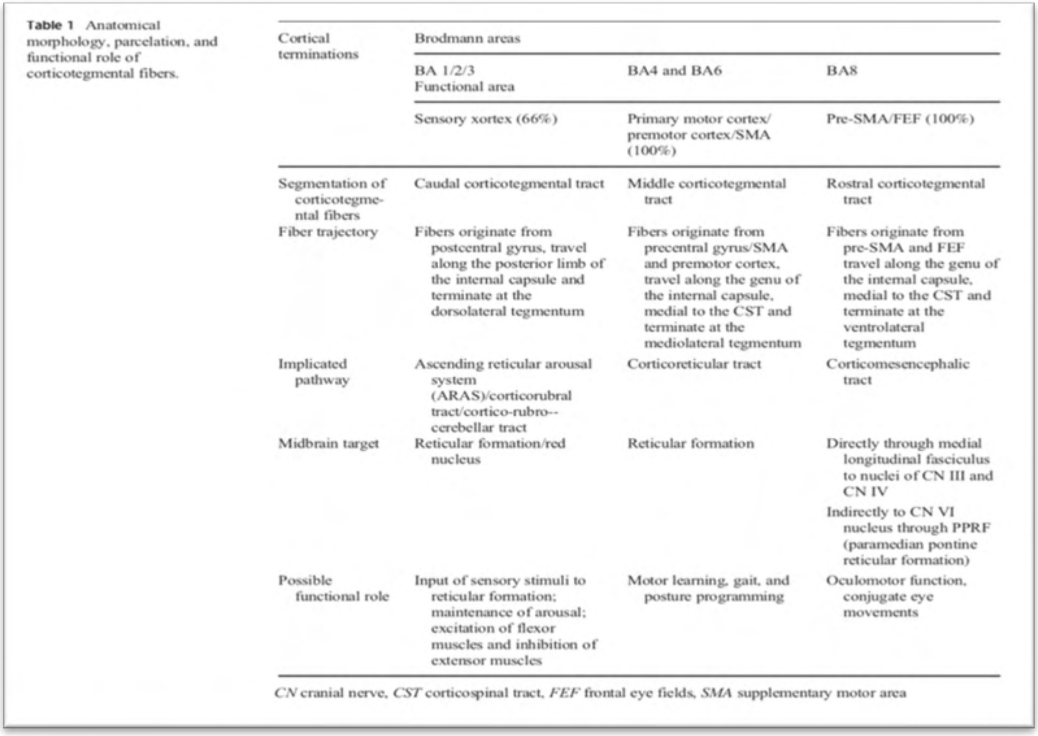


Table 1 Anatomical morphology, parcelation, and functional role of corticotegmental fibers.

Cortical terminations	Brodmann areas		
	BA 1/2/3 Functional area	BA4 and BA6	BA8
	Sensory xortex (66%)	Primary motor cortex/ premotor cortex/SMA (100%)	Pre-SMA/FEF (100%)
Segmentation of corticotegmental fibers	Caudal corticotegmental tract	Middle corticotegmental tract	Rostral corticotegmental tract
Fiber trajectory	Fibers originate from postcentral gyrus, travel along the posterior limb of the internal capsule and terminate at the dorsolateral tegmentum	Fibers originate from precentral gyrus/SMA and premotor cortex, travel along the genu of the internal capsule, medial to the CST and terminate at the mediolateral tegmentum	Fibers originate from pre-SMA and FEF travel along the genu of the internal capsule, medial to the CST and terminate at the ventrolateral tegmentum
Implicated pathway	Ascending reticular arousal system (ARAS)/corticorubral tract/cortico-rubro--cerebellar tract	Corticoreticular tract	Corticomesencephalic tract
Midbrain target	Reticular formation/red nucleus	Reticular formation	Directly through medial longitudinal fasciculus to nuclei of CN III and CN IV Indirectly to CN VI nucleus through PPRF (paramedian pontine reticular formation)
Possible functional role	Input of sensory stimuli to reticular formation; maintenance of arousal; excitation of flexor muscles and inhibition of extensor muscles	Motor learning, gait, and posture programming	Oculomotor function, conjugate eye movements

CN cranial nerve, *CST* corticospinal tract, *FEF* frontal eye fields, *SMA* supplementary motor area

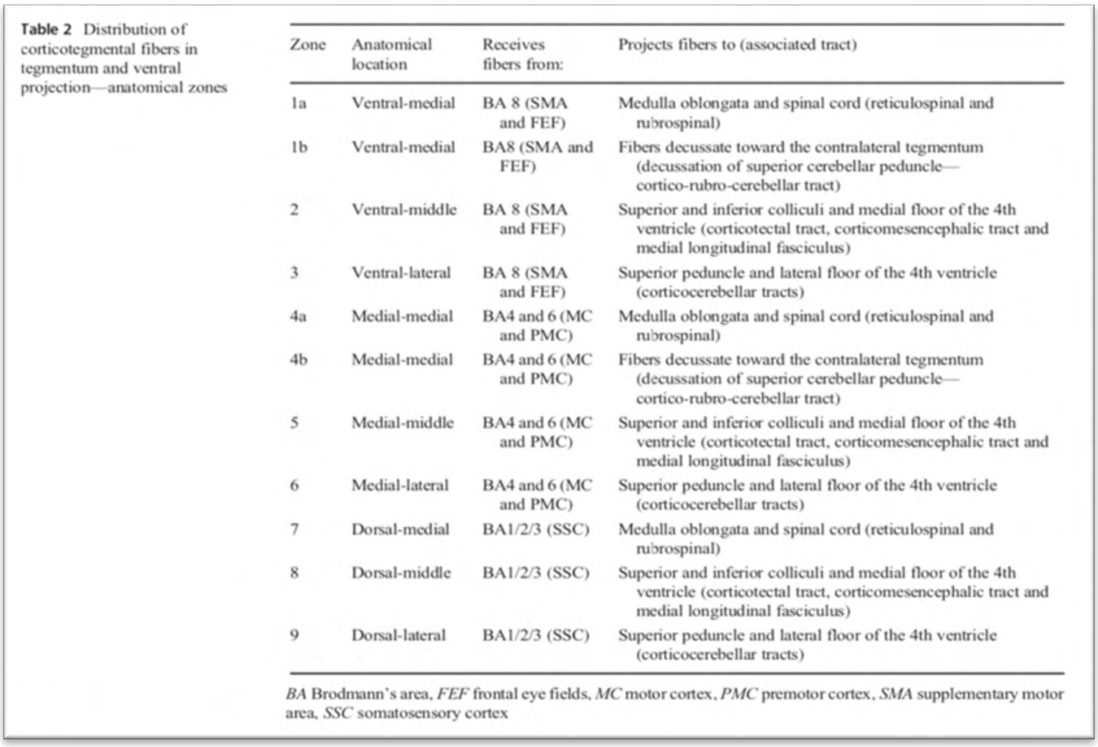


Table 2 Distribution of corticotegmental fibers in tegmentum and ventral projection—anatomical zones

Zone	Anatomical location	Receives fibers from:	Projects fibers to (associated tract)
1a	Ventral-medial	BA 8 (SMA and FEF)	Medulla oblongata and spinal cord (reticulospinal and rubrospinal)
1b	Ventral-medial	BA8 (SMA and FEF)	Fibers decussate toward the contralateral tegmentum (decussation of superior cerebellar peduncle—cortico-rubro-cerebellar tract)
2	Ventral-middle	BA 8 (SMA and FEF)	Superior and inferior colliculi and medial floor of the 4th ventricle (corticotectal tract, corticomesencephalic tract and medial longitudinal fasciculus)
3	Ventral-lateral	BA 8 (SMA and FEF)	Superior peduncle and lateral floor of the 4th ventricle (corticocerebellar tracts)
4a	Medial-medial	BA4 and 6 (MC and PMC)	Medulla oblongata and spinal cord (reticulospinal and rubrospinal)
4b	Medial-medial	BA4 and 6 (MC and PMC)	Fibers decussate toward the contralateral tegmentum (decussation of superior cerebellar peduncle—cortico-rubro-cerebellar tract)
5	Medial-middle	BA4 and 6 (MC and PMC)	Superior and inferior colliculi and medial floor of the 4th ventricle (corticotectal tract, corticomesencephalic tract and medial longitudinal fasciculus)
6	Medial-lateral	BA4 and 6 (MC and PMC)	Superior peduncle and lateral floor of the 4th ventricle (corticocerebellar tracts)
7	Dorsal-medial	BA1/2/3 (SSC)	Medulla oblongata and spinal cord (reticulospinal and rubrospinal)
8	Dorsal-middle	BA1/2/3 (SSC)	Superior and inferior colliculi and medial floor of the 4th ventricle (corticotectal tract, corticomesencephalic tract and medial longitudinal fasciculus)
9	Dorsal-lateral	BA1/2/3 (SSC)	Superior peduncle and lateral floor of the 4th ventricle (corticocerebellar tracts)

BA Brodmann's area, *FEF* frontal eye fields, *MC* motor cortex, *PMC* premotor cortex, *SMA* supplementary motor area, *SSC* somatosensory cortex

CHAPTER 5: COCLUSIONS

5.1 THE DORSAL COMPONENT OF THE SLF

Although the SLF-I has been investigated through a number of sophisticated DTI protocols and anatomical studies, indeed ambiguity remains not only regarding its exact structural architecture but also as to whether it represents a discrete anatomical entity or instead an intrinsic part of the cingulum. Through a focused fiber micro-dissection technique, we were able to record the SLF-I as a distinct fiber pathway of the medial cerebral aspect in all cases and elucidate its precise morphological characteristics. Further studies focusing on the axonal connectivity and functional significance of the SLF-I both in normal and in pathologic conditions will add on a more refined concept of the cerebral anatomo-functional organization.

5.2 THE FRONTAL LONGITUDINAL SYSTEM

We were able to consistently identify and record the Frontal Longitudinal System as a group of fibers that reside within the frontal area and run between the prefrontal and premotor cortices. We additionally managed to elucidate its exact anatomical characteristics including its morphology, correlative anatomy and termination pattern and readily differentiate it from adjacent group of fibers such as the Superior Longitudinal Fasciculus. Our results provide sound structural evidence supporting the theory of a direct axonal connectivity between the prefrontal and premotor cortices which are believed to underpin the cognitive aspect of motor behavior.

Future studies are definitely needed in order to refine the FLS structure to function relationship and offer a more sophisticated concept of the circuitry conveying motor actions.

5.2 THE FRONTOCAUDATE TRACT

Literature on the structure of the human fronto-caudate tract (FCT) has been not only scarce but also vague and at times inconsistent. With the fiber micro-dissection technique in our armamentarium, we were able provide direct evidence of high accuracy on the topography, morphology and axonal connectivity of the FCT. We therefore consistently recorded the FCT as a discrete group of fibers stemming from a wide cortical area, including the pre-SMA, prefrontal cortex and frontal pole and terminating to the head and anterior part of the body of the caudate nucleus. The tract could be divided into two segments - dorsal and ventral- according to the respective connectivity pattern observed. These findings seem to be in agreement with the putative functional significance attributed to the frontostriatal circuitry in the neuroscientific literature and can potentially inform current surgical practice in the area of neuro-oncology and functional neurosurgery.

5.3 THE CORTICOTEGMENTAL TRACT

We were able to readily identify the Corticotegmental Tract(CTT), a group of fibers connecting the frontal and parietal cortex to the tegmental area. The fibers of the CTT are putatively assigned to the descending component of the extrapyramidal pathway and are allegedly implicated in complex motor behavior. In the current study, the intrahemispheric architecture, morphology and correlative anatomy of the CTT is elucidated for the first time in the current literature. Our results provide sound structural evidence on the anatomy of the descending extrapyramidal system and at the same time offer anatomical information that can be integrated in the preoperative and intraoperative planning in neuro-oncological cases. Future studies are needed in order to gain new insights on the CTT structure to function relationship and to offer a more sophisticated concept of the possible clinical repercussions of this fiber tract.

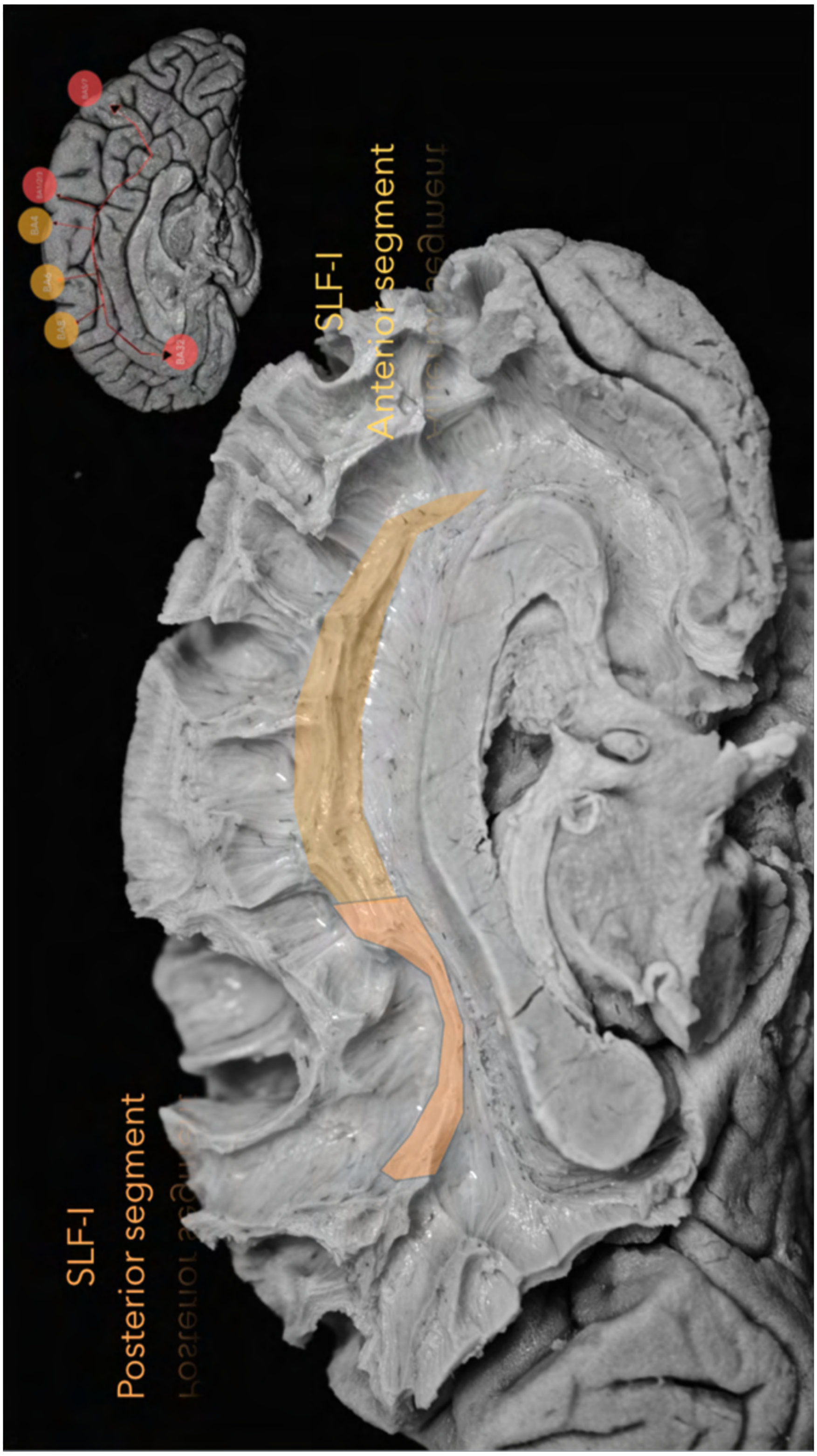
CHAPTER 6

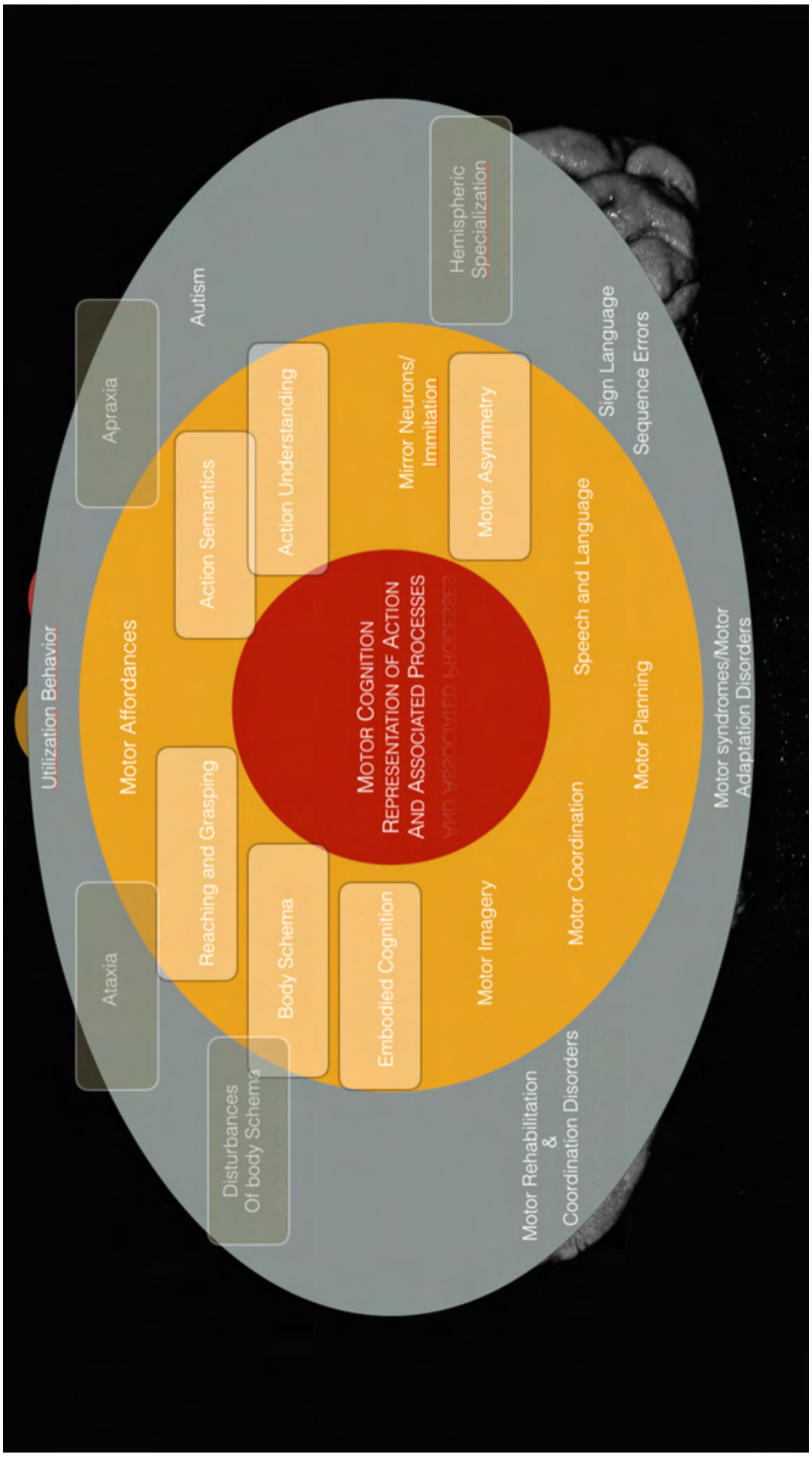
INSET OF WHITE MATTER PATHWAYS IMPLICATED IN THE MOTOR/PREMOTOR CONNECTIVITY

SLF I

SUPERIOR LONGITUDINAL FASCICULUS I

MOTOR/PREMOTOR/SMA/PRECUNEUS/ANTERIOR CINGULATE CORTEX CONNECTIVITY

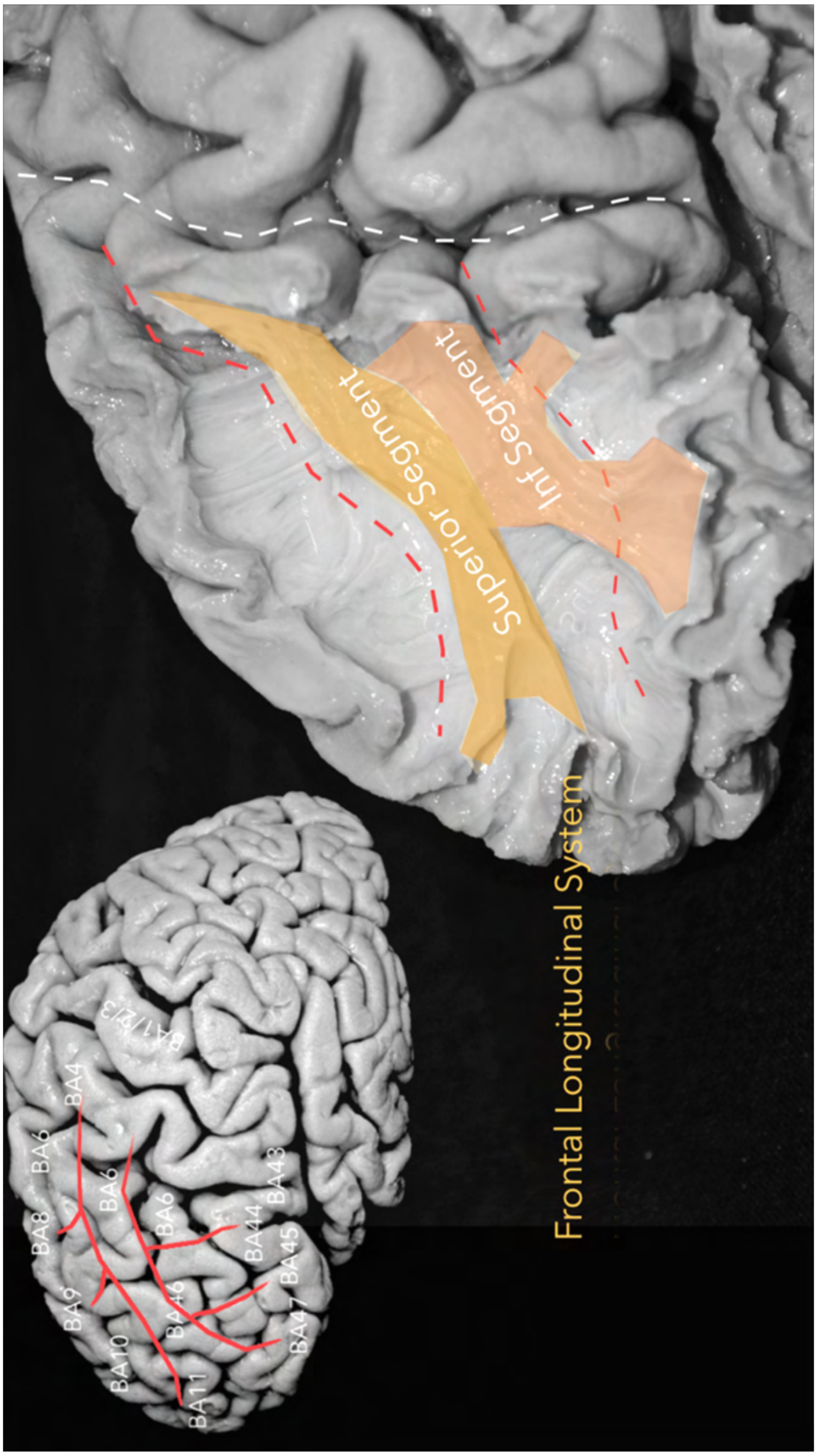

BA5/7
BA1/2/3
BA4
BA6
BA8
BA32
SLF-I
Anterior segment
SLF-I
Posterior segment

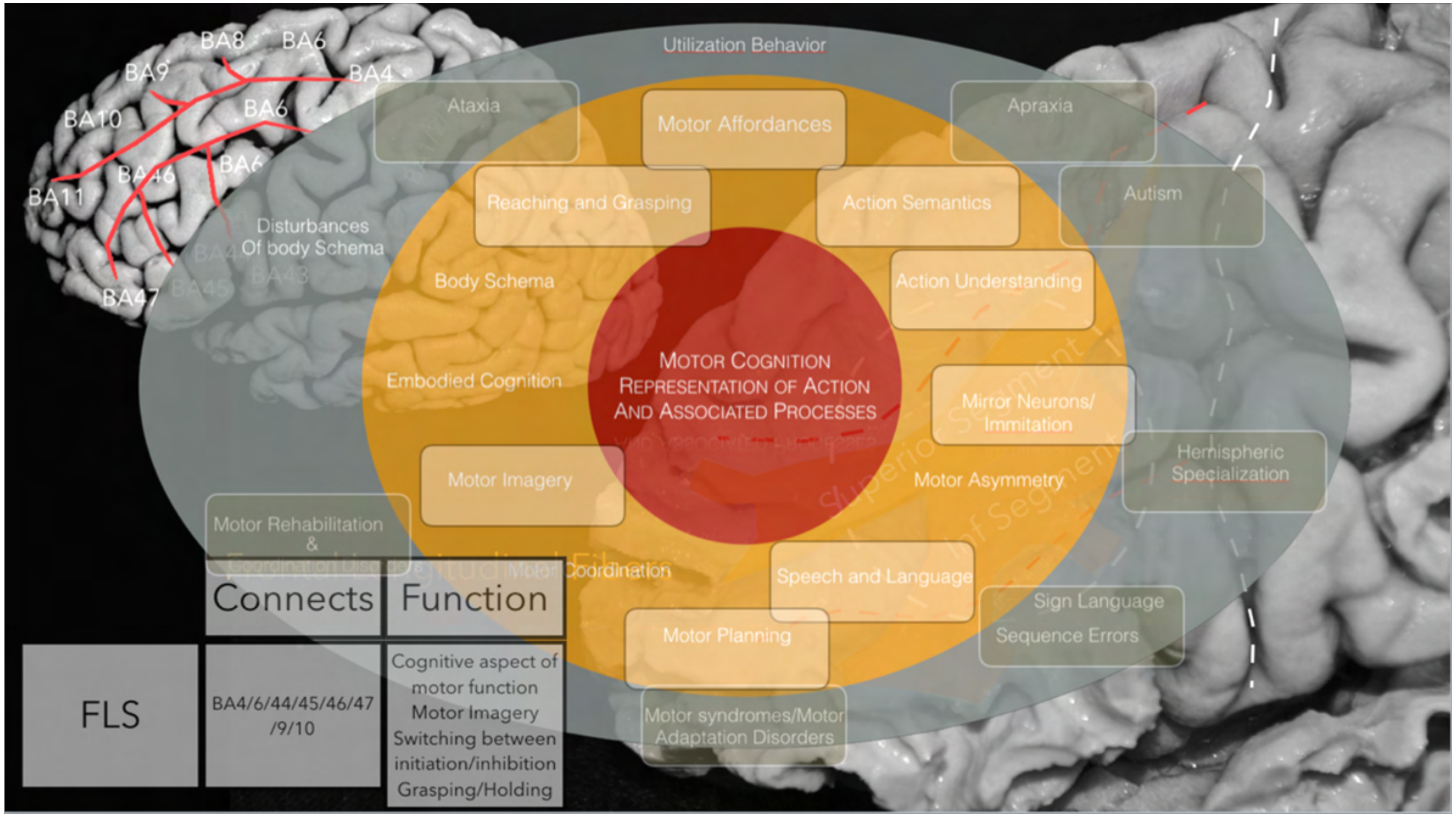

MOTOR COGNITION
REPRESENTATION OF ACTION
AND ASSOCIATED PROCESSES
Motor Affordances
Action Semantics
Action Understanding
Mirror Neurons/
Immitation
Motor Asymmetry
Speech and Language
Motor Planning
Motor Coordination
Motor Imagery
Embodied Cognition
Body Schema
Reaching and Grasping
Utilization Behavior
Apraxia
Autism
Hemispheric
Specialization
Sign Language
Sequence Errors
Motor syndromes/Motor
Adaptation Disorders
Motor Rehabilitation
&
Coordination Disorders
Disturbances
Of body Schema
Ataxia

FLS

FRONTAL LONGITUDINAL SYSTEM

PREMOTOR / PREFRONTAL CONNECTIVITY

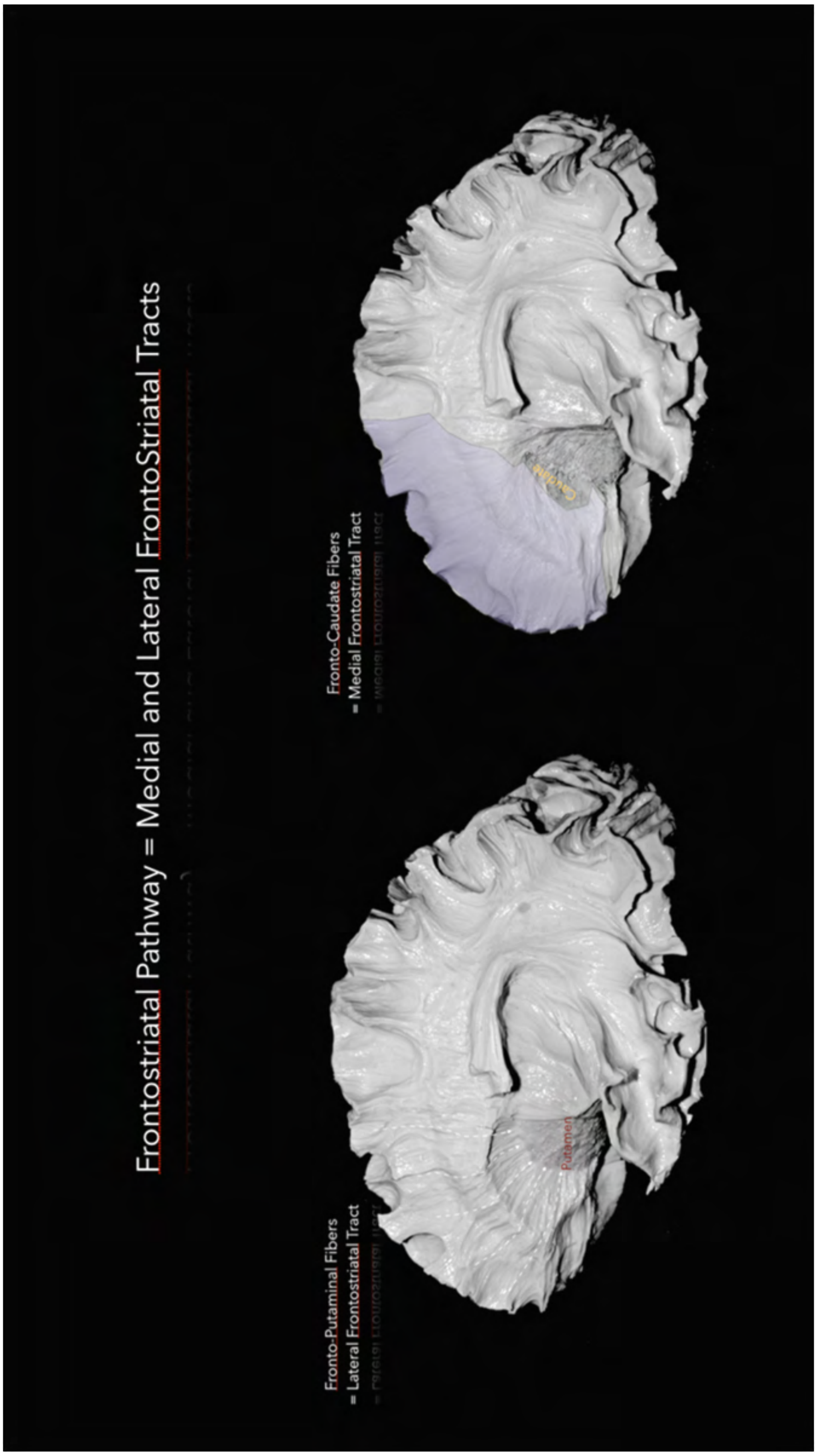

Inf Segment
Superior Segment
Frontal Longitudinal System
BA1/2/3
BA4
BA6
BA8
BA6
BA6
BA43
BA44
BA9
BA46
BA45
BA10
BA47
BA11


BA8
BA6
BA9
BA4
BA10
BA6
BA46
BA6
BA11
BA47
BA44
BA45
BA43
Utilization Behavior
Ataxia
Motor Affordances
Apraxia
Reaching and Grasping
Action Semantics
Autism
Disturbances
Of body Schema
Body Schema
Action Understanding
Embodied Cognition
MOTOR COGNITION
REPRESENTATION OF ACTION
AND ASSOCIATED PROCESSES
Mirror Neurons/
Immitation
Hemispheric
Specialization
Motor Imagery
Motor Asymmetry
Motor Rehabilitation
&
Coordination Disorders
Frontal Longitudinal Fibers
Motor Coordination
Speech and Language
Sign Language
Sequence Errors
Connects
Function
Motor Planning
FLS
BA4/6/44/45/46/47
/9/10
Cognitive aspect of
motor function
Motor Imagery
Switching between
initiation/inhibition
Grasping/Holding
Motor syndromes/Motor
Adaptation Disorders

FCT/FST

FRONTOCAUDATE TRACT/FRONTOSTRIATAL TRACTS

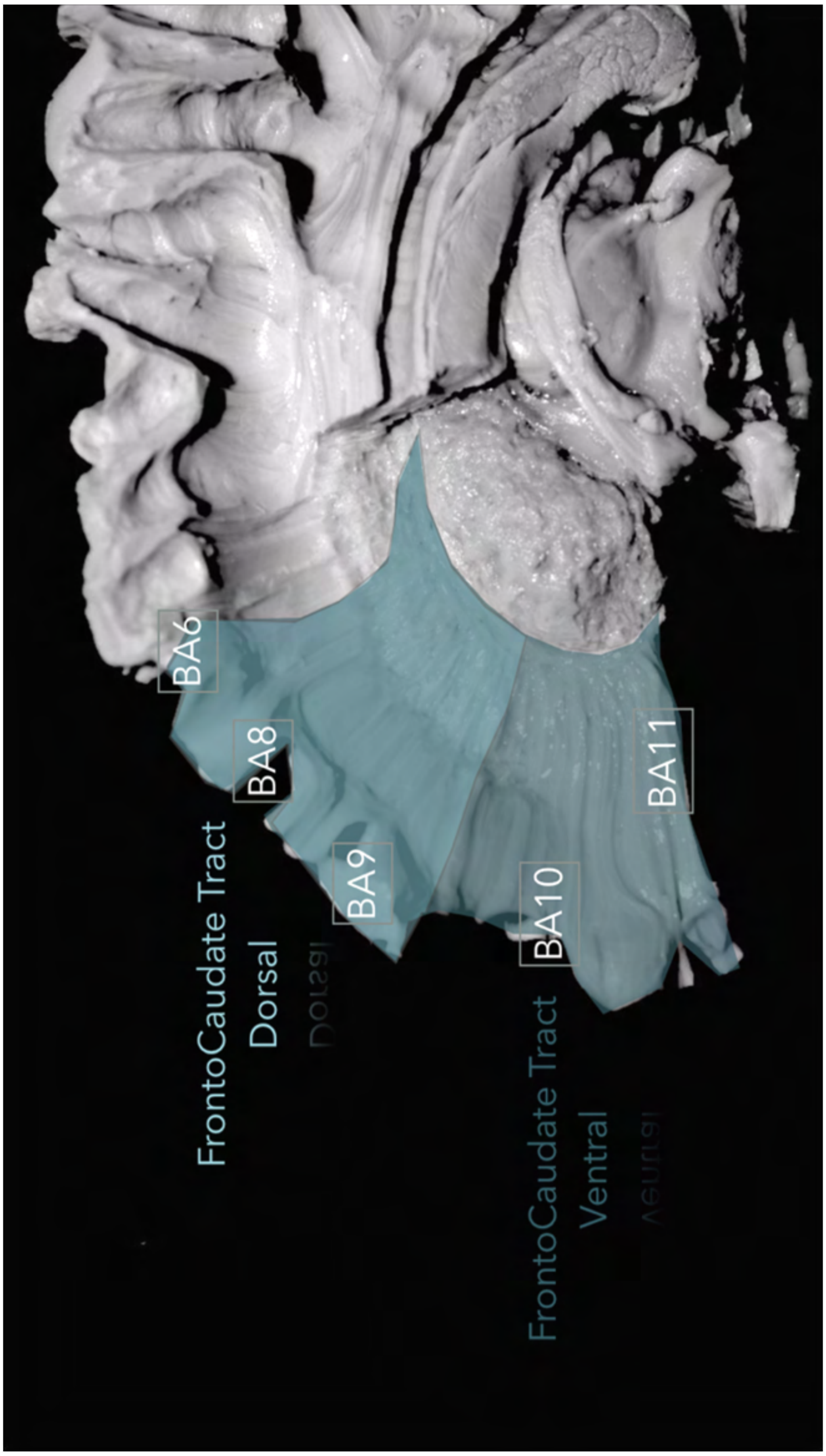
MOTOR/PREMOTOR / PREFRONTAL/CAUDATE CONNECTIVITY



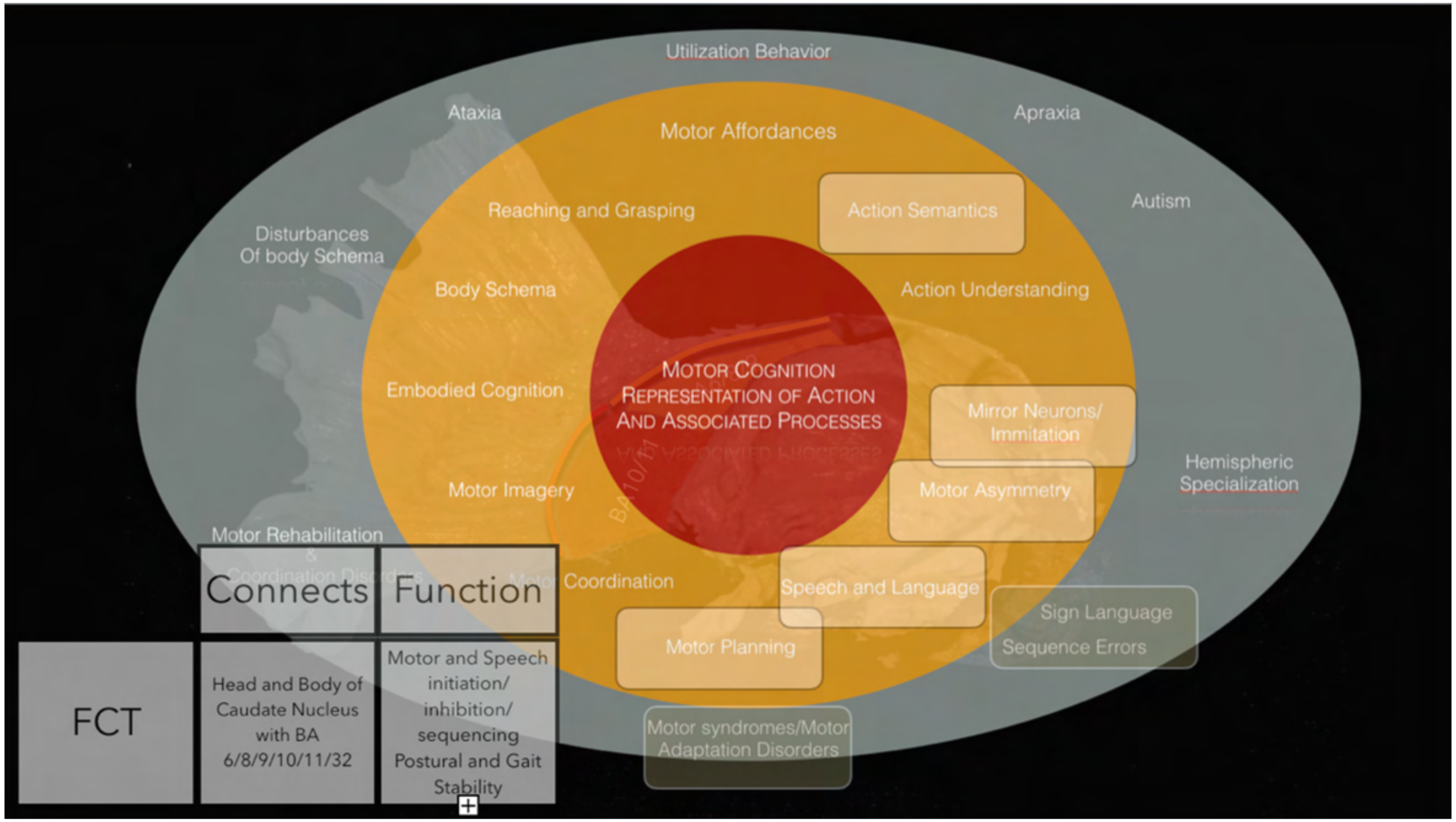
Frontostriatal Pathway = Medial and Lateral FrontoStriatal Tracts

Fronto-Caudate Fibers
= Medial Frontostriatal Tract

Fronto-Putaminal Fibers
= Lateral Frontostriatal Tract


BA6
BA8
BA9
BA10
BA11
FrontoCaudate Tract
Dorsal
FrontoCaudate Tract
Ventral

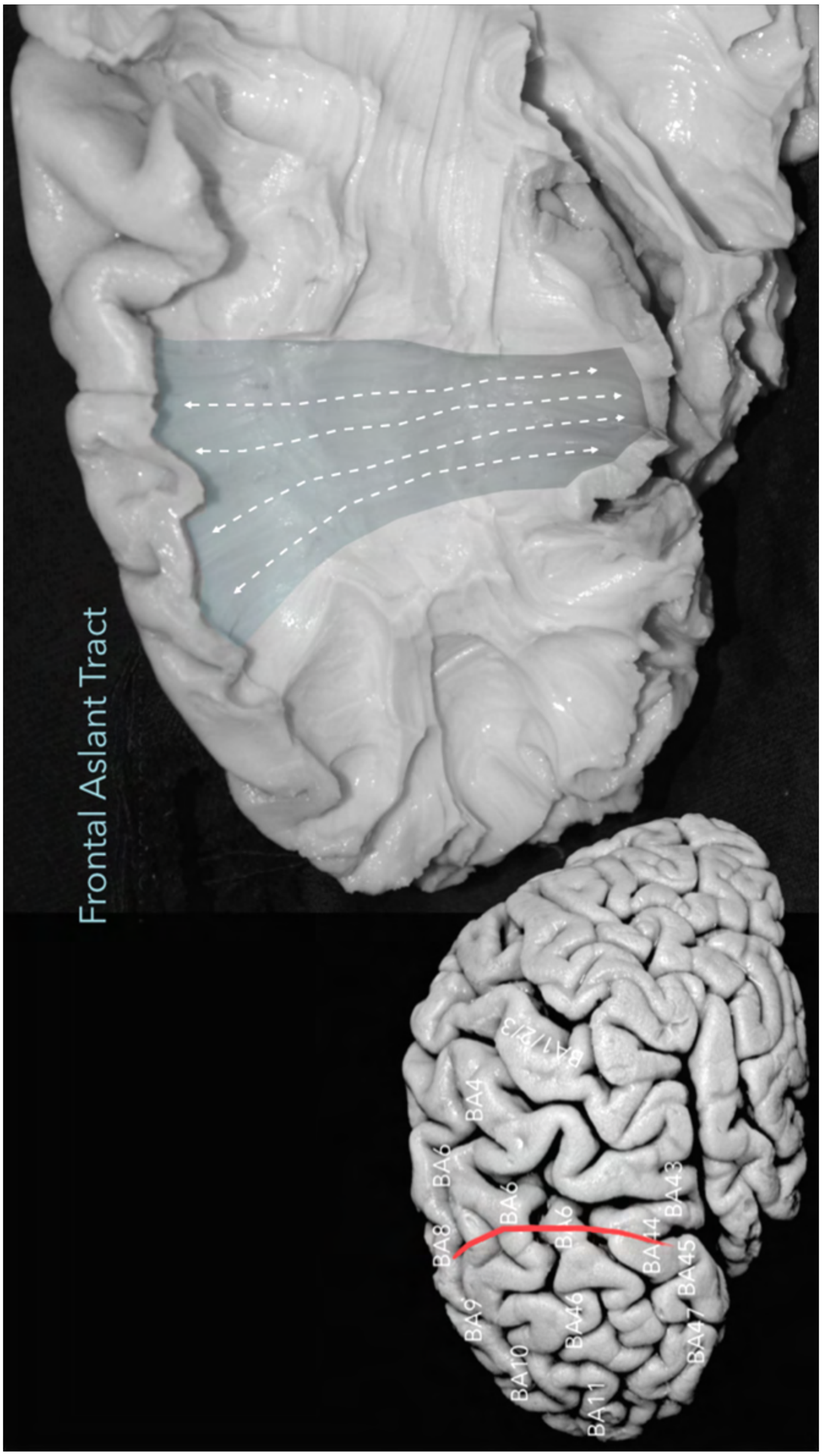

BA6/8/9
BA10/11

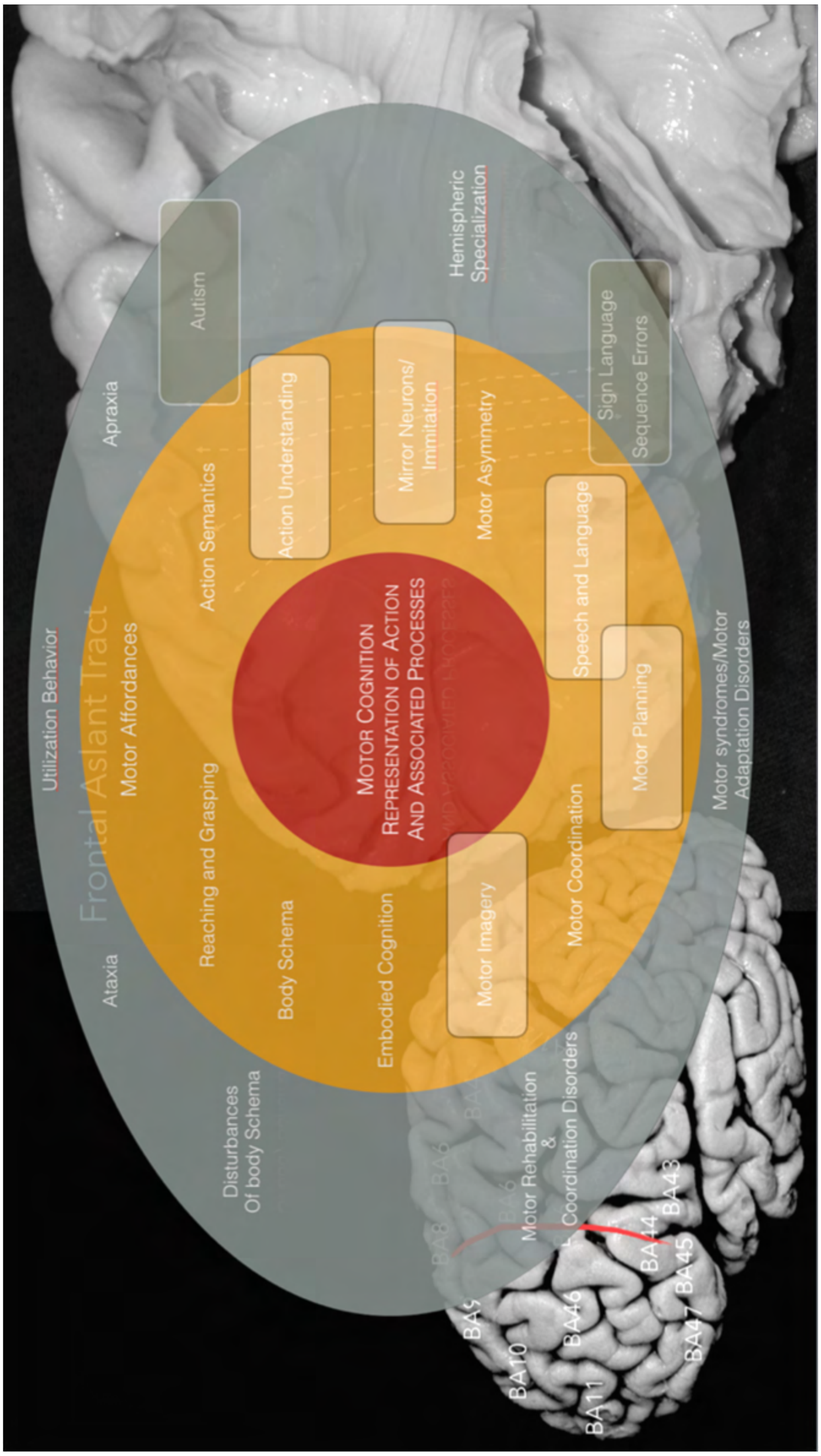

Utilization Behavior
Ataxia
Apraxia
Motor Affordances
Autism
Reaching and Grasping
Action Semantics
Disturbances
Of body Schema
Body Schema
Action Understanding
Embodied Cognition
Motor Cognition
Representation of Action
And Associated Processes
Mirror Neurons/
Immitation
Hemispheric
Specialization
Motor Imagery
Motor Asymmetry
BA10/11
Motor Rehabilitation
&
Coordination Disorders
Motor Coordination
Speech and Language
Sign Language
Sequence Errors
Motor Planning
Motor syndromes/Motor
Adaptation Disorders
FCT
Connects
Function
Head and Body of
Caudate Nucleus
with BA
6/8/9/10/11/32
Motor and Speech
initiation/
inhibition/
sequencing
Postural and Gait
Stability

FAT

FRONTAL ASLANT TRACT

SMA/preSMA/PREMOTOR CONNECTIVITY


Frontal Aslant Tract
BA1/2/3
BA4
BA6
BA6
BA8
BA6
BA44
BA43
BA45
BA9
BA46
BA10
BA11
BA47

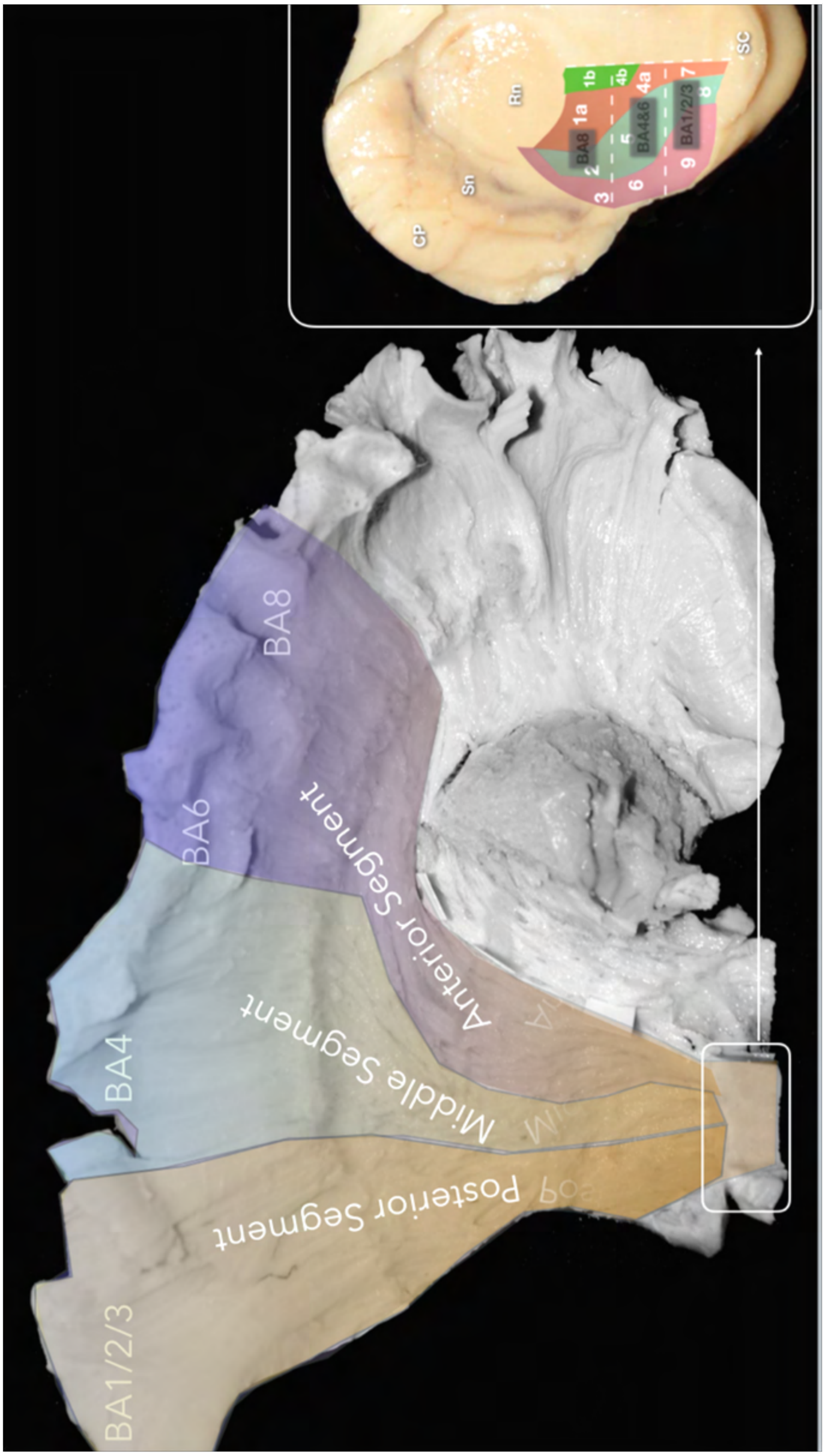

Utilization Behavior
Frontal Aslant Tract
Motor Affordances
Apraxia
Ataxia
Autism
Action Semantics
Reaching and Grasping
Body Schema
Action Understanding
Disturbances
Of body Schema
Embodied Cognition
Mirror Neurons/
Immitation
MOTOR COGNITION
REPRESENTATION OF ACTION
AND ASSOCIATED PROCESSES
Hemispheric
Specialization
Motor Asymmetry
Motor Imagery
Motor Rehabilitation
&
Coordination Disorders
Sign Language
Sequence Errors
Speech and Language
Motor Coordination
Motor Planning
Motor syndromes/Motor
Adaptation Disorders
BA8
BA9
BA6
BA10
BA11
BA46
BA44
BA43
BA45
BA47

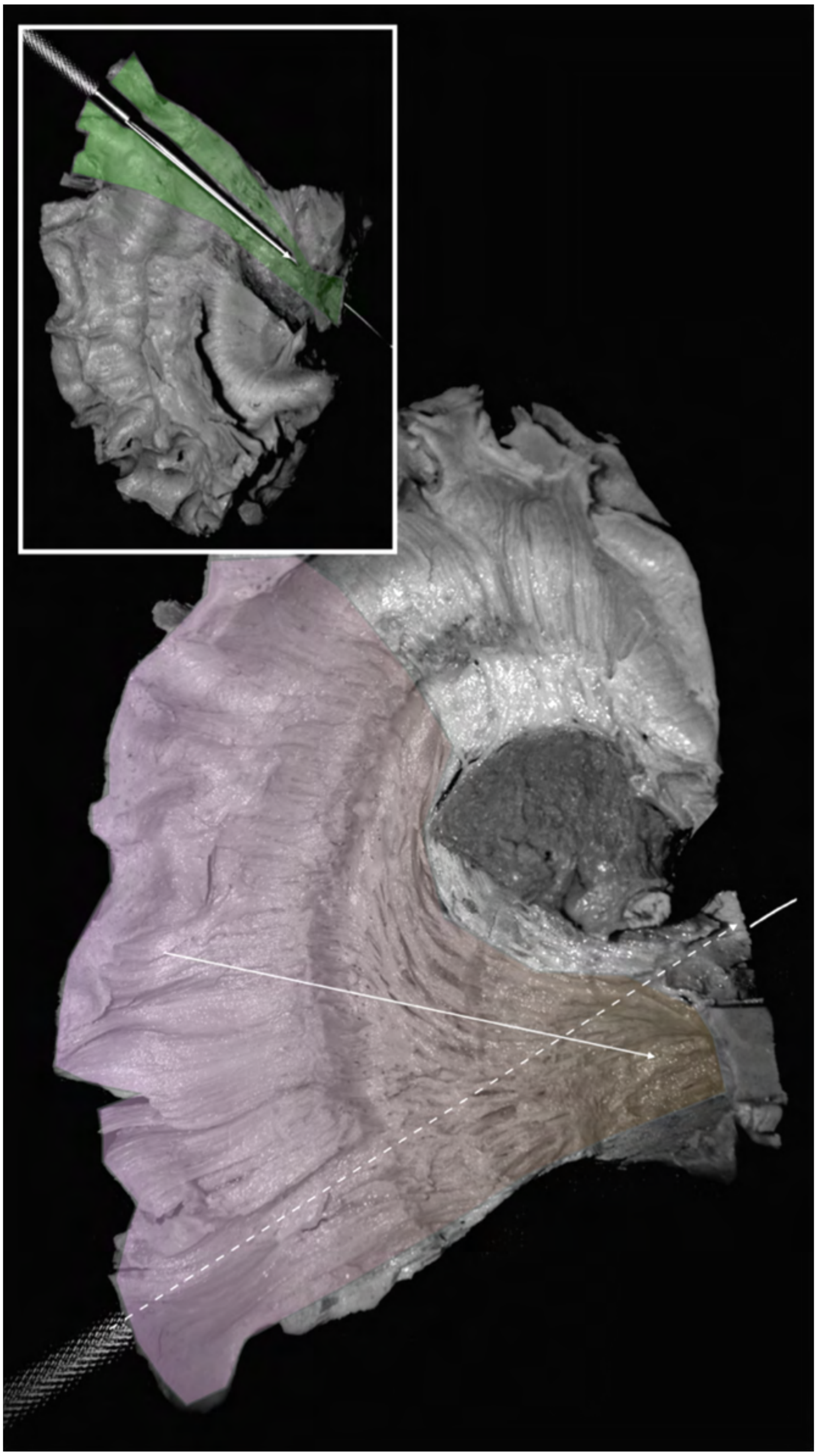
CTT/CST

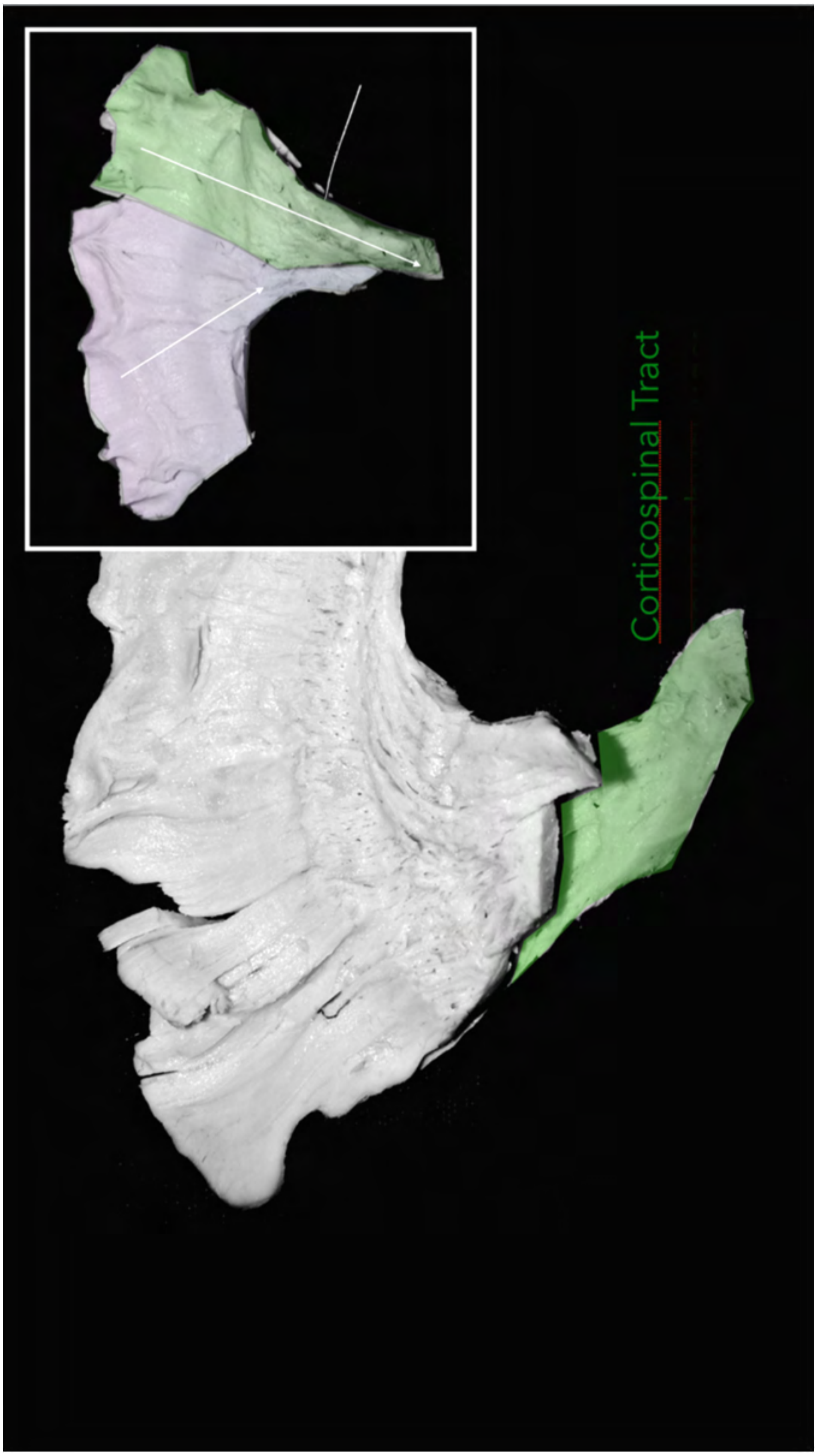
CORTICOTEGMENTAL TRACT/ CORTICOSPINAL TRACT

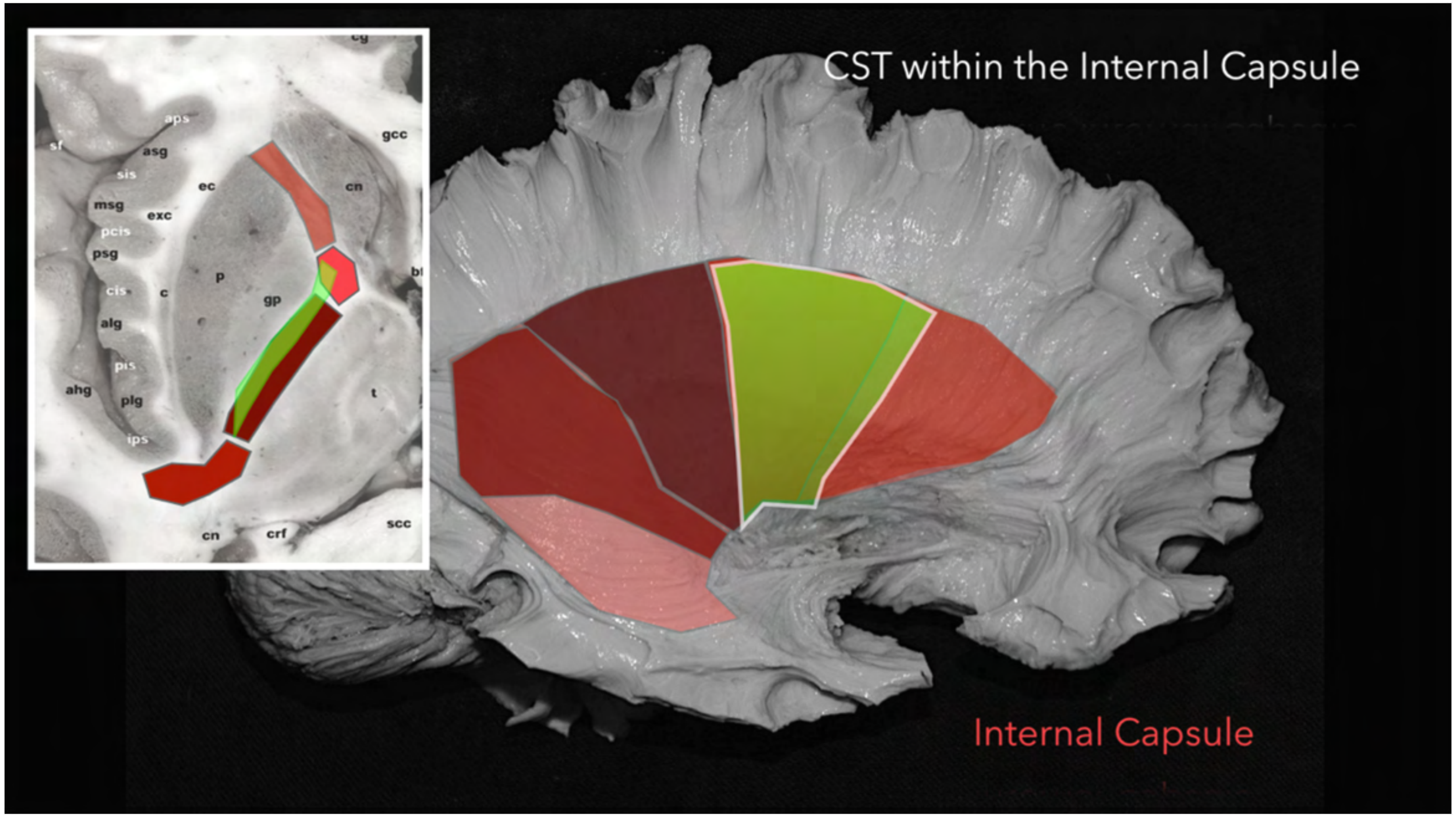
MOTOR/SMA/preSMA/PREMOTOR/PREFRONTAL/SOMATOSENSORY/

TEGMENTAL CONNECTIVITY


SC
1b
4b
4a
7
Rn
1a
5
BA4&6
BA1/2/3
8
BA8
2
6
9
3
Sn
CP
BA8
BA6
Anterior Segment
BA4
Middle Segment
Posterior Segment
BA1/2/3




Corticospinal Tract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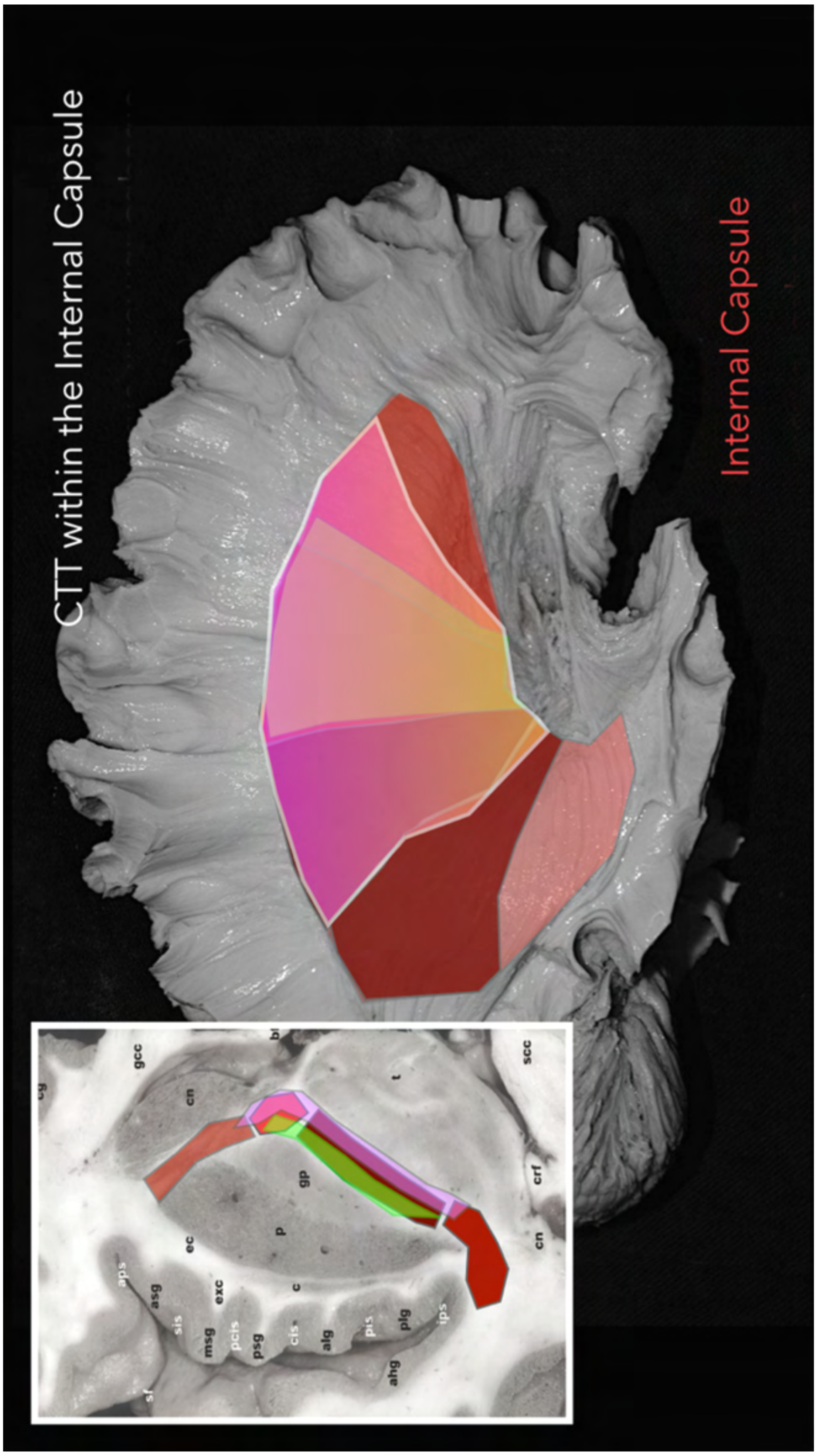
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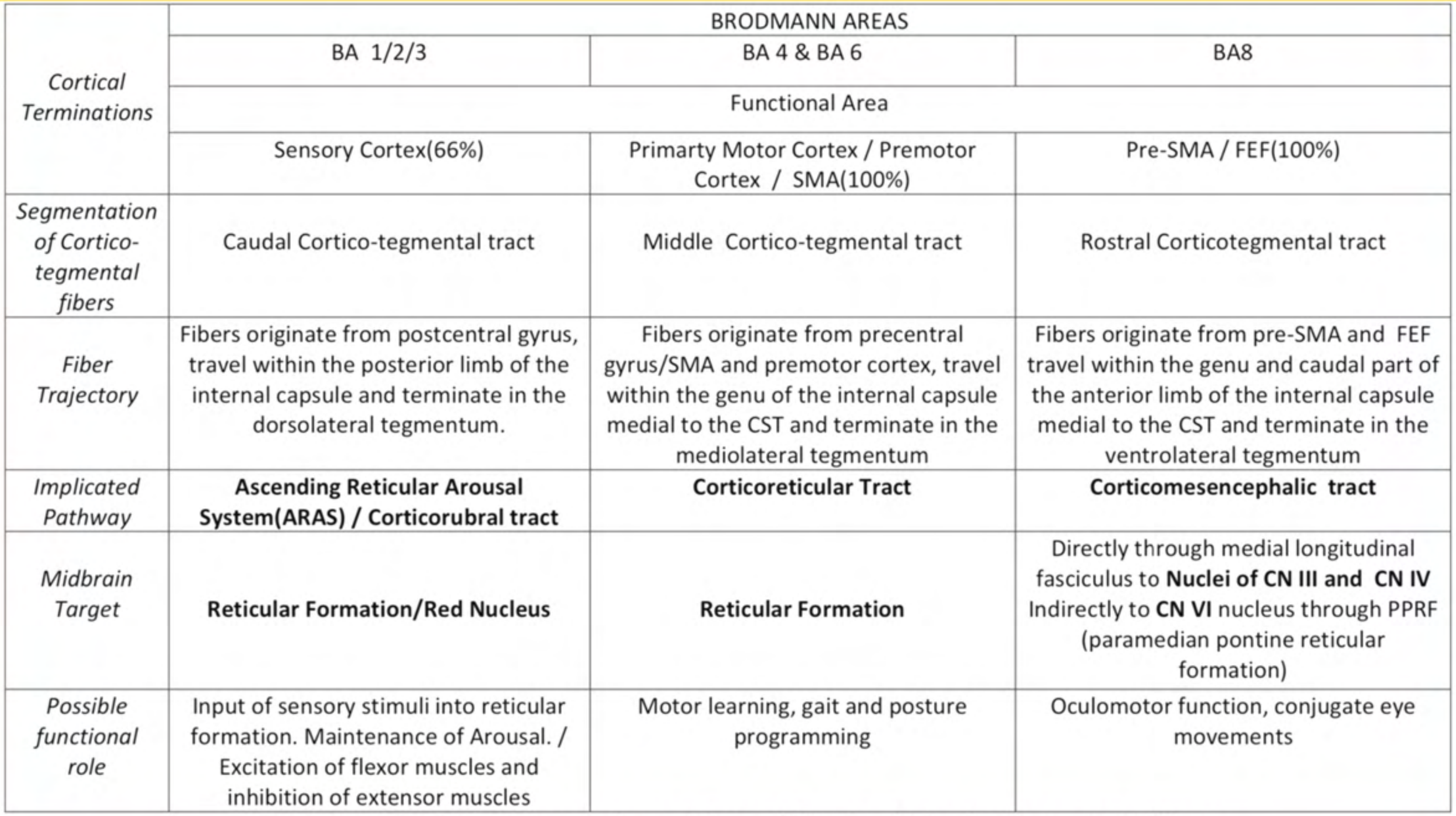

Cortical Terminations	BRODMANN AREAS		
	BA 1/2/3	BA 4 & BA 6	BA8
	Functional Area		
	Sensory Cortex(66%)	Primarty Motor Cortex / Premotor Cortex / SMA(100%)	Pre-SMA / FEF(100%)
Segmentation of Cortico-tegmental fibers	Caudal Cortico-tegmental tract	Middle Cortico-tegmental tract	Rostral Corticotegmental tract
Fiber Trajectory	Fibers originate from postcentral gyrus, travel within the posterior limb of the internal capsule and terminate in the dorsolateral tegmentum.	Fibers originate from precentral gyrus/SMA and premotor cortex, travel within the genu of the internal capsule medial to the CST and terminate in the mediolateral tegmentum	Fibers originate from pre-SMA and FEF travel within the genu and caudal part of the anterior limb of the internal capsule medial to the CST and terminate in the ventrolateral tegmentum
Implicated Pathway	**Ascending Reticular Arousal System(ARAS) / Corticorubral tract**	**Corticoreticular Tract**	**Corticomesencephalic tract**
Midbrain Target	**Reticular Formation/Red Nucleus**	**Reticular Formation**	Directly through medial longitudinal fasciculus to **Nuclei of CN III and CN IV** Indirectly to **CN VI** nucleus through PPRF (paramedian pontine reticular formation)
Possible functional role	Input of sensory stimuli into reticular formation. Maintenance of Arousal. / Excitation of flexor muscles and inhibition of extensor muscles	Motor learning, gait and posture programming	Oculomotor function, conjugate eye movements

TABLE 1. Anatomical morphology and parcelation and functional role of corticotegmental fibers.

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.(141) 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.(20) 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.(18)

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.(142, 143)

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