# 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

*Faidon Liakos[1,4], Spyridon Komaitis[1,2,4], Evangelos Drosos[1,2], Eleftherios Neromyliotis[1,2,5], Georgios P. Skandalakis[1], Apostolos I. Gerogiannis[1], Aristotelis V. Kalyvas[1,2,4], Theodore Troupis[1,4], George Stranjalis[1,2,5], Christos Koutsarnakis[1-5]*

BACKGROUND: **Recent studies advocate a connectivity pattern wider than previously believed of the uncinate fasciculus that extends to the ventrolateral and dorsolateral prefrontal cortices. These new percepts on the connectivity of the tract suggest a more expansive role for the uncinate fasciculus. Our aim was to shed light on this controversy through fiber dissections.**

METHODS: **Twenty normal adult human formalin-fixed cerebral hemispheres were used. Focused dissections on the insular, orbitofrontal, ventromedial, ventrolateral, and dorsolateral prefrontal areas were performed to record the topography of the frontal terminations of the uncinate fasciculus.**

RESULTS: **Three discrete fiber layers were consistently disclosed: the first layer was recorded to terminate at the posterior orbital gyrus and pars orbitalis, the second layer at the posterior two thirds of the gyrus rectus, and the last layer at the posterior one third of the paraolfactory gyrus. The insular apex was documented as a crucial landmark regarding the topographic differentiation of the uncinate and occipitofrontal fasciculi (i.e., fibers that travel ventrally belong to the uncinate fasciculus whereas those traveling dorsally are occipitofrontal fibers).**

CONCLUSIONS: **The frontal terminations of the uncinate fasciculus were consistently documented to project to the posterior orbitofrontal area. The area of the insular apex is introduced for the first time as a crucial surface landmark to effectively distinguish the stems of the uncinate and occipitofrontal fasciculi. This finding could refine the spatial resolution of awake subcortical mapping, especially for insular lesions, and improve the accuracy of in vivo diffusion tensor imaging protocols.**

## INTRODUCTION

The uncinate fasciculus (UF) has attracted increasing scientific interest because of its potential involvement in the pathophysiology of various psychiatric and neurologic diseases.[1-15] In addition, the propagation of elegant microneurosurgical approaches in awake conditions for the treatment of lesions residing in or extending to the temporal stem and insular region have further stressed the need for a more accurate understanding of the anatomic architecture and functional significance of the tract.[16-22] To this end, fiber dissection and tractographic studies focusing on the structural silhouette of the UF have converged toward a hooklike morphology, with the main stem of the tract traveling through the extreme and external capsules (close to the inferior occipitofrontal fasciculus) and its terminations radiating toward the orbitofrontal area and anteromedial temporal lobe, respectively.[23-36]

**Key words**
- Axonal connectivity
- Brain anatomy
- Fiber dissection technique
- Insula
- Occipitofrontal fasciculus
- Orbitofrontal cortex
- Uncinate fasciculus

**Abbreviations and Acronyms**
DWI: Diffusion-weighted imaging
IFOF: Inferior fronto-occipital fascicle
UF: Uncinate fasciculus

*From the [1]Athens Microneurosurgery Laboratory, Evangelismos Hospital, Athens, Greece; [2]Department of Neurosurgery, Evangelismos Hospital, National and Kapodistrian University of Athens, Athens, Greece; [3]Edinburgh Microneurosurgery Education Laboratory, Department of Clinical Neurosciences, Edinburgh, United Kingdom; [4]Department of Anatomy, Medical School, National and Kapodistrian University of Athens, Athens, Greece; [5]Hellenic Center for Neurosurgical Research, "Petros Kokkalis", Athens, Greece*

*To whom correspondence should be addressed: Christos Koutsarnakis, M.D., M.Sc. [E-mail: ckouts@hotmail.co.uk]*

*Faidon Liakos and Christos Koutsarnakis equally contributed to this study.*

*Citation: World Neurosurg. (2021) 152:e625-e634.*
*https://doi.org/10.1016/j.wneu.2021.06.012*

*Journal homepage: www.journals.elsevier.com/world-neurosurgery*

*Available online: www.sciencedirect.com*

Although the main anatomic characteristics of this elegant tract have been outlined, ambiguity has recently emerged regarding the exact topographic and morphologic pattern of its frontal terminations. According to the classic description, the UF connects the medial and lateral orbitofrontal cortices to the anterior segment of the 3 temporal gyri, the temporal pole, and uncus.[23] However, recent data stemming from modern, sophisticated anatomoimaging studies support the presence of an additional dorsal segment, which projects to the dorsolateral and ventrolateral prefrontal cortices of the inferior, middle, and superior frontal gyri, thus adding perplexity and obscurity to the structural architecture and putative functional role of the tract.[37-40]

To shed light on this current controversy, we carried out a fiber dissection study focusing on the morphology and topography of the frontal extensions of the UF. We implemented the white matter dissection technique as the stand-alone method of investigation because the anatomic results obtained are of high accuracy and because it is used as the gold-standard procedure for validating diffusion-weighted imaging (DWI) tractographic data.[41-49]

## METHODS

Twenty normal adult human cadaveric cerebral hemispheres (12 right hemispheres and 8 left hemispheres) previously fixed in a 10%–15% formalin solution for a minimum period of 8 weeks were studied. All specimens underwent the freeze–thaw process and were explored through the white matter fiber microdissection technique.[47,50,51]

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

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

## RESULTS

### Mapping the Orbitofrontal Terminations of the UF

On removing the gray matter of the 4 orbital gyri, gyrus rectus, inferior and middle frontal gyrus, anterior part of T1, 2, 3, and temporal operculum, we expose the superficial short U fibers and gain access to the insular surface (Figure 1). We then peel away the cortex of the limen insula, anterior insular surface, and insular apex to show fibers of the extreme capsule. Dissecting the most superficial part of the extreme capsule at the level of the limen insula and insular apex aids in the exposure of the main stems of the UF and occipitofrontal fascicule. By following the direction of these fibers under the microscope, we were able to adequately distinguish the 2 tracts, because they show different trajectories and termination patterns (i.e., the UF curves around the limen insula in a hook-shape fashion to radiate to the temporal pole, whereas the occipitofrontal fasciculus travels diagonally through the anterior part of the insula to fan out to the middle and posterior temporo-occipital cortices). At this point, we consistently recorded the most superficial fibers of the UF (what we define as the first layer of uncinate fibers) to terminate at the area of the posterior orbital gyrus and adjacent posterior part of the pars orbitalis, after exhibiting a short course (Figure 2).

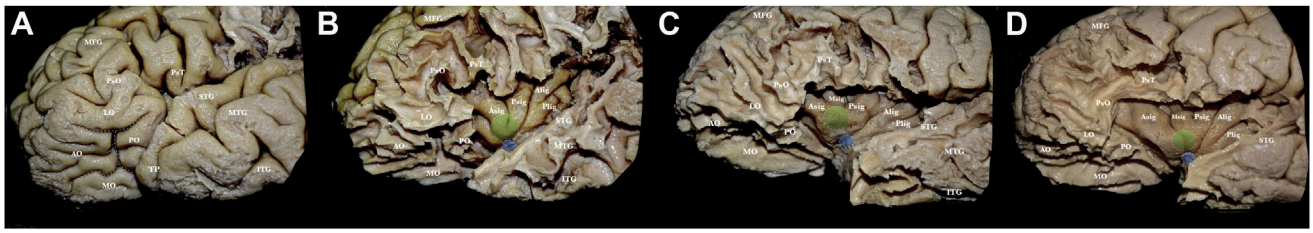


**Figure 1.** (**A**) Lateral aspect of a left hemisphere. The regional surface anatomy is shown. Inferolateral view of a left hemisphere. The surface anatomy of the orbitofrontal area is shown. The cruciform sulcus divides the basal frontal area into 4 orbital gyri. (**B**–**D**) Variations of the insular surface anatomy. Lateral aspect of 3 left hemispheres. The cortex of the orbital surface, inferior frontal gyrus, part of the middle frontal gyrus, and anterior temporal lobe has been removed and the short arcuate fibers become apparent. In (**C**) and (**D**) the temporal pole has also been removed for better access to the insular and orbitofrontal areas. The morphologic variation of the surface anatomy of the insula is shown particularly regarding the area of the insular apex. *Green disk*, insular apex; *blue disk*, limen insula. Alig, anterior long insular gyrus; AO, anterior orbital gyrus; Asig, anterior short insula gyrus; ITG, inferior temporal gyrus. LO, lateral orbital gyrus; MFG, middle frontal gyrus; MO, medial orbital gyrus; Msig, middle short insular gyrus; MTG, middle temporal gyrus; Plig, posterior long insular gyrus; PO, posterior orbital gyrus; Psig, posterior short insular gyrus; PsO, pars orbitalis; PsT, pars triangularis; RS, sulcus of Rolando; STG, superior temporal gyrus.

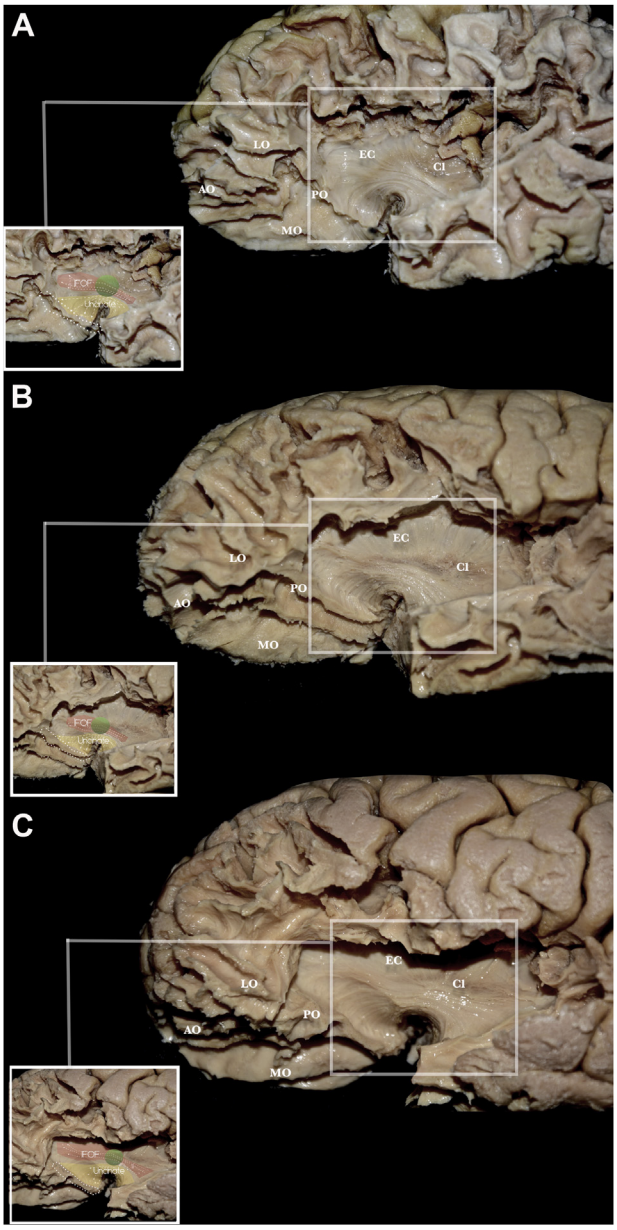


**Figure 2.** (**A**–**C**) The same specimens and same views as in Figure 1. The first fiber layer of the uncinate fasciculus is shown. The insular apex is introduced as a surface landmark for differentiating the uncinate from the occipitofrontal fasciculus. Progressive dissection of the short arcuate fibers of the anterior insular and orbitofrontal areas shows the first layer of fibers of the uncinate fasciculus (*yellow bundle*), which are followed and seen to terminate at the posterior orbital gyrus and pars orbitalis (*dotted area*). Fibers proved to belong to the occipitofrontal fasciculus (*magnified area with the red bundle*) are also evident, traveling close to the uncinate fasciculus. The area of the insular apex is marked with a *green disk*. Note that in all cases, fibers that travel just under and dorsal to the area of the insular apex are occipitofrontal fibers, whereas those that lie ventrally to the insular apex belong to the uncinate fasciculus. *Yellow bundle*, trajectory of the first layer of the uncinate fasciculus; *red bundle*, trajectory of the occipitofrontal fasciculus; *green disk*, insular apex. AO, anterior orbital gyrus; Cl, claustrum; EC, external capsule; IFOF, inferior fronto-occipital fascicle; LO, lateral orbit gyrus; MO, medial orbital gyrus; PO, posterior orbital gyrus.

Progressive dissection of the orbitofrontal area, part of the lateral prefrontal U fibers of the inferior frontal gyrus, and inferior part of the middle frontal gyrus helps identify the trajectory of the second fiber layer of the UF. These fibers, which are longer in relation to those of the first layer, are consistently recorded to terminate at the posterior two thirds of the gyrus rectus (Figure 3). At this stage of dissection, we did no track any fibers branching off the main stem of the UF and projecting toward the inferior or middle frontal gyri.

Proceeding deeper and removing the U fibers of the gyrus rectus, we expose the third fiber layer of the UF, seen to travel toward the medial surface of the hemisphere and to wrap around the ventral surface of the putamen (Figure 4).

## Differentiating the Stems of the UF and Occipitofrontal Fasciculus at the Area of the Insular Apex

By following the trajectory and direction of the fibers seen to travel through the anterior part of the temporal stem (an area in which the 2 tracts lie in close proximity), we were able to thoroughly distinguish the UF from the occipitofrontal fasciculus. In that respect, fibers that were found to curve around the limen insula and project toward the temporal pole were designated to belong to the UF, whereas fibers that were recorded to pass posterior to the limen insula, obliquely through the temporal stem and toward the temporo-occipital area, were defined as occipitofrontal fibers. In all specimens studied, the area of the insular apex (i.e., the area in which the short insular gyri converge to form a pyramidal prominence) proved to be a crucial landmark regarding the topographic differentiation of these subcortical pathways. More specifically, all fibers that reside ventral to the area of the insular apex belong to the stem of the UF, whereas fibers that travel just under and dorsal to the level of the insular apex clearly belong to the stem of the occipitofrontal fasciculus. In that way, we could confidently follow the fibers of the UF up to their respective frontal terminations.

## Exploring the Ventromedial Frontal Terminations of the UF—Evidence from Medial to Lateral Dissections

We applied stepwise medial to lateral dissections focused on the ventromedial frontal area to identify and record the regional distribution of the fibers of the UF (Figure 5A). On removing the cortex, we exposed the short arcuate U fibers connecting the cingulate gyrus with the paraolfactory gyrus and gyrus rectus (Figure 5B and C). Further dissection showed the ventral fibers of the cingulum radiating to the area of the paraolfactory gyrus. We then consistently identified a group of fibers seen to terminate at the posterior third of the paraolfactory gyrus and showed a close spatial relationship with the fibers of the ventral end of the cingulum. These fibers were carefully followed along their course and were found to merge with the main stem of the UF (Figure 5D and E).

We invariably identified 3 consecutive fiber layers seen to radiate from the main stem of the UF and recorded to terminate at the posterior area of the orbitofrontal territory, pars orbitalis, and ventromedial frontal lobe (Brodmann areas 11, 47, and 25, respectively) (Figure 6). It is therefore clear that the frontal terminations of this tract project to the posterior orbitofrontal region and that there are no fibers documented to follow a

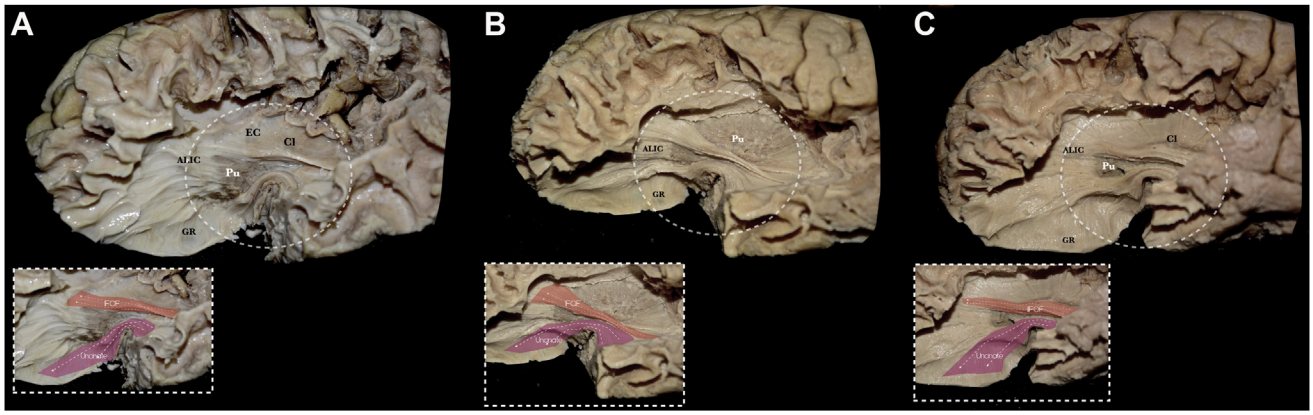


**Figure 3.** (**A**–**C**) Same specimens and same views as in Figure 2, showing the second layer of the uncinate fasciculus. Progressive dissection shows the second layer of uncinate fibers radiating to the posterior two thirds of the gyrus rectus. At this stage, a clear cleavage plane between the stems of the uncinate and inferior occipitofrontal fasciculi can be developed. Between these 2 fiber pathways, the plane of dissection deepens so as to show the ventral surface of the putamen centrally and the lateral part of the anterior limb of the internal capsule at the periphery. *Pink bundle,* trajectory of the second layer of the uncinate fasciculus;, *orange bundle,* trajectory of the occipitofrontal fasciculus. ALIC, anterior limb of the internal capsule; Cl, claustrum; EC, external capsule; GR, gyrus rectus; IFOF, inferior fronto-occipital fascicle; Pu, putamen.

more dorsal trajectory toward the prefrontal cortex of the inferior, middle, or superior frontal gyrus.

## DISCUSSION

Ever since the seminal fiber dissection study of the structure of the human UF by Ebeling and Von Cramon, most of the anatomoimaging literature has converged toward a common topographic and morphologic architecture of the tract. According to this literature, the UF connects the pars orbitalis, lateral and medial orbital gyri, gyrus rectus, and subcallosal area with the anterior part of the superior, middle, and inferior temporal gyri and uncus by traveling in a hooklike shape around the limen insula and through the anterior third of the temporal stem. This anatomic description, with some minor differences concerning the frontal terminations of the tract, is encountered in most studies of research groups that have shed light into the cerebral subcortical architecture and brain anatomofunctional connectivity.[23-27,29-31,33-36]

However, recent evidence stemming primarily from tractographic protocols suggests a wider distribution pattern of the frontal terminations of the tract, thus introducing ambiguity and perplexity into its structural silhouette. More specifically, apart from the orbitofrontal cortex and pars orbitalis, which are constantly and traditionally described as cortical termination territories, Hau et al.[37,38] have proposed that the UF in addition radiates to a large area of the dorsolateral and ventrolateral prefrontal cortices, including the superior, middle, and inferior frontal gyri. In a similar vein, a tractographic study by Leng et al.[39] and a fiber dissection investigation by Baydin et al.[40] showed widespread terminations of the tract to the inferior and middle frontal gyri, lending support to the emerging concept of a more extended pattern of axonal connectivity than previously believed.'

In an effort to elucidate this controversial topic, we used focused white matter dissections with the aim of identifying, following, and recording the topographic pattern of the frontal termination of the UF. We intentionally used the fiber dissection technique as our stand-alone method of investigation because it has been microscopically documented to preserve the anatomic integrity of the neural axons,[52] thus providing structural evidence of high accuracy. In addition, we opted to implement a method that offers robust and direct anatomic data and is considered as the gold-standard technique for validating results coming from tensor tractographic studies.[53-59]

With this method of investigation in our armamentarium, we invariably identified 3 consecutive and discrete layers of uncinate fibers, which were found to project and terminate in 3 distinct cerebral areas. More specifically and in a lateromedial direction of dissection, the first and most superficial layer was seen to terminate at the posterior orbital gyrus and adjacent part of the pars orbitalis; the second, intermediate layer projects to the posterior two thirds of the gyrus rectus; and the third, deeper layer was documented to radiate to the posterior one third of the paraolfactory gyrus. All these fiber layers were meticulously followed along their trajectory and were found to blend into the main stem of the UF. In Table 1, we provide a summary of the pertinent literature and compare the available data with our study.

We were diligent in the process of differentiating the fibers of the UF from those of the occipitofrontal fasciculus, because we believe that this is the most crucial step in defining the spatial relationship of these tracts and, in our view, is the main source of confusion and perplexity to have emerged. In this vein, special attention has to be paid to the narrow insular area in which the stems of these 2 pathways meet and travel in close proximity, because the correct differentiation of these tracts at this point accurately shows their respective frontal termination pattern. To this end, one has to follow the trajectory of the fibers either to the

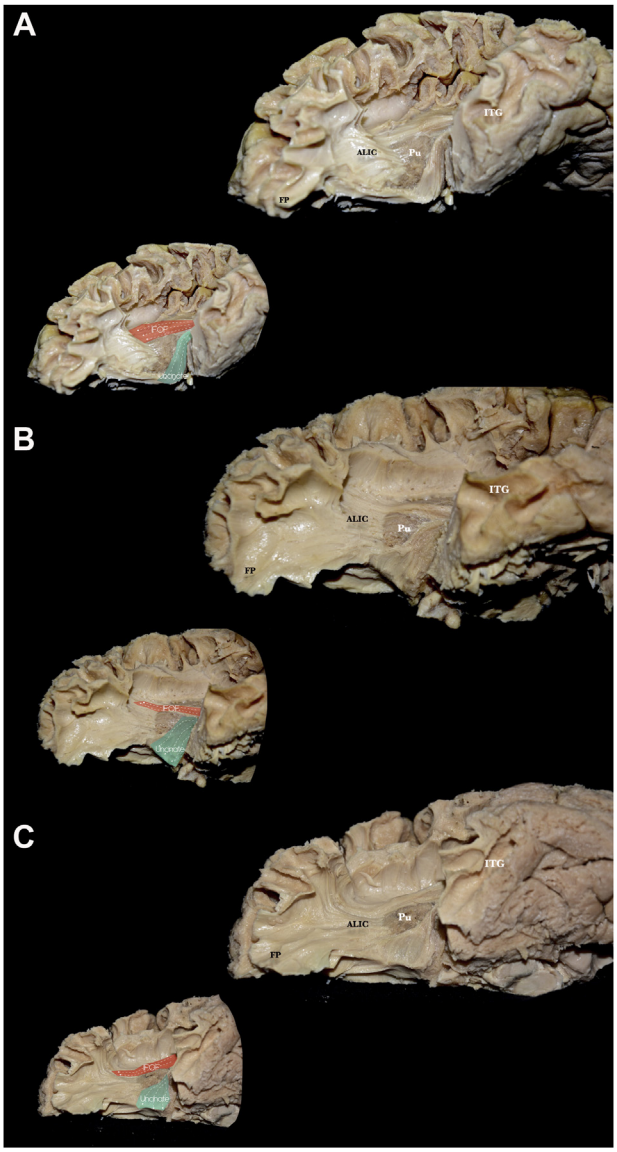


**Figure 4.** (**A**–**C**) Inferior views of the same specimens as in **Figure 2**, exposing the third layer of fibers of the uncinate fasciculus. Progressive dissection exposes the third layer of uncinate fibers seen to radiate toward the medial surface of the hemisphere. These fibers are exposed and their termination pattern shown in **Figure 5**. *Aqua bundle*, trajectory of the third layer of uncinate fibers; *red bundle*, trajectory of the occipitofrontal fasciculus. ALIC, anterior limb of the internal capsule; FP, frontal pole; IFOF, inferior fronto-occipital fascicle; ITG, inferior temporal gyrus; Pu, putamen.

anterior temporal lobe for the UF or to posterior temporo-occipital areas for the occipitofrontal tract. In this endeavor, we have consistently identified the area of the insular apex to be the most important surface landmark in differentiating with confidence these adjacent tracts. In all studied specimens, the fibers seen to travel ventrally in relation to the insular apex were recorded to belong to the stem of the UF, whereas the fibers that course just under and dorsal to the level of the insular apex proved to belong to the stem of the occipitofrontal bundle, because they all radiate to posterior temporo-occipital cortices. Hence, by following the trajectory of the designated uncinate fibers, we could thoroughly map their frontal termination pattern. In that respect and with a high level of accuracy, we did not show any uncinate fibers as projecting and radiating toward the inferior, middle, and superior frontal gyri apart from the area of the pars orbitalis. On the contrary, fibers that project from temporo-occipital areas blend to form the main stem of the occipitofrontal fasciculus and fan out to project and terminate abundantly at dorsolateral and ventrolateral prefrontal cortices.

We believe that the current controversy regarding the distribution pattern of the frontal termination of the UF mainly derives from the different methods that research groups have used to differentiate and allocate adjacent fibers either to the UF or to the occipitofrontal fasciculus. Because the area in which the stems of the tracts meet is narrow and their respective regional morphology similar, the level of difficulty and uncertainty increases for tractographic and white matter dissection techniques to accurately map the respective connectional anatomy of the tracts. In a further step, both tensor and nontensor diffusion tensor imaging protocols are proved to be prone to false-positive results, mainly because of noisy peaks or ambiguous bending and fanning fiber populations.[60-63] This effect is accentuated when long distance connections are explored, because the reconstruction error accumulates with each tracking step. The literature has particularly stressed the fact that, even in ideal experimental conditions, the accuracy of an indirect method such as DWI is suboptimal and the application of a direct anatomic procedure is mandatory for validating or ruling out tractographic data. In this context, the white matter dissection technique stands as a direct anatomic process providing structural evidence of high accuracy and reproducibility, should it be properly used (see section on "Study strengths and limitations").

Our results are largely in agreement with the classic description of the tract and support its structure to function relationship.[23,26,30,31,64,65] Although the pertinent literature on the functional significance of the UF and its possible involvement in conditions such as anxiety, epilepsy, autism, frontotemporal dementia, and antisocial behavior is extensive and, in a way, generalistic, there is converging evidence that the tract is primarily associated with certain aspects of episodic memory, language and social-emotional processing. More specifically, the role of the dominant UF in language is linked to processes that underpin the explicit lexical retrieval of certain aspects of semantic memory as those implicated in the retrieval of proper names of famous faces. Sound evidence for this claim has been provided by a study by Papagno et al.,[64] in which the preoperative and postoperative status of retrieval of proper names of famous faces was assessed and was found to be impaired in patients submitted to obligatory removal of the anatomic area of the UF. More basic linguistic processes such as speech production, speech comprehension, phonology, semantics, and syntax do not seem to be associated with the function of the UF and therefore the notion that advocates a more widespread projection of the tract to specific language-related cortices is not favorable. Further and in relation to memory and emotion, the

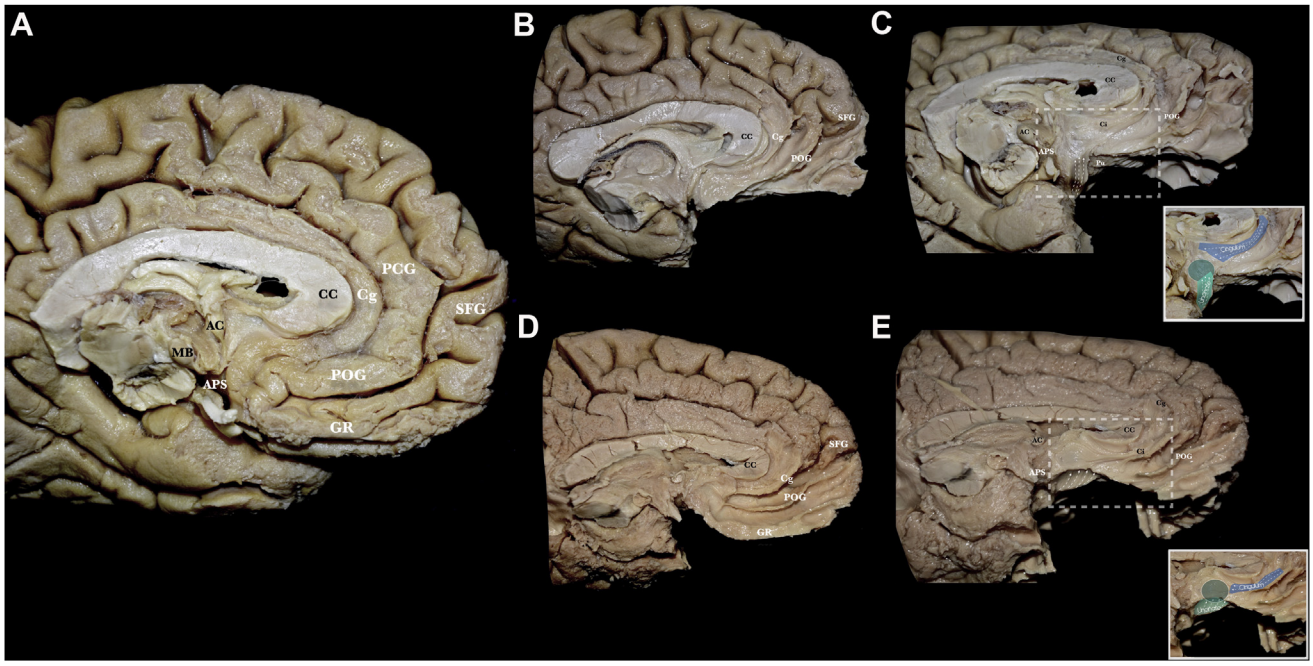


**Figure 5.** Medial view of a left hemisphere. (**A**) The regional surface anatomy is shown. The paracingulate gyrus continues ventrally as the paraolfactory gyrus. The gyrus rectus continues as the superior medial frontal gyrus. The mammillary body, the anterior commissure, and the anterior perforated substance are also shown. (**B** and **C**) Exposing the short arcuate fibers. Medial views of 2 left hemispheres. On removing the cortex of paraolfactory gyrus, gyrus rectus, and cingulate gyrus, the short arcuate U fibers connecting adjacent gyri are exposed. (**D** and **E**) Medial aspect of the third layer of the uncinate fasciculus. Inferomedial views of the specimens in **Figure 5B** and **C**. Progressive fiber dissection shows the fibers of the third layer of the uncinate fasciculus (*green bundle in the magnified area*) that are followed to their lateral extension. These fibers are documented to terminate at the posterior paraolfactory gyrus (*green disk in the magnified area*) close to the ventral end of the cingulum (*deep blue bundle*). *Green bundle*, trajectory of the third layer of the uncinate fasciculus; *green disk*, posterior end of the paraolfactory gyrus; *deep blue bundle*, cingulum. AC, anterior commissure; APS, anterior perforated substance; CC, corpus callosum; CG, cingulate gyrus; GR, gyrus rectus; MB, mammillary body; PCG, paracingulate gyrus; POG, paraolfactory gyrus; SFG, superior frontal gyrus.

tract seems to play a crucial role in linking temporal cortical areas that are implicated in encoding and storing mnemonic and emotionally colored representations to regions of the orbitofrontal cortex that are believed to assign values of reward or punishment to the presented stimuli and consequently underlie associative learning, behavioral shaping, and decision making.[65-69] The UF is potentially involved in the connectivity of areas that integrate memory and executive functions in a way that memory-based representations alter the way we behave.[65] A good body of evidence both on human and nonhuman primates lends support to these contentions but clearly more data need to be aggregated for a better understanding of the anatomofunctional significance of the tract.

## The Concept of the Insular Apex in Differentiating the Inferior Fronto-Occipital Fascicle from the UF and its Potential Implication in Clinical Practice

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

By introducing the area of the insular apex as a landmark related to subcortical structures and particularly to the structural architecture of the IFOF, one could improve the spatial resolution of subcortical brain mapping carried out when treating patients harboring tumors in and around the insula. In these cases, the proper identification and preservation of the IFOF, which serves as the primary ventral semantic language pathway, is imperative in decreasing language-related morbidity and in achieving an optimal oncofunctional balance in each patient. When the insular apex comes into view, the surgeon can form a mental picture of the trajectory and subcortical architecture of the IFOF, which subsequently allows for a faster and more effective brain mapping strategy. This accurate knowledge of the cortical and subcortical

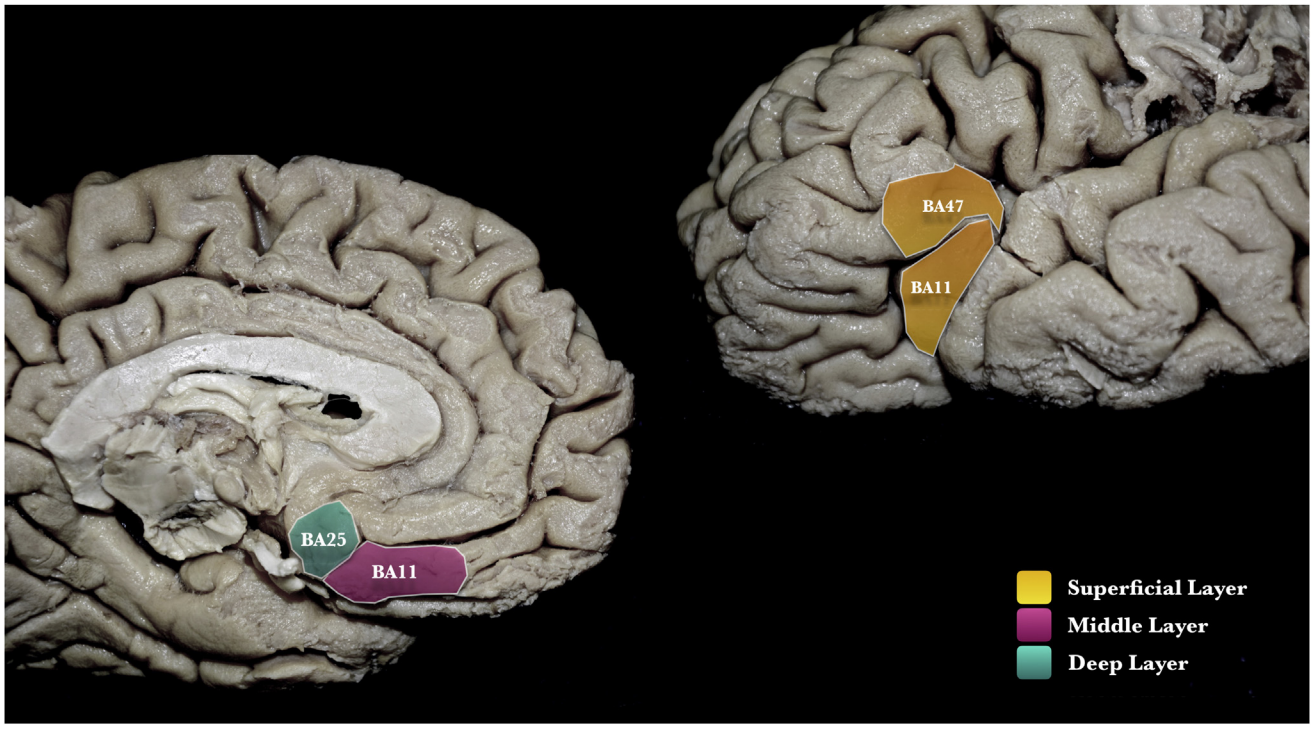


**Figure 6.** The termination areas of uncinate fasciculus projected in the surface anatomy of the frontal lobe. The lateral and medial aspects of the same specimen are shown. The first layer projects in the posterior orbital gyrus and the adjacent segment of the pars orbitalis (Brodmann areas 11 [BA11] and 47 [BA47]). The second layer terminates at the gyrus rectus (Brodmann area 11) and the third layer ends at the posterior third of the paraolfactory gyrus (Brodmann area 25 [BA25]). *Yellow area,* first layer; *pink area,* second layer; *green area,* third layer.

anatomy, what is known as the three-dimensional surgical view, supplemented with the proper use of the intraoperative neuronavigation system, is the cornerstone in optimizing outcomes in surgical neuro-oncology.

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

### Study Strengths and Limitations

The white matter fiber dissection technique is an anatomic method that involves the freezing and defrosting of formalin-fixed cerebral hemispheres before their blunt dissection. During the freezing process, ice crystals separate the cerebral fibers, and in that way, they can be subsequently identified and dissected. Recently, this technique has been microscopically documented to preserve the integrity of the nerve axons, intervening only with the extracellular matrix, and hence the direct structural evidence provided is of high accuracy.[52] For this reason, the fiber dissection technique is considered as one of the gold-standard procedures to validate indirect anatomic data from both tensor and nontensor tractographic protocols and has been our method of choice for exploring the intricate subcortical architecture and fiber tract silhouette.[41,47]

Apart from being an expensive, ex vivo, delicate, time-consuming, and operator-dependent process, the fiber dissection method provides data of lower spatial resolution compared with polarized light imaging, optical coherence tomography, and classic histology. However, it maintains the three-dimensional architecture of the subcortical structures. The sensitivity of the technique can be reduced when exploring white matter pathways that show perpendicular trajectories, because the proper dissection of the one involves the partial destruction of the other.

## CONCLUSIONS

By using the white matter dissection technique, we were able to provide direct anatomic evidence of high sensitivity and accuracy of the intricate morphologic pattern of the frontal termination of the UF. We consistently showed terminations of the tract on the posterior orbital gyrus, pars orbitalis, gyrus rectus, and posterior part of the paraolfactory gyrus. We did not record any fibers projecting from the main stem of the UF and radiating toward the cortices of the superior, middle, or inferior frontal gyrus apart from the pars orbitalis. This finding seems to be consistent with the putative functional significance of the tract. To our knowledge,

**Table 1.** Literature Review Summarizing Evidence of the Structural Morphology of the Uncinate Fasciculus and Comparison with the Current Study

| Reference | Type of Study | Frontal Termination Area | Additional Comments | Proposed Segmentation of UF |
|---|---|---|---|---|
| Ebeling and Von Cramon, 1992[23] | Fiber dissection | Retro-orbital cortex and gyrus rectus (BA11 and 25) | IFOF and UF can be separated by following their different trajectories | NA |
| Ture et al., 2000[35] | Fiber dissection | Fronto-orbital cortex | No exact delineation between UF and IFOF | NA |
| Catani et al., 2002[24] | DTI | Medial and lateral orbitofrontal cortex | NA | Ventral and dorsal component |
| Peuskens et al., 2004[31] | Fiber dissection | Ventromedial part: subcallosal area and gyrus rectus; dorsolateral part: orbital gyrus | IFOF joins UF in the area of the limen insulae | Ventromedial and dorsolateral part |
| Kier et al., 2004[26] | DTI | Subcallosal area, gyrus rectus, orbital gyri | IFOF and UF enter extreme and external capsules—the 2 bundles intermingle at the frontal pole | Ventral part: connects orbital cortex with amygdala; dorsal part: connects temporal pole with rostral end of middle frontal gyrus |
| Wang et al., 2008[34] | DTI | Orbital gyri and inferior frontal gyrus | UF joins the IFOF at its anatomic midpoint | NA |
| Fernandez-Miranda et al., 2008[25] | Fiber dissection and DTI | Lateral part of orbitofrontal region, gyrus rectus and subcallosal area | IFOF located dorsal to the UF | NA |
| Peltier et al., 2010[30] | Fiber dissection and DTI | Gyrus rectus and retro-orbital cortex (BA11), subcallosal area (BA25) | IFOF travels rostral to the UF | Three parts: ventral, intermediate, and dorsal |
| Martino et al., 2011[29] | Fiber dissection and DTI | Medial and lateral orbitofrontal cortex | UF passes through anterior temporal stem and limen insulae | NA |
| Thiebaut de Schotten et al., 2012[33] | DTI | Ventrolateral branch: orbital frontal cortex (BA11 and 47). Anteromedial branch: frontal pole (BA10) and cingulate gyrus (BA32) | NA | Ventrolateral and anteromedial branch |
| Hau et al., 2016[38] | DTI | Middle frontal gyrus, inferior frontal gyrus, gyrus rectus, fronto-orbital gyri | NA | NA |
| Leng et al., 2016[39] | Fiber dissection and DTI | Middle frontal gyrus, pars orbitalis (BA47), pars triangularis (BA45) | IFOF travels ventral to the UF. Can be differentiated according to its termination pattern | 2 branches: 1 toward ventrolateral frontal cortex and 1 toward rostral middle frontal cortex |
| Bhatia et al., 2017[27] | DTI | Frontal pole, orbital gyri and subgenual area | NA | Frontopolar stem, lateral orbital gyrus stem, medial orbital gyrus stem, and subgenual stem |
| Hau et al., 2017[37] | Fiber dissection and DTI | Superior frontal gyrus, middle frontal gyrus, inferior frontal gyrus. fronto-orbital gyri, gyrus rectus | NA | 5 subcomponents: dorsolateral, ventrolateral, ventromedial, posteromedial, anteromedial |
| Baydin et al., 2017[40] | Fiber dissection | Fronto-orbital area, septal area, nucleus accumbens, superolateral part of the frontal lobe | NA | 2 subcomponents: ventromedial and anterolateral part |
| Gungor et al., 2017[36] | Fiber dissection and DTI | Orbitofrontal and septal areas | IFOF and UF travel along the ventral part of the external capsule | Anteroinferior and posterosuperior parts |
| Current Study | Fiber dissection | Posterior orbital lobule (BA11), pars orbitalis (BA47), posterior 2/3 of the gyrus rectus (BA11), subgenual area (BA25) | Insular apex can be used as a superficial landmark to differentiate the UF from the IFOF. UF fibers travel ventral to the apex, whereas IFOF fibers travel under and dorsal to the level of the apex | 3 subcomponents: superficial, middle, and deep layer |

UF, uncinate fasciculus; BA, Brodmann area; IFOF, inferior fronto-occipital fascicle; NA, not available; DTI, diffusion tensor imaging.

the insular apex is introduced for the first time in the relevant literature as a crucial landmark regarding the accurate topographic differentiation of the UF from the occipitofrontal fasciculus in the area in which the main stems of these fasciculi converge. In that respect, axons that travel ventrally to the insular apex belong to the uncinate stem, whereas fibers that reside just under and dorsal to the insular apex are documented to radiate from the stem of the occipitofrontal fasciculus. This finding could inform surgical practice by refining the spatial resolution of awake subcortical mapping and by improving the accuracy of in vivo diffusion tensor imaging fiber dissection protocols used for preoperative planning.

## CRediT AUTHORSHIP CONTRIBUTION STATEMENT

**Faidon Liakos:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Spyridon Komaitis:** Data curation, Formal analysis, Investigation, Methodology, Writing - review & editing. **Evangelos Drosos:** Data curation, Formal analysis, Investigation, Writing - review & editing. **Eleftherios Neromyliotis:** Investigation, Writing - review & editing. **Georgios P. Skandalakis:** Investigation, Writing - review & editing. **Apostolos I. Gerogiannis:** Investigation, Writing - review & editing. **Aristotelis V. Kalyvas:** Data curation, Formal analysis, Methodology, Writing - review & editing. **Theodore Troupis:** Project administration, Resources, Writing - review & editing. **George Stranjalis:** Project administration, Resources, Writing - review & editing. **Christos Koutsarnakis:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

## REFERENCES

1. Burns J, Job D, Bastin ME, et al. Structural disconnectivity in schizophrenia: a diffusion tensor magnetic resonance imaging study. *Br J Psychiatry*. 2003;182:439-443.
2. Kubicki M, Westin CF, Maier SE, et al. Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. *Am J Psychiatry*. 2002;159:813-820.
3. McIntosh AM, Munoz Maniega S, Lymer GK, et al. White matter tractography in bipolar disorder and schizophrenia. *Biol Psychiatry*. 2008;64:1088-1092.
4. Price G, Cercignani M, Parker GJ, et al. White matter tracts in first-episode psychosis: a DTI tractography study of the uncinate fasciculus. *Neuroimage*. 2008;39:949-955.
5. Motzkin JC, Newman JP, Kiehl KA, et al. Reduced prefrontal connectivity in psychopathy. *J Neurosci*. 2011;31:17348-17357.
6. Craig MC, Catani M, Deeley Q, et al. Altered connections on the road to psychopathy. *Mol Psychiatry*. 2009;14:946-953, 907.
7. Sussmann JE, Lymer GK, McKirdy J, et al. White matter abnormalities in bipolar disorder and schizophrenia detected using diffusion tensor magnetic resonance imaging. *Bipolar Disord*. 2009;11:11-18.
8. Rodrigo S, Oppenheim C, Chassoux F, et al. Uncinate fasciculus fiber tracking in mesial temporal lobe epilepsy. Initial findings. *Eur Radiol*. 2007;17:1663-1668.
9. Diehl B, Busch RM, Duncan JS, et al. Abnormalities in diffusion tensor imaging of the uncinate fasciculus relate to reduced memory in temporal lobe epilepsy. *Epilepsia*. 2008;49:1409-1418.
10. McDonald CR, Ahmadi ME, Hagler DJ, et al. Diffusion tensor imaging correlates of memory and language impairments in temporal lobe epilepsy. *Neurology*. 2008;71:1869-1876.
11. Matsuo K, Mizuno T, Yamada K, et al. Cerebral white matter damage in frontotemporal dementia assessed by diffusion tensor tractography. *Neuroradiology*. 2008;50:605-611.
12. Acosta-Cabronero J, Patterson K, Fryer TD, et al. Atrophy, hypometabolism and white matter abnormalities in semantic dementia tell a coherent story. *Brain*. 2011;134:2025-2035.
13. Whitwell JL, Avula R, Senjem ML, et al. Gray and white matter water diffusion in the syndromic variants of frontotemporal dementia. *Neurology*. 2010;74:1279-1287.
14. Bhatia KD, Henderson LA, Hsu E, et al. Reduced integrity of the uncinate fasciculus and cingulum in depression: a stem-by-stem analysis. *J Affect Disord*. 2018;235:220-228.
15. Riva-Posse P, Choi KS, Holtzheimer PE, et al. Defining critical white matter pathways mediating successful subcallosal cingulate deep brain stimulation for treatment-resistant depression. *Biol Psychiatry*. 2014;76:963-969.
16. Duffau H. A personal consecutive series of surgically treated 51 cases of insular WHO Grade II glioma: advances and limitations. *J Neurosurg*. 2009;110:696-708.
17. Duffau H, Capelle L, Denvil D, et al. Usefulness of intraoperative electrical subcortical mapping during surgery for low-grade gliomas located within eloquent brain regions: functional results in a consecutive series of 103 patients. *J Neurosurg*. 2003;98:764-778.
18. Duffau H, Capelle L, Lopes M, et al. The insular lobe: physiopathological and surgical considerations. *Neurosurgery*. 2000;47:801-810 [discussion 810-801].
19. Lang FF, Olansen NE, DeMonte F, et al. Surgical resection of intrinsic insular tumors: complication avoidance. *J Neurosurg*. 2001;95:638-650.
20. Sanai N, Polley MY, Berger MS. Insular glioma resection: assessment of patient morbidity, survival, and tumor progression. *J Neurosurg*. 2010;112:1-9.
21. Kim YH, Kim CY. Current surgical management of insular gliomas. *Neurosurg Clin North Am*. 2012;23:199-206. vii.
22. Hameed NUF, Qiu T, Zhuang D, et al. Transcortical insular glioma resection: clinical outcome and predictors. *J Neurosurg*. 2018;131:706-716.
23. Ebeling U, von Cramon D. Topography of the uncinate fascicle and adjacent temporal fiber tracts. *Acta Neurochir (Wien)*. 1992;115:143-148.
24. Catani M, Howard RJ, Pajevic S, et al. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *Neuroimage*. 2002;17:77-94.
25. Fernandez-Miranda JC, Rhoton AL Jr, Alvarez-Linera J, et al. Three-dimensional microsurgical and tractographic anatomy of the white matter of the human brain. *Neurosurgery*. 2008;62:989-1026 [discussion 1026-1028].
26. Kier EL, Staib LH, Davis LM, et al. MR imaging of the temporal stem: anatomic dissection tractography of the uncinate fasciculus, inferior occipitofrontal fasciculus, and Meyer's loop of the optic radiation. *AJNR Am J Neuroradiol*. 2004;25:677-691.
27. Bhatia K, Henderson L, Yim M, et al. Diffusion tensor imaging investigation of uncinate fasciculus anatomy in healthy controls: description of a subgenual stem. *Neuropsychobiology*. 2017;75:132-140.
28. Martino J, De Lucas EM. Subcortical anatomy of the lateral association fascicles of the brain: a review. *Clin Anat*. 2014;27:563-569.
29. Martino J, De Witt Hamer PC, Vergani F, et al. Cortex-sparing fiber dissection: an improved method for the study of white matter anatomy in the human brain. *J Anat*. 2011;219:531-541.
30. Peltier J, Verclytte S, Delmaire C, et al. Microsurgical anatomy of the temporal stem: clinical relevance and correlations with diffusion tensor imaging fiber tracking. *J Neurosurg*. 2010;112:1033-1038.
31. Peuskens D, van Loon J, Van Calenbergh F, et al. Anatomy of the anterior temporal lobe and the frontotemporal region demonstrated by fiber dissection. *Neurosurgery*. 2004;55:1174-1184.
32. Schmahmann JD, Pandya DN, Wang R, et al. Association fibre pathways of the brain: parallel

observations from diffusion spectrum imaging and autoradiography. *Brain*. 2007;130:630-653.

33. Thiebaut de Schotten M, Dell'Acqua F, Valabregue R, et al. Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex*. 2012;48:82-96.

34. Wang F, Sun T, Li XG, et al. Diffusion tensor tractography of the temporal stem on the inferior limiting sulcus. *J Neurosurg*. 2008;108:775-781.

35. Ture U, Yasargil MG, Friedman AH, et al. Fiber dissection technique: lateral aspect of the brain. *Neurosurgery*. 2000;47:417-426 [discussion 426-427].

36. Gungor A, Baydin S, Middlebrooks EH, et al. The white matter tracts of the cerebrum in ventricular surgery and hydrocephalus. *J Neurosurg*. 2017;126:945-971.

37. Hau J, Sarubbo S, Houde JC, et al. Revisiting the human uncinate fasciculus, its subcomponents and asymmetries with stem-based tractography and microdissection validation. *Brain Struct Funct*. 2017;222:1645-1662.

38. Hau J, Sarubbo S, Perchey G, et al. Cortical terminations of the inferior fronto-occipital and uncinate fasciculi: anatomical stem-based virtual dissection. *Front Neuroanat*. 2016;10:58.

39. Leng B, Han S, Bao Y, et al. The uncinate fasciculus as observed using diffusion spectrum imaging in the human brain. *Neuroradiology*. 2016;58:595-606.

40. Baydin S, Gungor A, Tanriover N, et al. Fiber tracts of the medial and inferior surfaces of the cerebrum. *World Neurosurg*. 2017;98:34-49.

41. Catani M, Jones DK, ffytche DH. Perisylvian language networks of the human brain. *Ann Neurol*. 2005;57:8-16.

42. Komaitis S, Kalyvas AV, Skandalakis GP, et al. The frontal longitudinal system as revealed through the fiber microdissection technique: structural evidence underpinning the direct connectivity of the prefrontal-premotor circuitry [e-pub ahead of print]. *J Neurosurg*. https://doi.org/10.3171/2019.6.JNS191224, accessed October 4, 2019.

43. Komaitis S, Skandalakis GP, Kalyvas AV, et al. Dorsal component of the superior longitudinal fasciculus revisited: novel insights from a focused fiber dissection study. *J Neurosurg*. 2019;132:1265-1278.

44. Koutsarnakis C, Kalyvas AV, Komaitis S, et al. Defining the relationship of the optic radiation to the roof and floor of the ventricular atrium: a focused microanatomical study [e-pub ahead of print]. *J Neurosurg*. https://doi.org/10.3171/2017.10.JNS171836, accessed March 1, 2019.

45. Koutsarnakis C, Kalyvas AV, Skandalakis GP, et al. Sledge runner fasciculus: anatomic architecture and tractographic morphology. *Brain Struct Funct*. 2019;224:1051-1066.

46. Koutsarnakis C, Liakos F, Kalyvas AV, et al. Approaching the atrium through the intraparietal sulcus: mapping the sulcal morphology and correlating the surgical corridor to underlying fiber tracts. *Oper Neurosurg (Hagerstown)*. 2017;13:503-516.

47. Koutsarnakis C, Liakos F, Kalyvas AV, et al. A laboratory manual for stepwise cerebral white matter fiber dissection. *World Neurosurg*. 2015;84:483-493.

48. Koutsarnakis C, Liakos F, Liouta E, et al. The cerebral isthmus: fiber tract anatomy, functional significance, and surgical considerations. *J Neurosurg*. 2016;124:450-462.

49. Liakos F, Koutsarnakis C. The role of white matter dissection technique in modern neuroimaging: can neuroradiologists benefit from its use? *Surg Radiol Anat*. 2016;38:275-276.

50. Klingler J, Ludwig E. *Atlas Cerebri Humani*. Basel: Karger; 1956.

51. Klingler J. *Erleichterung der makrokopischen Präparation des Gehirns durch den Gefrierprozess*. Zurich: Orell Füssli; 1935.

52. Zemmoura I, Blanchard E, Raynal PI, et al. How Klingler's dissection permits exploration of brain structural connectivity? An electron microscopy study of human white matter. *Brain Struct Funct*. 2016;221:2477-2486.

53. Thomas C, Ye FQ, Irfanoglu MO, et al. Anatomical accuracy of brain connections derived from diffusion MRI tractography is inherently limited. *Proc Natl Acad Sci U S A*. 2014;111:16574-16579.

54. Maier-Hein KH, Neher PF, Houde JC, et al. The challenge of mapping the human connectome based on diffusion tractography. *Nat Comm*. 2017;8:1349.

55. Schilling KG, Petit L, Rheault F, et al. Brain connections derived from diffusion MRI tractography can be highly anatomically accurate-if we know where white matter pathways start, where they end, and where they do not go. *Brain Struct Funct*. 2020;225:2387-2402.

56. Schilling K, Gao Y, Janve V, et al. Confirmation of a gyral bias in diffusion MRI fiber tractography. *Hum Brain Mapp*. 2018;39:1449-1466.

57. Sinke MRT, Otte WM, Christiaens D, et al. Diffusion MRI-based cortical connectome reconstruction: dependency on tractography procedures and neuroanatomical characteristics. *Brain Struct Funct*. 2018;223:2269-2285.

58. Knosche TR, Anwander A, Liptrot M, et al. Validation of tractography: comparison with manganese tracing. *Hum Brain Mapp*. 2015;36:4116-4134.

59. Aydogan DB, Jacobs R, Dulawa S, et al. When tractography meets tracer injections: a systematic study of trends and variation sources of diffusion-based connectivity. *Brain Struct Funct*. 2018;223:2841-2858.

60. Fernandez-Miranda JC, Pathak S, Engh J, et al. High-definition fiber tractography of the human brain: neuroanatomical validation and neurosurgical applications. *Neurosurgery*. 2012;71:430-453.

61. Le Bihan D, Poupon C, Amadon A, et al. Artifacts and pitfalls in diffusion MRI. *J Magn Reson Imaging*. 2006;24:478-488.

62. Jones DK. Determining and visualizing uncertainty in estimates of fiber orientation from diffusion tensor MRI. *Magn Reson Med*. 2003;49:7-12.

63. Alexander DC, Barker GJ. Optimal imaging parameters for fiber-orientation estimation in diffusion MRI. *Neuroimage*. 2005;27:357-367.

64. Papagno C, Miracapillo C, Casarotti A, et al. What is the role of the uncinate fasciculus? Surgical removal and proper name retrieval. *Brain*. 2011;134:405-414.

65. Von Der Heide RJ, Skipper LM, Klobusicky E, et al. Dissecting the uncinate fasciculus: disorders, controversies and a hypothesis. *Brain*. 2013;136:1692-1707.

66. Tsapkini K, Frangakis CE, Hillis AE. The function of the left anterior temporal pole: evidence from acute stroke and infarct volume. *Brain*. 2011;134:3094-3105.

67. Semenza C. Naming with proper names: the left temporal pole theory. *Behav Neurol*. 2011;24:277-284.

68. Waldron EJ, Manzel K, Tranel D. The left temporal pole is a heteromodal hub for retrieving proper names. *Front Biosci*. 2014;6:50-57.

69. Lu LH, Crosson B, Nadeau SE, et al. Category-specific naming deficits for objects and actions: semantic attribute and grammatical role hypotheses. *Neuropsychologia*. 2002;40:1608-1621.

*Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

*Received 2 May 2021; accepted 4 June 2021*

*Citation: World Neurosurg. (2021) 152:e625-e634. https://doi.org/10.1016/j.wneu.2021.06.012*

*Journal homepage: **www.journals.elsevier.com/world-neurosurgery***

*Available online: **www.sciencedirect.com***

*1878-8750/$ - see front matter* 