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Neuroanatomical study

Inferior Fronto-Occipital fascicle anatomy in brain tumor surgeries: From anatomy lab to surgical theater

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ABSTRACT

The Inferior Fronto-Occipital fascicle (IFOF) is a multitasking white matter (WM) bundle bridging frontal, temporal, parietal and occipital lobe. Many papers describe its role in the physiology of language, attention and affective behavior but its anatomical components and cortical terminations remain unclear.

We analyze the surgical anatomy of the IFOF in the light of our experience with awake surgery, anatomical dissection on 10 human adult hemispheres (Klingler method) and literature review.

Dissecting the specimens from lateral to medial we can describe 3 segments: a vertical segment that runs along the frontal lobe; an horizontal segment that runs along frontal lobe; an horizontal segment that runs from the limen insulae, passes into to the temporal stem and arrives at the parietal and occipital lobes. We retrospectively analyzed also 23 awake surgeries. 2 responses were elicited at subcortical stimulation at the third segment of the IFOF; stimulation gave paraphasias on the first segment of the IFOF in one case. All IFOF responses were founded in the left hemisphere.

Anatomical knowledge is the cornerstone of surgical orientation, it allows eloquent structures to be reached quickly and it is of primary importance in awake surgery to avoid patient fatigue with lack of concentration.

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1. Introduction

Intrinsic brain tumors remain a surgical challenge because, as far as we know, any technique used to reach a tumor may imply some damage to brain structures [5,6,20]. Therefore, to minimize damage, it is of great importance to know the anatomy and related functions of each brain region and how each region is functionally related to the other ones [2–4,15]. The new philosophy of connectome overcomes the old concept of localizationism and special attention is now focused on the white matter (WM) [9,14,17].

WM consists of millions of myelinated axons densely packed into organized fascicles or fiber tracts that form a complex three-dimensional architecture within the brain [17]. We can admit that its role is of great importance as a bridge between all structures in the brain. Thus, the anatomical and functional knowledge of WM is crucial in tumor resections.

The Inferior Fronto-Occipital fascicle (IFOF) is a cornerstone of brain connectivity. It is a multitasking WM bundle bridging frontal lobe, temporal lobe, parietal and occipital lobe. Many papers describe its role in the physiology of language, attention and affective behavior but its anatomical components and cortical terminations remain unclear [24].

Our aim was to analyze the surgical anatomy of the IFOF in the light of our surgical experience, anatomical dissection and literature review.

2. Materials and methods

We retrospective analyzed our surgical experience in awake surgery in the light of anatomical knowledge acquired in the anatomy lab and with a literature review.

All patients were operated on by the same surgical team under local anesthesia with a cortical and subcortical brain mapping achieved by direct electrical stimulation (DES).

Dexmedetomidine (0.7–2.0 μg/kg/hour) was used for sedation during the surgical procedure. Sedation was discontinued after the craniotomy and prior to incision of the dura.

The craniotomy was made to expose the tumor and up to 2–3 cm of surrounding cortical surface.

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Brain mapping was performed in every case by the same dedicated surgeon (R.A.). DES was performed using bipolar electrodes separated by a distance of 5 mm. Electrocorticography was performed in every patient. Stimulation-induced seizures were suppressed by irrigating the exposed brain surface with cold saline solution. If seizures were refractory to cold irrigation, intravenous levetiracetam (1 g) was administered. The initial stimulation intensity was 2.5 mA, and it was then increased up to a maximum of 10 mA. In all subjects, we found a response in that range. The typical stimulation current was 5 mA. The stimulation intensity was recorded for each patient's mapping procedure. We started with double task (controlateral arm movement and counting) in order to identify the Negative Motor Network (NMN) around the inferior frontal gyrus (IFG) and sensori-motor area. When we evocated a totally motor arrest (TMA), we followed the mapping with the same amplitude stimulus. DO80, PPT and REM are administered in order to identify language and mentalizing responses. We considered the point in which there were already 3 consecutive responses after the DES positive.

The labeled mapping sites were recorded by digital photography prior to and following tumor resection. Tumor resection was performed using frameless navigational guidance based on the preoperative MRI.

All patients underwent a post-operative MRI within 48 h and a neuropsychological assessment before and after surgery (5 days after, 1 month, 3 months and 6 months after surgery) according to a recent European Survey.

We also performed an anatomical dissection on 10 human adult hemispheres using the Klingler dissection method.

3. Results

3.1. Dissection

White matter dissection was carried out in the anatomy lab. Five human adult brains embalmed with the Klingler technique were examined.

Describing the surgical anatomy of the brain from lateral to medial we found that the longer association fibers interconnecting distant areas were positioned at a deeper (more medial) level than shorter ones. The IFOF, which is a large fronto-occipital association fiber pathway, connects the middle and inferior frontal gyri to the posterior part of the parietal and occipital lobes.

We can describe 3 segments:

1) a vertical segment that runs along the frontal lobe
2) a horizontal segment that runs along frontal lobe
3) a horizontal segment that runs from the limen insulae, passes into to the temporal stem and arrives at the parietal and occipital lobes.

The first segment arises from the mid part of F2. Removing the cortex we found, from lateral to medial, the U fibers, the second component of superior longitudinal fascicle (SLF2), the frontal termination of arcuate fascicle (AF) and then the vertical segment of the IFOF. Therefore, it was located lateral (superficial) to the corona radiata and medial (deep) to the SLF II and AF.

The second one arises from pars orbitalis and triangularis of F3. Under the cortex we can find the U fibers, the third component of the superior longitudinal fascicle (SLF3), AF and the IFOF. This segment runs anteromedially to the inferior third of the vertical part (Fig. 1).

These two segments of IFOF pass deep to the insula just above the Uncinate Fascicle (UF) at the level of the limen insulae. At this point, it continues in the third segment that has a horizontal direction. IFOF, in the tract covered by insula, constitutes the ventral part of the external capsule (the dorsal part is constituted by claustro-cortical fibers). It passes into the temporal stem and continues backward within the superior and middle temporal gyri to reach the occipital lobe. Removing the cortex of T1 and T2 we can see, from lateral to medial, the U fibers, AF, Middle Longitudinal Fascicle (MLF) and the third segment of the IFOF. Therefore, this horizontal segment passes deep to the T1, T2; AF and MLF; covers the optic radiation fibers running

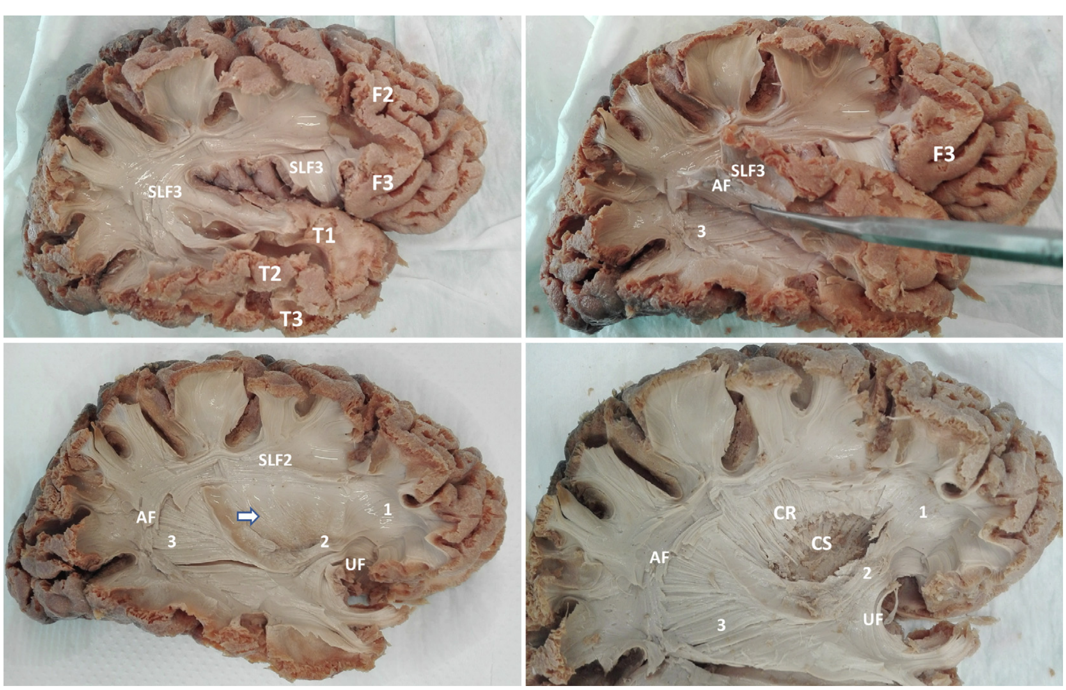

Fig. 1. SLF: superior longitudinal fascicle; AF: Arcuate fascicle; 1: vertical segment of the IFOF; 2: horizontal segment of frontal part of IFOF; 3: horizontal segment of temporo-parieto-occipital part of IFOF; CR: corona radiata; CS: corpus striatum; UF: uncinate fascicle; Arrow: claustro-cortical fibers.

superolateral to the temporal horn, atrium, and occipital horn of the lateral ventricle.

After passing deep to the inferior limiting sulcus, the upper limit of the cortical distribution of the IFOF at the parieto-occipital cortex is located below a line connecting the midpoint of the limen insulae and the upper end of the parieto-occipital sulcus. This line is also positioned at the posterior edge of the claustrocortical fibers (Fig. 2).

3.2. Surgery

Between 1/1/2017 and 05/08/2018 we performed 23 awake surgeries. Thirteen (57%) patients were male and 10 (43%) female, 43% of patients had a tumor located in the right hemisphere and the remaining 57% had a tumor located in the left. In the first group (right hemisphere) there were 2 fronto-temporo-insular tumors (20%), 3 frontal tumors near the Rolandic region (30%), 2 fronto-parietal tumors (20%), 1 fronto-insular tumor (10%), 1 parieto-insular tumor (10%), and 1 parietal tumor (10%). In the second group (left hemisphere) there were 1 fronto-temporo-insular tumor (7%), 5 frontal tumors (39%), 1 parietal tumor (7%), and 6 temporal tumors (47%).

Pathological findings showed 38% glioblastomas, 33% grade II (WHO 2016) oligodendrogliomas (IDH1 mutated 1p/19q co deleted), 29% grade II astrocytomas (IDH 1 mutated not 1p/19q co deleted).

At subcortical stimulation, 9 responses were obtained. In 2 cases contraction was seen eliciting the Corona Radiata (CR) (22.2%); one case of alteration at the PPT Test was described stimulating the SLF (11.1%) and other 2 cases stimulating the third segment of the IFOF (22.2%); anomia was induced in 2 cases by stimulation respectively of the inferior longitudinal fascicle (ILF) (11.1%) and the middle longitudinal fascicle (MLF) (11.1%); stimulation gave paraphasias on the first segment of the IFOF in one case (11.1%) and so it did on the MLF in one patient (11.1%). All IFOF responses were founded in the left hemisphere (Figs. 3 and 4).

We achieved an EOR of 100% of EN in every enhancing tumor. Overall, the median preoperative Total Tumor Volume (TTV) (Flair hyperintense region in LGG and Enhancing Nodule plus FLAIR hyperintense region in High Grade Gliomas (HGG)) were 30.25 cc (range between 9.8 and 199.34). The median post-operative TTV was 3.2 cc (range between 0 and 40.25 cc). The median EOR of TTV was 82.42% (range 12.60%–100%). In our series there were no patients in whom an impairment on writing and motor speech capacity was registered. Overall we experienced a slight early post-operative impairment on comprehension, expression, reading, pragmatics, attention, memory, problem solving and visuoperceptive functions with a complete recovery at 30 days after surgery for all of these, except for memory.

4. Discussion

Nowadays, thanks to the research of Duffau, many surgeons have rediscovered the importance of WM [10,11,14]. In this charming road across centuries of understanding of WM we can recognize some important people. Early observations demonstrated WM as heterogeneous and complex.

Galen described the corpus callosum and the fornix in animals. In 1543, Vesalius distinguished white and gray matter. Through the centuries great anatomists have discovered, described and named most of the WM systems [23].

In the 20th century, Klingler did so much to increase our knowledge on WM. Klingler worked with anatomists, surgeons, and other scientists, and his models and dissections of white matter tracts remain arguably the most elegant ever created. He stressed 3-dimensional anatomic relationships and laid the foundation for defining mesial temporal, limbic, insular, and thalamic fibers and functional relationships. He used formalin-fixed brains after freezing them for dissection [1,23].

The IFOF, which is a fronto-occipital association fiber pathway, connects the middle and inferior frontal gyri to the posterior part of the parietal and occipital lobes. In some cases, precise

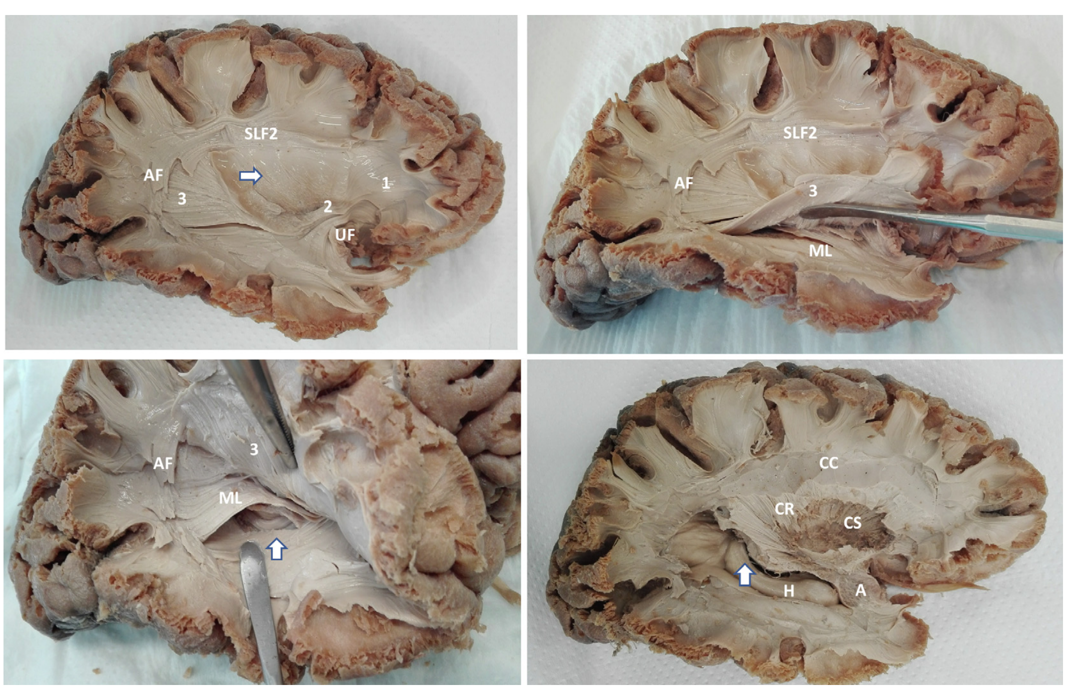

Fig. 2. SLF: superior longitudinal fascicle; AF: Arcuate fascicle; 1: vertical segment of the IFOF; 2: horizontal segment of frontal part of IFOF; 3: horizontal segment of temporo-parieto-occipital part of IFOF; CR: corona radiata; CS: corpus striatum; UF: uncinate fascicle; Horizontal Arrow: claustro-cortical fibers; Vertical Arrow: fimbria; A: Amygdala; H: hippocampus; ML: Meyer's loop; CC: Corpus callosum.

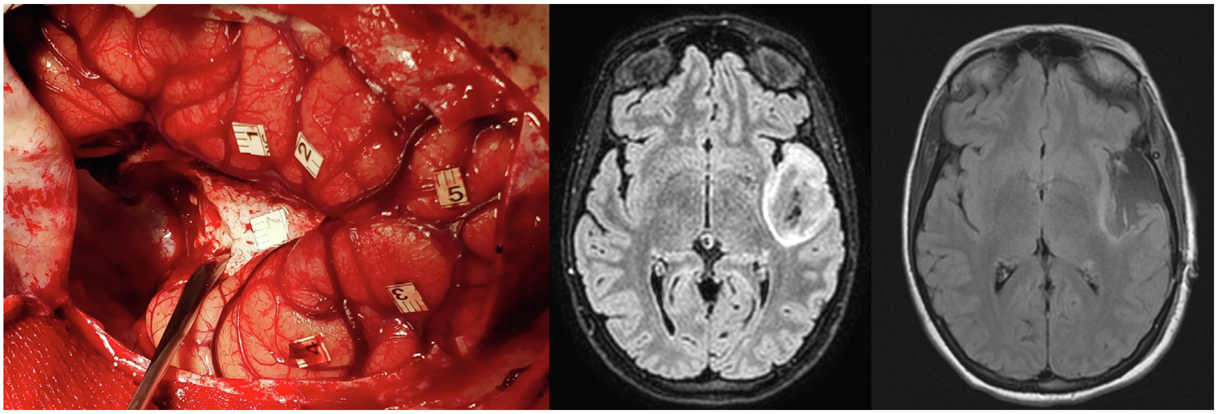

Fig. 3. This figure shows a brain mapping after resection of the left temporal LGG. 1,2: TMA, 3–5: Paraphasias, 7: PPT test impairment. Penfield dissector shows the anatomical correlation between the head of the hippocampus and the roof of the temporal horn of the lateral ventricle that corresponds to the IFOF. Pre and post-operative MRI shows a complete resection of the tumor.

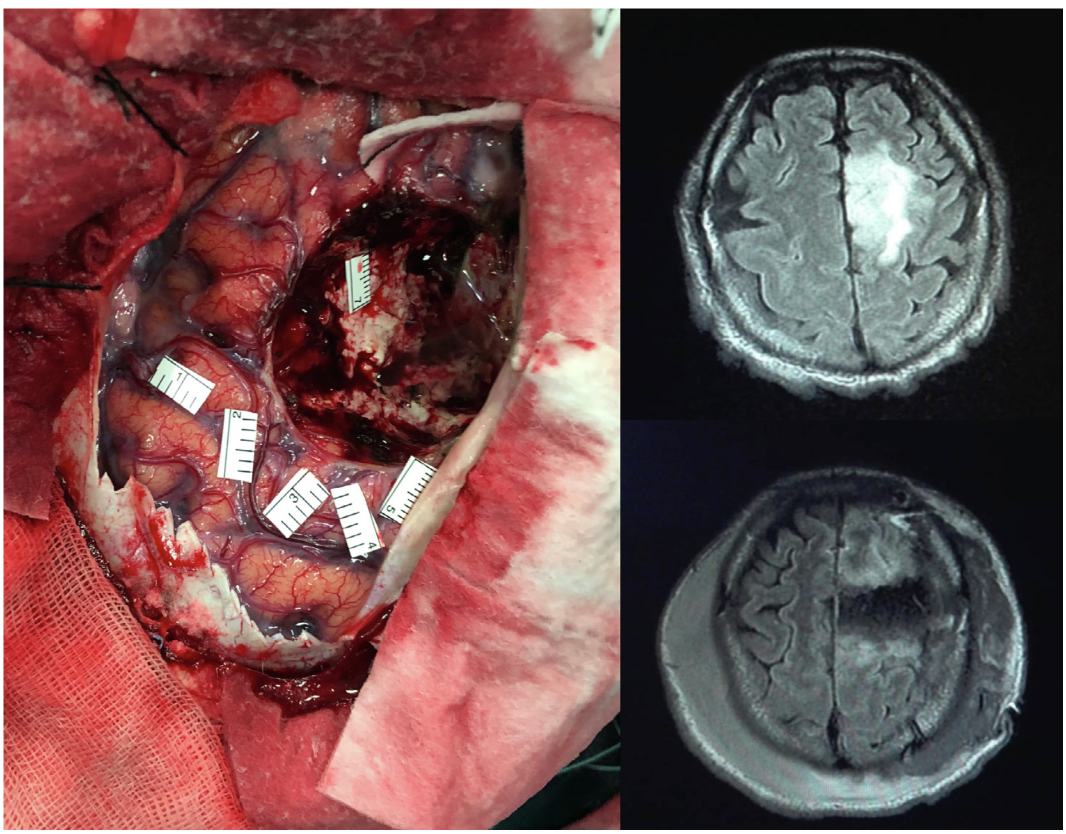

Fig. 4. This figure shows a brain mapping after resection of the left frontal LGG. 1–5: TMA, 7: Paraphasias at DES of the vertical segment of the frontal part of IFOF. Pre and post-operative MRI shows a complete resection of the tumor.

distinction between lateral association fascicles is difficult. It is particularly true for IFOF, UF and optic radiation [18].

First, the IFOF belongs to a layer of more superficial white matter, and appeared to be superior to the uncinate fasciculus. In the dissections by Peltier et al., this structure was sometimes difficult to separate from the UF, this structure had a long anteroposterior course within the temporal lobe, passing into the extreme and external capsules [19].

Various recent neurosurgical anatomical studies have used Klingler dissection preparations in delineating, for example, the precise anatomic course of the IFOF, combining diffusion tensor imaging with electrostimulation studies, combining fiber dissection with diffusion tensor imaging to define the functional implications of the claustrocortical system, and tracking fibers of the uncinate fasciculus [1].

The IFOF role seems to be primarily associated with semantic language processing and transmission but some authors have described that the IFOF connects the salience network to the executive control network, thus potentially playing an important role in goal-oriented behavior. In a recent DTI study Conner et al. provided a detailed map of the macro-connectivity of the ventral stream demonstrating that the IFOF more or less begins in the parietal and occipital lobes, traverses anteriorly lateral to the insula via the extreme and external capsule, and terminates in the inferior frontal lobe along the opercular gyri [8].

DTI tractography studies have also revealed the frontal connections of the IFOF with the dorso-lateral prefrontal and orbito-frontal cortex [7]. A recent study combining DTI tractography with fiber dissection revealed connections to the middle frontal gyrus, inferior frontal gyrus, dorso-lateral prefrontal cortex, orbito-frontal cortex, and frontal pole [21].

DES of the IFOF reproducibly induced semantic paraphasias (i.e., errors regarding the meaning of the word target) whatever portion of the bundle was stimulated (frontal, insular, or occipito-temporal) [17].

Recent publications report high rates of learning and memory impairment after insula glioma surgery, probably due to the IFOF damage suggesting its role also in memory [17].

Duffau et al. described the importance of the IFOF in both hemispheres and the possibility to identify it intraoperatively using a PPT test [12,13,22]. In our surgical series, we easily found a response in the left hemisphere especially in the third segment of the IFOF and using the DO80 test. The lack of responses in the vertical part of the IFOF could be due to the better plasticity of this region [9,14,16]. We intraoperatively confirmed the IFOF role as a crucial part of the double stream language theory, however, the immediate post-operative results seemed to confirm that it is only one aspect of a more complex and multitasking function. Unfortunately, we were not able to identify intraoperatively other domains and further tests should be carried out to identify all fields of "mentalization" in order to respect the identity of every single patient.

5. Conclusion

Anatomical knowledge is the cornerstone of surgical orientation, it allows eloquent structures to be reached quickly and it is of primary importance in awake surgery to avoid patient fatigue with lack of concentration. A specific intraoperative test, with high sensitivity and specificity to better individualize the IFOF, could be a way to improve the outcome of patients and their quality of life.

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