

# Characterization of limbic system connectivity through fiber dissection and diffusion imaging techniques

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## REPORT INFO

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## ABSTRACT

Although cortical elements of the limbic system are quite well defined, the underlying white matter pathways are not well detailed. This project aimed to better describe white matter tracts of the limbic system using both fiber dissection, and in and ex vivo Diffusion Weighted Imaging (DWI) techniques. In vivo data (from DWI and neuropsychological evaluations) were obtained from healthy subjects aged 82 and over previously enrolled in the FIBRATLAS project funded by the French Research Agency and run in the host laboratory. Correlations between neuropsychological and white matter characteristics on DWI were examined in this group to infer function of the limbic white matter tracts. Ex vivo data from the FIBRATLAS project database and from the Tours Body Donation Program were examined. The brains were extracted and used to study the anatomy of the limbic white matter tracts employing both DWI and fiber dissection according to a variant of the Klingler's method.

## 1- Introduction

In the nineteenth century, Paul Broca proposed the term “*great limbic lobe*” for a ring of convolutions around the corpus callosum in two seminal papers published in *Bulletins de la Société d'Anthropologie de Paris* and *Revue d'Anthropologie* (Broca, 1877, 1878). While the remaining cortex was regarded as “intellectual”, the limbic lobe was considered the “brutal” part of the brain. He thus introduced a dichotomy between the limbic lobe and surrounding cortex. Such a perspective, which relegated the limbic lobe to relatively primitive tasks, became very popular. That was the first attempt to group structures that are presently recognized as the **limbic system**. The identity of the limbic system is, however, a concept in evolution that continues to provoke

debate. There is, for instance, discussion surrounding which are the exact structures that should be considered as limbic or extra-limbic, given the richness of their connections (Olry & Nicolay, 1994).

The **cingulum** has regularly appeared as the main communication element of the limbic system. It was one of the central structures of the circuit described by Papez in 1937 as the “seat of dynamic vigilance by which environmental experiences are endowed with an emotional awareness” (Papez, 1937). We have however witnessed a very important development of related research over the last decades that has been at the origin of multiple updates and is pleading for a revolution in the way we think about the cingulum. This fasciculus crosses large distances within the frontal, parietal, occipital, and temporal lobes. Beyond

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being an anatomical substrate of limbic connections, it is a major route for association fibers from cortical regions with distinct functional roles. This subject is of great importance for modeling of higher functions, with applications in cognitive neuroscience, neuropsychology, and a significant impact on how we interpret clinical manifestations of white matter diseases.

Studies on connectivity multiplied greatly in the 20<sup>th</sup> century. This was mainly related to methodological advances. In Switzerland, Joseph Klingler developed an anatomical method associating formaldehyde fixation with one or more freezing and defrosting cycles (Klingler, 1935; Klingler & Gloor, 1960; Ludwig & Klingler, 1956). He noticed that, curiously, freezing was able to change the texture of tissues and slightly separate structures. This phenomenon enabled the development of a method of **fiber dissection** and identification of white matter fasciculi that would be imperceptible in conventional preparations (Alarcon, et al., 2014; Arnts, Kleinnijenhuis, Kooloos, Schepens-Franke, & van Cappellen van Walsum, 2014; Bozkurt, et al., 2017; Costa, et al., 2018; Koutsarnakis, Liakos, Kalyvas, Sakas, & Stranjalis, 2015; I. Maldonado, E. Mandonnet, & H. Duffau, 2012; Maldonado, et al., 2013; I. L. Maldonado, E. Mandonnet, & H. Duffau, 2012; Mandonnet, et al., 2017; Martino, et al., 2013; Pascalau, Popa Stanila, Sfrangeu, & Szabo, 2018; Shah, Jhawar, & Goel, 2012; Zemmoura, Vons, Velut, & Destrieux, 2015). In animals, tract-tracing techniques developed intensively, and autoradiography became notable for its accuracy and high level of detail. Based on the axonal transport of injected radioactively labeled amino acids, this method required animal sacrifice and was impossible to apply to humans (Mufson & Pandya, 1984; Petrides & Pandya, 1984; Woolsey, 2016). In such a context of methodological challenge and absence of a research strategy that would be both effective *in vivo* and practicable in humans, significant effort came from magnetic resonance imaging (MRI) research. Magnetic resonance based **diffusion imaging** is the primary group of techniques used to infer tissue architecture from how it constrains diffusion of water molecules (Basser, Mattiello, & LeBihan, 1994a, 1994b; Conturo, et al., 1999; D. Le Bihan, et al., 1986). This is currently the most frequently used category of non-invasive methods to study the three-dimensional organization of the fasciculi that compose the cerebral white matter in both

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clinical and research contexts (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Catani & Thiebaut de Schotten, 2008; Denis Le Bihan, et al., 2001; Mukherjee, Berman, Chung, Hess, & Henry, 2008).

Examined together, data from the aforementioned techniques and an explosion in the number of publications on cerebral connectivity made opportune and necessary to rethink the main role of the cingulum in the human brain. In our works, we have been exposed to morphological and functional arguments that highlight a tangible shift in perspective. In this research project we studied the morphology of **white matter tracts** using fiber dissection, *in* and *ex vivo* Diffusion Weighted Imaging (DWI), with a special focus on the limbic system.

## 2- Experimental details

To carry out the project, the following steps were developed (results were presented in the same order):

- 1) A **literature review**, describing the state of the art and the up-to-date anatomy of limbic connectivity, especially that of the cingulum, the main fasciculus of the limbic system in human and non-human primates;
- 2) A **fiber dissection** study from the medial, ventral and lateral aspects of the human cerebral hemisphere, with special attention to the medial aspect and the limbic system. The dissected hemispheres were also subjected to MRI scanning;
- 3) A study in diffusion tensor imaging (DTI) through ***in vivo* DWI** of the connections ensured by this fasciculus, whether they are completely inside the limbic system or interconnecting extra-limbic areas using the cingulum as a route;
- 4) Compilation of the morphological results of the *in vivo* MRI with those of the **neuropsychological assessment**, checking for associations between white matter characteristics and the performance profiles;
- 5) ***Ex-vivo* DWI** scanning in high magnetic field (7T, 11.7T) of human cerebral hemispheres;
- 6) A theoretical and epistemological study of the role of the cingulum in humans for **synthetization** of the available data from resonance and fiber dissection studies, taking into account its limbic and extra-limbic connectivity, as recently evidenced.

## 2-1 Volunteers

*In vivo* and part of *ex vivo* data were collected in the frame of the FIBRATLAS project (<https://sites.google.com/site/fibratlas/>) funded by the French Research Agency and ran by the host laboratory. FIBRATLAS aims at producing a database containing *in vivo* (DWI MRI and neuropsychological testing) and *ex vivo* data (DWI and dissection) obtained for the same subjects involved in the body donation program of one of the following university body donation programs: Tours, Angers, Amiens, Brest, Lyon, Nancy. Part of this database will be available to the community for validation of tractography algorithms.

The volunteers, previously enrolled in the body donation program and aged 82 and over, were scanned *in vivo* for anatomical three-dimensional T1-weighted and DWI and underwent an extensive neuropsychological examination. The parameters of acquisition for *in vivo* MRI examination were as follows:

- B0 cartography - FOV 256x256; matrix 64x64; 4mm joined slices; TR 800ms; TE 4.92/7.38ms; NEX=1;
- 3D T1 anatomic images - matrix=256x256; voxel size=1x1x1mm ; TR 2300ms; TE 2.98ms; TI 900ms; NEX=1 ; angle 9°; phase direction A/P;
- DWI - FOV=256x256; voxel size : 1.7x1.7x1.7 mm]: 21 directions with b=300 mm/s<sup>2</sup>, 25 directions with b=1200 mm/s<sup>2</sup>, and 66 directions with b=1200 mm/s<sup>2</sup>.

For DTI tractography, the tensor was computed in each voxel using fiber assignment by continuous tracking. Tracts were defined by regions of interest located according to published atlases. For image post-processing, the Trackvis (<http://www.trackvis.org/>) and Connectomist (CEA Neurospin, Saclay, France) packages were used.

## 2-2 Neuropsychological assessment

The level of education of each participant was systematically recorded and several psychometric fields were explored using standardized tests as follows.

- Manual dominance - Edinburgh test (Oldfield, 1971);
- Global evaluation – Mini Mental State Examination (Folstein et al., 1975);

- Language - DO80 (Deloche and Hannequin, 1997);
- Memory - RL/RI 16 test for verbal (Van der Linder et al, 2004) and DMS4 48 for visual memory (Barbeau et al, 2004);
- Visuo-spatial abilities: Rey's figure (copy) (Rey, 1959; Fastenau et al., 1999);
- Executive functions: verbal fluency (semantic and orthographic) (Godefroy and GREFEX, 2008), Stroop test (Grefex) (Stroop, 1935; Godefroy et al., 2008), Trail Making test (Reitan, 1955; Godefroy et al., 2008; Azouvi et al., 2017), Direct and indirect digit span (Wechsler, 2000);
- Attention and speed processing: Digit Symbol (Wechsler, 2011), TMTA (Godefroy and GREFEX 2008);
- Praxis: Mahieux-Laurent's battery (Mahieux-Laurent et al., 2009);
- Depressive symptoms: MADRS (Montgomery and Asberg, 1979).

For each of the studied tract, a mean value for each scalar parameter obtained from DWI acquisition was computed. The results of neuropsychological examinations were then examined together with those obtained mean values. Any potential association between tract morphology and neuropsychological performance was detailed and discussed.

## 2-3 Ex-vivo data

*Ex vivo* specimens were collected from two different sources: participants of the FIBRATLAS project, and extra volunteers of the Body Donation Program of the University of Tours School of Medicine. The brain was first extracted from the skull and fixed by immersion in a 5% formaldehyde solution in water for at least two to three months. Each body was treated in the first 36 hours after death. Both common carotid arteries were catheterized with the catheter directed upwards. One litter of a 10% formaldehyde buffered solution was injected in each carotid artery during 15 minutes thanks to a peristaltic pump. The day after, a circular craniotomy was performed; the encephalon was extracted after sectioning the falx, tentorium and medullary spinal junction, and suspended by the basilar artery in a 10 % buffered formalin solution for further fixation. Up to the end of the fellowship, a total of 12 hemispheres were scanned for post mortem DWI: 1 at

11.7T, 9 at 7T, and 2 at 3T with different protocols. The 11.7T scanner allowed high resolution imaging with voxels as small as 100 $\mu$ m, isotopically.

For fiber dissection, an adaption of the method described by Ludwig and Klingler was used. After freezing of the specimens for two weeks and defrosting, dissection of the white matter fibers was carried out using fine wooden spatulas. The grey substance, friable, was then gradually separated from the firmer white matter. Identifiable fibers revealed by ablation of the grey matter and neighboring structures were tracked as long as possible towards their cortical or subcortical origins and/or terminations. A surgical microscope (Leica OH4, Leica Microsystems, Wetzlar, Germany) was used as well as additional microsurgical instruments when the naked eye and the mono or binocular loupes were no longer sufficient.

## 2-4 Ethic issues

This work respected all Ethical Principles for Medical Research Involving Human Subjects stated in the Helsinki declaration. In addition, the authors warrant that was developed in respect to the current rules of good practices for research in all participating countries. It is in conformity with the Clinical Trial Regulation of the European Union number 536/2014 as well as the resolution number 466/2012 from the Brazilian Council of Health. The donors who gave their body to science signed a will by which they allow any research on their body after death. In addition, the FIBRATLAS project, from which part of the data was obtained, was approved by the ethical committee of Tours (Comité de protection des Personnes, 2015-R8) and by the ANSM (*Agence Nationale de Sûreté du Médicament et des Produits de Santé*, EudraCT/ID RCB: 2015-A00363-46). The confidentiality of the identity of all subjects that have donated their bodies to science were and will continue to be ensured in all stages, including in scientific communications and future publications.

## 3- Results and discussion

### 3-1 Results of the comparative connectivity review

For this part of the work, a total of **80 publications** was examined. In monkeys and chimpan-

zees, the structure of the white matter that composes the cingulum is complex and heterogeneous (Vogt *et al.* 1992). The bundle is organized as an associative complex, even though it has the appearance of a single compact fasciculus in gross anatomy. Charles Beever (1891) offered one of the first descriptions of the cingulum anatomy in the nineteenth century. He noted that in the Marmoset monkey, the bundle almost does not vary in diameter throughout its course, because of the continuous addition and exiting of fibers (Beever 1891; Jeremy D. Schmahmann 2006).

The **Rhesus monkey** has been the most frequent non-human primate used in investigations of cerebral connectivity historically. The cingulum subdivisions that have been proposed were mostly based on the results of radioisotope tracing and autoradiography, considered as a golden standard technique (Mufson and Pandya 1984; Jeremy D. Schmahmann 2006; Schmahmann *et al.* 2007). Such studies showed that fibers coming from the prefrontal cortex may travel large distances inside the cingulum, and some extend up to the retrosplenial cortex. Those from the parietal cortex could reach the parahippocampal gyrus of the temporal lobe through a different portion of the same bundle (Jeremy D. Schmahmann 2006). A population of small overlapping tracts responsible for regional connections, were also described with consideration of specific functional roles (Mogenson *et al.* 1980; Morgane *et al.* 2005; Catani *et al.* 2013). Consequently, the microstructural characteristics of the cingulum are not homogenous (Yeterian *et al.* 2011; Petrides *et al.* 2012) and its fibers may be grouped according to their anatomical terminations and functionalities. Two main types are considered: those that originate or terminate in the cingulate gyrus itself and those that travel inside the cingulum as a route for distant or adjacent cortical areas (Jeremy D. Schmahmann 2006).

Several authors agree that the cingulum is part of the route of several projection and association bidirectional pathways (Forkel *et al.*; Mufson and Pandya 1984; Petrides *et al.* 2012). Fibers from the anterior thalamic nuclei and the frontal lobe travel inside the fasciculus before reaching the retrosplenial cortex and to the cingulate gyrus itself (area 23) (Yeterian *et al.* 2012). Furthermore, those from the dorsolateral thalamic nuclei and the parietal cortex run in the cingulum before

reaching the presubiculum and the parahippocampal gyrus in the temporal lobe (Forkel *et al.*; Mufson and Pandya 1984; Jankowski *et al.* 2013; Heilbronner and Haber 2014). Other fibers connect post-Rolandic, parietal, and pre-occipital areas with the dorsal and ventrolateral prefrontal cortices (Aggleton *et al.* 2012; Petrides *et al.* 2012).

Association fibers spread to cortical areas at different points. While the rostral ones terminate in the prefrontal cortex, other groups leave the bundle in the frontal, parietal, and temporal lobes (Mufson and Pandya 1984). The longest fibers are afferent and travel along the periphery, and thalamic fibers adopt a more ventral position (Jeremy D. Schmahmann 2006).

Efferent pathways from the anterior cingulate gyrus, including monkey area 24, travel in the cingulum before reaching a large number of destinations in the same cerebral hemisphere: the orbitofrontal, the ventrolateral and dorsolateral prefrontal cortex, as well as the primary motor cortex, infero-rostral portions of the parietal lobe, the amygdala, the perirhinal cortex (Jeremy D. Schmahmann 2006), the extreme capsule, and insula (Petrides *et al.* 2012). Those from area 23 are dorsolateral and stream caudally to the parahippocampus and presubiculum (Mufson and Pandya 1984).

Most evidence from autoradiography suggests a general organization of the cingulum connectivity in two main components. The anterior (ventral) component connects most of the cingulate gyrus, orbitofrontal, septal, sub-callosal, and pericallosal regions (Mufson and Pandya 1984; Schmahmann *et al.* 2007). The posterior (dorsal) component connects the precuneus, presubiculum, parahippocampal gyrus, and hippocampus (Jeremy D. Schmahmann 2006; Aggleton *et al.* 2012).

Publications on findings of fiber dissection became more frequent after the seminal works of Ludwig and Klingler in 1956 (Ludwig and Klingler 1956) but received substantial impulse after the advent of methods for diffusion imaging and peri-operative subcortical stimulation in the last twenty years (Duffau 2016). Fiber dissection allows visualization of macroscopic organization of the fiber bundles and their three-dimensional disposition in the cerebral parenchyma (Fernández-Miranda *et al.* 2008; Insausti *et al.* 2017), goals that would be difficult to achieve using traditional anatomical preparations. Some variants

of the original technique were described, although the main methodological principle remains (i.e. the addition of freezing steps in the fixation protocol). The crystallization of the water and formalin increases volume and slightly separates groups of fibers, rendering them visible and dissectible (Zemmoura *et al.* 2015).

In fiber dissection studies, the cingulum appears as a compact and well-defined bundle travelling in the depth of the cingulate gyrus. After removal of the cingulate cortex, made friable by the preparation, a relatively firm layer of subcortical white matter is identified. This thin layer is roughly amorphous to the naked eye and accompanies the curvature of the medial aspect of the cingulate gyrus (Fernández-Miranda *et al.* 2008). Deeper to that, fibers are easily identifiable, grouped within a compact bundle, with a predominant antero-posterior direction. The lateral aspect of the white matter in the core of the cingulate gyrus is continuous with the medial portion of the centrum semiovale, where the compact subcortical layer is absent (Mollink *et al.* 2017).

The region of the centrum semiovale that is in direct anatomical relationship with the cingulum is rich in fibers from callosal and thalamic radiations (Fernández-Miranda *et al.* 2008). Inferiorly, the trunk of the cingulum is in contact with transversal fibers of the corpus callosum (Lawes *et al.* 2008; Maldonado *et al.* 2012). Lateral-most fibers are then in direct contact with the rostrum, genu, body, isthmus, and splenium without the interposition of cingulate cortex. The anterior extremity of the cingulum sharpens progressively as its fibers leave the main bundle to terminate in the subgenual gray matter and septal areas (Ribas 2010; Chaddad-neto *et al.* 2017).

In its trajectory around the corpus callosum, the anterior cingulum also has indirect anatomical relationships (through the cerebral cortex and the cingulate sulcus) with surrounding cortical areas, namely the superior frontal gyrus, the paracentral lobe, and the precuneus. There is evidence of extensions of the cingulate white matter with well-defined fibers penetrating the superior frontal gyrus (Li *et al.* 2013), the paracentral lobe, and precuneus (Cavanna and Trimble 2006; Wu *et al.* 2016).

Inferiorly and anteriorly to the splenium, cingulate fibers penetrate the parahippocampal gyrus. On their way, they maintain indirect relationships with the posterior column of the fornix (crus fornicis) and with the cistern spaces through the parahippocampal cortex (Concha *et al.* 2005).

The inferior extremity of the cingulum extends anteriorly in the depth of the parahippocampal gyrus and advances toward the hippocampal formation (Jones *et al.* 2013a).

The white matter of the parahippocampal gyrus and precuneus is a continuous structure. Inferiorly to the subparietal sulcus, the precuneus is connected with the cingulate and the parahippocampal gyrus (Ribas 2010). This is related to the presence of parahippocampal-precuneal direct association pathways, as a subcomponent of the cingulum. Similarly, irradiation of cingulate fibers to the upper frontal gyrus and the upper precuneus proposed the cingulum as a path for direct fronto-parietal associative connections (Burzynska *et al.* 2011; Maldonado *et al.* 2012; Ekman *et al.* 2016).

Diffusion imaging techniques have provided indirect information on the anatomy of fiber tracts in the last twenty years with increasing levels of confidence. The representation of the cingulum as a complex connective system, because of the assembling of smaller bundles, is a conception that was recently strengthened by imaging studies. Some authors have proposed systematization of its parts to characterize each of them (Catani and Thiebaut de Schotten 2008; Beckmann *et al.* 2009; Jones *et al.* 2013a; Heilbronner and Haber 2014).

In DTI, deterministic tractography of the cingulum may be obtained by placing regions of interest in specific anatomical sites (Jellison *et al.* 2004; Catani and Thiebaut de Schotten 2008; Jones *et al.* 2013b). In several studies, their locations were based on previous knowledge from autoradiography studies in monkeys. Using this technique, the general appearance of the human cingulum is similar to that observed in fiber dissection studies. The cingulum arches almost 180 degrees around the splenium and continues anteriorly. After traveling inside the cingulate gyrus, above the isthmus and trunk of the corpus callosum, it curves again around the genu. It terminates by spreading its fibers in the subcallosal gyrus and the paraolfactory area (Catani and Thiebaut de Schotten 2008; Sarkar *et al.* 2012). The human cingulum seems to contain **fibers with different lengths and with distinct connectivity profiles**, in the context of a complex population of pathways (Jones *et al.* 2013a). This was detailed through virtual dissection employing simultaneous regions of interest.

The middle portions of the cingulum contain long fibers that travel to the frontal lobe, terminating in the premotor or motor cortices (Gong *et al.* 2005; Xie *et al.* 2009; Bliss *et al.* 2016). The longest fibers seem to originate from the extremities of the bundle, as is the case of those arising from the subgenual cortex, amygdala, uncus, and parahippocampal gyrus (Thiebaut de Schotten *et al.* 2012). Additionally, some long fibers extend inferiorly, providing direct parieto-temporal connections (Jones *et al.* 2013a). Inferior portions of the cingulum may serve as a route for direct transcingular temporo-occipital connections.

Catani *et al.* proposed a systematization based on the anatomic division of the cingulum in two parts: the anterior-dorsal and the posterior-ventral (Catani and Thiebaut de Schotten 2008). The anterior-dorsal is composed of long fibers that follow the shape of the corpus callosum, go forward and around the genu, and continue in the subcallosal part towards the paraolfactory area. The posterior-ventral fibers travel along parahippocampal, retrosplenial and posterior precuneal areas (Catani *et al.* 2013).

Jones *et al.* (2013), using regions of interest based on the a priori anatomy of the Rhesus monkey, described three identifiable subdivisions with specific morphological and physiological features: the subgenual, the retrosplenial, and the parahippocampal (Jones *et al.* 2013a). Moreover, the authors described the parahippocampal subdivision in two different manners: restricted and unrestricted. In restricted reconstructions, the authors isolated transcingular temporo-parietal and temporo-occipital pathways. In unrestricted reconstructions, such fibers were depicted together with the “standard cingulum”. The subgenual subdivision is medial in relation to the others. The retrosplenial one is lateral to the subgenual in the portions in which they overlap. Finally, the parahippocampal subdivision contains the lateralmost fibers of the cingulum complex. Those subdivisions connect extensive areas around the corpus callosum. Few fibers run along the entire path. Indeed, further studies are required to detail the length, terminations, and functional roles of the smaller groups.

Using high-definition fiber tracking and a template from the Human Connectome Project, Wu *et al.* (2016) identified five potential subcomponents. The authors named them as CB I, II, III, IV, and V subcomponents (Wu *et al.* 2016). The CB-I subcomponent is anteromedial and extends from the orbitofrontal cortex to the precuneus,

running along most of the length of the corpus callosum, up to the splenium. The CB-II subcomponent travels from medial portions of the superior frontal gyrus to the retrosplenial, parahippocampal and perirhinal cortices. The CB-III subcomponent is the largest in terms of volume, originates in the medial aspect of the SFG, and ends in the precuneus, connecting many cortical areas. The CB-IV is the shortest, connecting the superior parietal lobe and precuneus with supplementary and premotor areas. It is located over the trunk of the corpus callosum and follows roughly the same trajectory of the dorsal component of the superior longitudinal fascicle (SFL-1). The author subdivided it into two parts: the paracingulate (paraCB) and supracingular (supraCB). Given these observations, the cingulum was suggested to comprise direct dorsal frontoparietal fibers, as it seems to be the case in fiber dissection. Lastly, the CB-V corresponds to the group of parahippocampal fibers that spread in the parietal and occipital lobes. The subdivision in five components also enabled some systematization of the three-dimensional disposition of different groups of fibers. While the CB-I subcomponent runs close to midline adjacent to the corpus callosum, CB-II, III, and IV occupy different portions of the cingulum above the corpus callosum, and most fibers of CB-IV have a predominant superior location in relation to the others. Finally, running exclusively in the temporal and occipital lobes, CB-V is the most inferior and laterally situated subcomponent (Wu *et al.* 2016).

### 3.2- Results from fiber dissection

#### 3.2.1- Medial and ventral aspect

After midline section of each human cerebral specimen, the initial examination enabled identification the non-cortical structures. Among the main ones were the olfactory tract and bulb, internal carotid artery, optic nerve (II cranial nerve), optic chiasm, oculomotor nerve, midbrain (cerebral peduncle, tegmentum and tectum), and the splenium at the posterior-most part of the corpus callosum.

The next step was examination of the sulco-gyral architecture. The main sulci of the medial aspect were identified at this stage, namely the sulcus of the corpus callosum, the cingulate, subparietal, parieto-occipital and calcarine sulcus. In the frontobasal area, the main superficial anatomical landmarks visible were the olfactory sulcus

delimiting medially the gyrus rectus (or straight gyrus) and laterally the medial orbital gyrus. The orbital sulcus had the shape of a letter "H" delimiting four orbital gyri (anterior, posterior, lateral and medial). In the medial and inferior aspects of the temporal and occipital lobe, the hippocampus sulcus was identified as well as the collateral and occipitotemporal and calcarine sulcus. These landmarks were used references for the next steps of dissection, and for localization of the medial aspect cerebral gyri, the main being the superior frontal gyrus, paracentral lobule, cuneus, precuneus, lingula, cingulate, parahippocampal, fusiform, and inferior temporal gyrus.

On a second layer, the cortex rendered spongy by the preparation was removed from the sulci and short association fibers ("U" fibers) exposed. The fibers recover the depth of each sulcus and then reproduce the sulco-gyral anatomy studied in the previous step.

On a third layer we used delicate wooden spatulas and forceps to gently remove "U" fibers from the sulci. This made it possible to expose and follow the most superficial fasciculi such as the cingulum, the inferior longitudinal fasciculus, and the dorsal callosal radiations.

On a fourth layer, we used a scalpel blade to cut the ventricular septum and open the lateral ventricle. We were able to identify the ependyma which lines the ventricular cavity and observed the fornix which is located partly in the floor ventricular cavity adjacent to the choroid plexus. The dissection progressed into the walls of the lateral and third ventricles at the same time as it progressed inside the cingulum bundle. The procedure enabled exposition of the anterior columns of the fornix inside the hypothalamus, the mammillothalamic tract, anterior and dorsal thalamic radiations. Finally, the atrium and temporal horn of the lateral ventricle were widely opened for exposure of the tapetum and optic radiations around the temporal horn itself (temporal loop) and the sagittal stratum.

The optical radiations occupied the last layer of this dissection. At the end stages, structures of the optic pathways were visible: the optic nerve, optic chiasma, lateral geniculate body, pulvinar, optical radiations, and the dissected primary visual cortex.

### 3.2.3. Lateral aspect

This phase enabled further detailing of the anatomy of structures that were not completely exposed from the medial aspect, such as those in the walls of the lateral ventricle and the study of anatomical relationships. After study of surface landmarks such as done for the medial aspect, removal of the cerebral cortex and short "U" association fibers was performed, allowing dissection of deep portions of the cerebral white matter. This procedure exposed the long association fasciculi of the semioval center and the sagittal stratum around the lateral ventricle. Given the lack of detailed description of this region in the literature, special attention was given to its structures. Fibers of the inferior longitudinal fasciculus were observed in the inferior margin of the preparation, intermingled with other elements of the region. Although most of these fibers ran at the ventral aspect of the temporal and occipital lobe, some of them could indeed be dissected from the lateral aspect. At this stage, the temporal operculum was preserved not to eliminate the Middle Longitudinal Fasciculus (MdLF) located superficially. The MdLF penetrated the superior temporal gyrus and planum temporale as an organized fiber contingent progressively more compact from posterior to anterior. Posteriorly, albeit superficial, MdLF was clearly intermingled with the surrounding fibers.

Running at a deeper level than the MdLF, the Inferior Fronto Occipital Fasciculus (iFOF) reached the temporal stem and the insula just posterior and dorsal to the limen insulae. Consequently, the superior temporal gyrus including the planum temporale, and the middle temporal gyrus had to be removed prior to its dissection. The posterior segment of the iFOF was partially covered laterally by the dorsal part of the MdLF. As the dissection progressed from the posterior to the middle segment (trunk) of the iFOF, the latter ran deeper to the MdLF, reaching the antero-inferior portion of the external and extreme capsules. The ventral part of the external and extreme capsules also contained the UF, which was ventral to the anterior segment of the iFOF.

The next fiber contingent crossed by the dissection was the optic radiations that originated from the lateral geniculate body and ran in the lateral wall of the atrium and occipital horn prior to the lips of the calcarine fissure. As previously described by other authors, the optic radiations

can be subdivided in three segments from anterior to posterior. The first segment, or Meyer's loop, is the most anterior one and forms a posteriorly concave curve in a lateral oblique plane in close relationships with the anterior commissure and, more anteriorly, the UF. The second segment, or body of the optic radiations, runs along the lateral aspect of the atrium and occipital horn. Finally, the third segment joins the lips of the calcarine fissure. As a whole, the optic radiations – from the thalamus to the cortex – can be considered as specific posterior thalamic radiations and share the same general organization as other adjacent thalamic radiations to the occipital and parietal cortices.

Finally, the tapetum was located medial to the optic, containing fibers in a vertical organization. This layer, which is derived from the corpus callosum, covered the lateral aspect of the ventricular atrium and occipital horn. This was the deepest white matter layer of the lateral wall of the atrium, only limited from the cerebrospinal fluid by the ependyma.

As a summary, the lateral wall of the ventricular atrium comprised from medial to lateral: the ventricular ependyma, tapetum, optic radiations, iFOF, MdLF, posterior portion of the Superior Longitudinal Fasciculus / Arcuate Fasciculus complex, short "U" association fibers, and the cerebral cortex. Some of them also participated to the lateral wall of the occipital ventricular horn. The Inferior Longitudinal Fasciculus occupied only the ventro-lateral aspect of the dissection, its fibers contributing little to the ventral aspect of the superficial layer of the sagittal stratum. Most of these structures were partially superimposed on a sagittal plane. The MdLF, narrower than the iFOF, covered only its upper portion. The iFOF, in turn, partially covered the optic radiations, which overflows ventrally at the level of Meyer's loop. The optic radiations spilled over into the anterior-inferior portion of the iFOF as they are more ventral in location and extend around the temporal horn. As it progressed forward, the iFOF moved away from it to reach the temporal stem and the insula. Therefore, a space was created behind the directional change of the UF fibers, ahead of the Meyer's loop and deep to the iFOF. This space was occupied by fibers from the anterior commissure, opened in a fan of which the more caudal ones joined the SS. Although a large number of fibers were intermingled, this phenomenon varied according to the location considered. As a result, the layers can be separated at



certain sites, whereas in others, the delamination procedure causes the fibers to rupture. This was for instance the case: for the posterior segment of the iFOF, interspersed with the optic radiations as both approach the occipital cortex; for the anterior commissure intermingled with those of the Meyer's loop; and for the fibers of the anterior commissure intermingled with those of the posterior portion of the uncinate fasciculus.

### 3.3- Results from in vivo DWI

MRI examinations of 120 volunteers are comprised so far in the database of the FIBRATLAS project. Datasets of fifteen participants were assessed for study of limbic and extralimbic connections with special focus on the cingulum bundle. Six (42.8%) of them were male, and the mean age was  $85 \pm 3.5$  years (mean  $\pm$  SD, range 82 - 93). Two male subjects (13.3%) reported more than twelve years of education, and three (21.4%) have completed primary school. All women and remaining four men have 12 years of education or less. Based on the ISCO-08 occupational map and the ISCED-97 classification of skill levels, a total of four (26.7%) participants had skill level I occupations (physical or manual activities), four (26.7%) level II (machinery or electronic equipment operation, driving, maintenance or manipulation of information), three (13.3%) level III (technical task with procedural knowledge in a specialized field), and four (26.7%) level IV (activities requiring complex problem-solving, creativity or decision-making based on extensive bodies of knowledge). In one case, no occupation was informed.

All thirty cingulum reconstructions were performed successfully. Direct frontoparietal transcingular tracks were observed in fifteen right and fourteen left cerebral hemispheres (not observed in the left hemisphere of one female subject). In these 29 tractograms, interconnections between the medial frontal cortex and the posterior precuneus were depicted. Interconnections involving frontal areas (the anterior middle frontal gyrus, the superior frontal gyrus, the precentral gyrus) and parietal areas (the postcentral gyrus and the precuneus, corresponding to the medial surface of the superior parietal lobe) were depicted. Pathways between the rostralateral and dorsal-lateral prefrontal cortex, Brodmann areas (BA) 10 and 8, 9, and the posterior medial parietal cortex (precuneus), BA 7, were observed in

twenty-four hemispheres; and between the primary motor cortex, BA 4, and the parietal medial areas in six right and seven left hemispheres. In the parietal lobe, most of interconnections (in 27 hemispheres) ended in the precuneus or the postcentral gyrus (in 13 hemispheres). Those between the anterior middle frontal gyrus (BA 10) and the precuneus were depicted in thirteen. Direct tracks between the posterior medial frontal cortex, supplementary motor area (BA 6), and the precuneus were observed in fourteen hemispheres. Inside the cingulum, tracks making direct connections between the superior frontal gyrus and precuneus assumed a more medial and inferior trajectory. In turn, fibers that interconnect the precuneus and supplementary motor area were more lateral in position.

The median fiber length and volume of the transcingular direct frontoparietal tracts were respectively  $102.2 \pm 30.8$  mm (median  $\pm$  SD) and  $2 \pm 2.5$  ml (median  $\pm$  SD) respectively for the right hemisphere, and  $128.18 \pm 19.4$  (median  $\pm$  SD) and  $5.6 \pm 4.2$  ml (median  $\pm$  SD) for the left hemisphere. The value of fractional anisotropy (FA) was  $0.23 \pm 0.049$  (mean  $\pm$  SD, median 0.24) for the right, and  $0.23 \pm 0.031$  (mean  $\pm$  SD, median of 0.24) for the left hemisphere. The number of tracks was  $201.9 \pm 223.22$  (mean  $\pm$  SD, median of 81) in the right, and  $424.9 \pm 396.46$  (mean  $\pm$  SD, median 369.50) in the left. The voxel count resulted in  $3158.6 \pm 2675.6$  (mean  $\pm$  SD, median 2009.0) for the right and  $4995.21 \pm 3730.3$  (mean  $\pm$  SD, median 3763.5) for the left hemisphere.

Sex was related to significant differences in the scalar measurements in our sample. Significantly higher FA was observed in women in the right hemispheres ( $p=0.04$ ,  $LI=-0.22$ ), and in males in the left hemisphere ( $LI=0.17$ ) in conjunction with higher voxel count values ( $p=0.01$ ). No other statistically significant difference of scalar measurements in the same sex was observed, but the volume laterality index indicated leftward lateralization ( $LI = 0.70$ ) in men. Also, a total volume inferior or equal to the median (2 ml in the left hemisphere was more frequent among women ( $p=0.03$ )). Leftward lateralization was observed for FA in three men, and for fiber length in one man and four women. Right lateralization was observed in one female subject for FA and length. There was no association of volume or fiber length with profession or educational scores.

### 3.4- Results of neuropsychological assessment

Fourteen volunteers completed the neuropsychological assessment. The basic cognitive assessment using the Folstein's Mini-Mental State Examination showed a mean score of 26 (19 to 29). Three participants scored under 24.

Concerning the Rey Complex Figure Test, five subjects copied it using a type 1 strategy, four using a type 2, one using copy type 3 and five a type 4. Visuospatial abilities varied widely across participants. The mean immediate recall score was  $11.1 \pm 1.6$  and the delayed recall score was  $10.9 \pm 1.3$  (mean  $\pm$  SD), both significantly lower than the initial copy score ( $29.8 \pm 0.4$ ,  $p < 0.01$ ). No statistical difference was observed between immediate and delayed recall scores. Negative correlation was observed between age and copy score (mean correlation coefficient of  $r = -0.559$ , leading to an equivalent corrected alpha of 0.047). Positive correlation was observed between immediate recall score and delayed recall score ( $r = 0.824$ ,  $p=0.001$ ), copy time and immediate recall time ( $0.700$ ,  $p=0.008$ ), copy time and delayed recall time ( $r = 0.726$ ,  $p=0.005$ ), and immediate recall and delayed recall time ( $r = 0.600$ ,  $p=0.03$ ).

For the RL/RI-16 free and cued recall task, Z-values and quantiles of the normalized results of the RL/RI-16 free and cued recall test were obtained. The total free recall and the sum of total recall scores were  $22.07 \pm 7.35$  and  $42.57 \pm 5.27$  (mean  $\pm$  SD,  $p < 0.01$ ) respectively. Two participants presented with low Z scores, under the pathological threshold (quantile 5,  $Z=-4.47$  in this sample).

In the Trail Making Test test the mean interval of time for completion of part A was  $58.29 \pm 16.6$  (mean  $\pm$  SD) and the median 58 seconds. For part B this figure was  $143.14 \pm 41.9$  seconds and the median 143.5 seconds. The difference of the time needed to complete parts A and B was  $84.8 \pm 31.2s$  (mean  $\pm$  SD) and the median 94 seconds. Quantiles of the Z scores were obtained. A linear regression analysis did not show significant effect of age, sex and level of study on performance in parts A and B in our sample.

In the Stroop test, participants took longer to name the ink color word when the color name was incongruent with the ink color in all subjects. In such "Interference" situation, in which participants had to inhibit the written word in order to correctly name the color of the ink, the mean time was  $167.83 \pm 43.8$  seconds. The mean difference

between the situation of interference and that of simple denomination was 80.87 seconds, with a median of  $92 \pm 47$  seconds. The mean of total uncorrected errors was  $2.08 \pm 2.32$  (mean  $\pm$  SD, range 0-8). In participants aged 85 years or older, the time necessary to complete the task in interference condition, mean time per word, and interference score were significantly higher.

Lastly, data from published studies were used to compare this sample to others of similar range of age (Supplementary Figure 1). For the Mini Mental State Examination Test, results were similar (Kalafat, 2003) or at the significance threshold (Kochhann et al. 2009,  $p=0.05$ ). For the Rey Complex Figure Test (Fastenau et al. 1999; Foss et al. 2010), results were similar for both the copy and the delayed recall scores. Similarities were also observed in the Trail Making Test part A (Tombaugh et al. 2003, Amieva et al. 2009) and in the number of errors in the interference condition of the Stroop test (Bayard et al. 2011). Nevertheless, a significant difference was observed with Zimmermann et al. 2015 since this score was inferior in our sample.

### 3.5- Results of compilation of morphological and neuropsychological findings

For analysis, scalar data were distributed in two groups in function of the median scores. Associations between scalar values and neuropsychological performance were observed in women only. Women with a volume of transcingular frontoparietal tracks inferior to the median in the left hemisphere presented with a Mini Mental State score  $\geq 25$  ( $p=0.02$ ). For the Rey figure, all women with median fiber length  $\leq 101.93$  mm in the right hemisphere were in the group above the mean copy normalized score ( $p=0.02$ ). For the immediate recall, all women had scores inferior to the mean ( $11.11 \pm 1.63$ , mean  $\pm$  SD).

A Spearman correlation analysis of scalar variables was performed with the performance on Rey Complex Figure, RL/RI-16 Free and Cued Recall Task, Trail Making and the Stroop test. In the left hemisphere, FA ( $r = -0.56$ ;  $p=0.029$ ) and volume ( $r = -0.53$ ;  $p=0.028$ ), but not voxel count or fiber length, were negatively correlated with Stroop interference time. Voxel count was negatively correlated with the difference of time necessary to complete parts B and A of the Trail Making Test (B-A) ( $r = -0.51$ ;  $p=0.035$ ). In the right hemisphere, voxel count ( $r = 0.58$ ;  $p=0.014$ )

and volume ( $r = 0.51$ ;  $p=0.031$ ) were correlated with memory reproduction, the immediate recall score of the Rey Complex Figure Test. Voxel count was also correlated with the delayed recall score ( $r = 0.49$ ;  $p=0.035$ ).

### 3.6- Results from ex vivo DWI

To date, a total of ten human brain specimens have been examined on MRI. Two were scanned at 3T (Martinos Center, Boston, USA). Other eight were scanned in high magnetic fields (CEA Neurospin, Saclay, France): seven at 7T, and one at 11.7T (with resolutions of 100, 150 and 200  $\mu\text{m}$ ).

These procedures resulted in a unique library of image datasets for future studies in detailed morphology of the human white matter. The datasets will be made available in the form of an open database on the FIBLATLAS project webpage (<https://fibratlas.univ-tours.fr/>), after an embargo period.

### 3.7- Synthesis of available data

In the present study, DTI tractography was used to detail the morphology of long association fibers interconnecting the frontal and parietal lobes through the dorsal cingulum. Exploration by two independent operators demonstrated transcingular tracks in 29 out of 30 cerebral hemispheres, which were anatomically detailed. These findings reinforce the idea of the cingulum as an important route of direct frontoparietal association pathways in parallel to those comprised in the Superior Longitudinal Fasciculus. A standardized neuropsychological assessment of the same volunteers suggested that faster planification and visuospatial processes were associated to the presence of longer tracks. To our best knowledge, this was the first study on diffusion imaging focusing on transcingular direct frontoparietal connections in the human brain. This is a subject of great importance in the field of modeling of mental functions. Beyond the participation of the cingulum in the limbic system, it seems to be an important element of highly functional dorsomedial circuits such as those related to motor activity initiation, executive functions, and the Default Mode Network.

Longer fibers were deeper (more lateral) inside the cingulum, an observation which is in line

with the findings in non-human primates (Mufson and Pandya 1984; Aggleton et al. 2012). The human cingulum is, however, larger in volume and looks richer in regional fibers. Connections to the Supplementary Motor Area (SMA) and precuneus were robust on left hemisphere. Hand preference and the importance of these connections to motor planning and visuospatial integration are possible explanations for this phenomenon. Asymmetries have been observed for other fascicles in humans. A classic example is the arcuate fasciculus (Parker et al. 2005; Rilling et al. 2008; Madhavan et al. 2014; Hecht et al. 2015; Keedwell et al. 2012; Fan et al. 2015) a phenomenon considered to be related to language dominance.

Our results investigated relevant relationships between scalar measurements of transcingular frontoparietal tracts and neuropsychometric parameters such as episodic memory (Rey complex figure delayed recall, RL/RI-16 free and cued recall), visuospatial processes and planification (Rey complex figure copy), cognitive inhibition (Stroop Test) and flexibility processes (Trail Making Test). Some structural particularities were identified in individuals with better results. Volunteers with better performance in immediate recall and delayed recall of the Rey Complex Figure Test presented with significantly larger volume and voxel count. A possible interpretation for this is the fact that the richness of interconnecting pathways tends to coexist with the increased activation of frontal and parietal areas that ensures better visuospatial abilities. In the Trail Making Test, individuals with less difference on time between parts A and B showed higher track voxel count in left transcingular pathways. In addition, more time needed to complete in Stroop test was related with smaller figures of fractional anisotropy and volume.

Cognitive inhibition (Stroop test) was associated with volume and FA on the left hemisphere, and memory reproduction (Rey complex figure test) was associated with volume and voxel count on the right. Lower microstructural organization of the cingulum was reported to be related to a decrease in performance in various cognitive domains and in the activation of the default mode network (Bathelt et al. 2019). In a study of 220 older adults without dementia, attention, and executive function performance correlated to the FA of the anterior cingulum. The same was observed in the posterior cingulum for memory, language, attention, executive and visuo spatial

function (Kantarci et al. 2011). The efficacy of cognitive control was also reported to be very sensitive to the cingulum microstructure (Metzler-Baddeley et al. 2012). Prior investigations that highlighted the link between a more developed functional connectivity and higher cognition have also pointed to the importance of frontoparietal connections in both adults (Charlton et al. 2010; Ritchie et al. 2015; Bettcher et al. 2016; Ekman et al. 2016) and children (Wendelken et al. 2016; Carter Wendelken, Emilio Ferrer, Simona Ghetti 2017). These findings are relevant to clinical neuroscience of both pathological and normal aging conditions. Indeed, executive functions are among the most commonly affected cognitive domain in older adults.

Anatomical and neuropsychological consequences of aging were certainly present in our series, such as the decline in white matter integrity and aging-functional modifications on episodic memory and executive functions. In a study with 94 older adults without dementia (90–103 years), loss of microstructural integrity within the cingulum was associated with chronological aging and global cognition (Bennett et al. 2017). These microstructural changes do not seem to occur homogeneously along the white matter tracks. An anterior-posterior gradient of FA decreases has been reported; the anterior portions of the dorsal cingulum being the most compromised portion of this bundle, particularly the left subgenual segment (Sibilia et al. 2017; Davis et al., 2009; Gunning et al. 2009). It is not clear whether white matter integrity losses are symmetrical or not. Comparisons with previously published results with samples with a similar age range showed similarity of most neuropsychological results.

Tract-tracing studies in non-human primates have demonstrated that the cingulum contains a very heterogeneous contingent of fibers, with at least three juxtaposed components with distinct cortical terminations (Mufson & Pandya, 1984). The first component emanates from in the anterior and lateral dorsal nucleus of the thalamus and occupies the ventral aspect of the bundle. Fibers from the anterior nuclei travel to the prefrontal, retrosplenial, and posterior cingulate cortices (monkey area 23), while those from the lateral dorsal nucleus terminate in the retrosplenial cortex, parahippocampal gyrus, and presubiculum. A second component originates from the cingulate cortex itself and has a dorsolateral position. It contains fibers from the anterior and ventral

cingulate cortex (area 24) that extend to the premotor cortex, area 23, and retrosplenial cortex, and fibers that leave area 23 to reach the prefrontal, parahippocampal gyrus, and presubiculum. Finally, a third component connects frontal and parietal associative areas. Fibers that originate in prefrontal areas travel to the retrosplenial cortex and those that originate with a posterior parietal topography extend to the prefrontal, parahippocampal, and presubicular cortices (Mufson & Pandya, 1984).

Inside the cingulate gyrus, fibers of different lengths make up the cingulum. The longest ones originate in the amygdala, uncus, and parahippocampal gyrus and travel to the subgenual area in the frontal lobe (Catani, et al., 2013; Husain & Schott, 2016; Nieuwenhuys, et al., 2008). On their way, they are joined by a large number of adjacent regional “U-shaped” association fibers interconnecting the temporal, occipital, parietal, and frontal lobes, and bringing them into relation with various parts of the cingulate gyrus (Bubb, et al., 2018; Catani & Thiebaut de Schotten, 2008).

A considerable amount of information on the functional aspects of the medial frontal cortex has been made available in the last years thanks to the multiplication in the number of studies in fMRI. In a recent term-based meta-analysis of 9721 publications, a division of the medial frontal cortex into three topographic zones was proposed (de la Vega, Chang, Banich, Wager, & Yarkoni, 2016). The activation peaks mostly reflected the functional anatomy described by previous authors. The anterior zone was significantly associated with episodic memory, social processes, decision making, reward and fear, the middle zone with aspects of cognitive control, decision making, fear and pain, and the posterior zone with motor aspects. In the middle zone itself, the anterior clusters were much more related to decision-making processes, those of the middle ventral cingulate cortex were related to affection (co-activating together with the amygdala and striatum), and the more dorsal ones were related to working memory (with greater co-activation of other regions associated to cognitive control). The posterior zone corresponded to regions previously known to be implicated on motor function in many studies, such as the SMA, the pre-SMA and the motor cingulate cortex. The SMA also showed association with pain processing, suggesting its involvement in the initiation of pain-induced movements, while the pre-SMA

was more related to cognitive control, co-activated with regions considered to be important for goal-driven cognitive processes (de la Vega, et al., 2016).

A recent discussion involved the significance of the cingulum for the connection of distant areas in the frontal and parietal lobes. In the Rhesus monkey, autoradiography studies in the 1980s indicated that dorsal frontoparietal interconnections were mainly ensured by the SLF-I component of the SLF/AF (Superior Longitudinal Fasciculus/Arcuate Fasciculus) complex, in the form of a long association bundle running parallel to the superior border of the cerebral hemisphere (Petrides & Pandya, 1984). Indeed, injected radioisotopes do migrate from the medial parietal cortex through the cingulum to reach distant regions of the frontal cortex (motor and premotor areas, areas 24 and 8) (Mufson & Pandya, 1984; Petrides & Pandya, 1984). In agreement with this, Schmahmann et al. (2007) depicted similar fibers extending to the medial (areas 8, 9, 14, 25, and 32) and dorsolateral (areas 8, 9, 11, and 46) aspects of the frontal and parietal (inferior parietal lobule and the retrosplenial cortex) lobes using diffusion spectrum imaging in non-human primates (Schmahmann, et al., 2007).

In humans, studies on this subject employing diffusion imaging or fiber dissection took place more than 20 years later than the initial descriptions with autoradiography (Jang & Hong, 2012; Kamali, Flanders, Brody, Hunter, & Hasan, 2014; Makris, et al., 2005; Yagmurlu, Middlebrooks, Tanriover, & Rhoton, 2016). Preferential anteroposterior diffusion was identified by means of diffusion imaging in a topography that was analogous to that of the monkey SLF-I (Makris, et al., 2005). However, fiber dissection studies did not isolate this bundle in a reproducible manner with less homogeneous results (Fernandez-Miranda, et al., 2008; I.L. Maldonado, E. Mandonnet, & H. Duffau, 2012; Pascalau, et al., 2018; Shah, et al., 2012; Wu, Sun, Wang, Wang, & Ou, 2016). A great number of regional connections were nonetheless described in that region and some controversy exists as they may be a confounding factor for diffusion imaging (I.L. Maldonado, et al., 2012). In this debate, the cingulum emerged as a potential additional source of long-distance pathways. Less affected by gyrification, it was estimated that this fasciculus may be the preferential route

of fibers directly connecting the dorsomedial cortex of the frontal and parietal lobes (I.L. Maldonado, et al., 2012; Wang, et al., 2016).

The presence of direct dorsal frontoparietal connections was suggested in the subgenual subdivision of the classification proposed by Jones et al. (2013) and in subcomponents III and IV in that proposed by Wu et al. (2016). Some authors have recently argued that fibers of the dorsal component of the superior longitudinal fasciculus (SLF-I) could actually be considered part of the cingulum (Wang, et al., 2016; Wu, et al., 2016). Once again, a debate arises - the very identity of the elements of the cerebral white matter is under discussion. Here, a discussion of nomenclature and the logic behind it is also pertinent, as detailed by Mandonnet et al. (2018). SLF-I was defined as the dorsal component of the SFL/AF complex, connecting areas of the cerebral cortex along the upper border of the cerebral hemisphere. The corona radiata physically separates this (laterally located) complex from the (more medial) cingulate fibers. This observation reinforces the importance of the detailed study of the arrangement of these association bundles in the coronal plane and the fact that cingulate fibers should not be labeled SLF-I (Mandonnet, Sarubbo, & Petit, 2018). Although they do indeed contribute to dorsal frontoparietal connectivity, they belong to a distinct anatomical structure.

#### 4- Conclusions

In the study of limbic connectivity through fiber dissection, diffusion tensor and examination of the available literature data, the importance of the cingulum for long distance (even extra-limbic) interconnections stands out. Nevertheless, a higher proportion of locoregional fibers in the subgenual and parahippocampal segments are observed in humans than in non-human primates. This difference is probably enhanced by the significant evolutionary increase in the volume of the frontal and occipital lobes.

A high level of agreement between the results of diffusion imaging and fiber dissection in humans is noticed. The white matter of the dorsal cingulum contains fibers responsible for direct interconnections between highly specialized frontal and parietal areas of the medial aspect of the cerebral hemisphere such as the superior frontal gyrus, supplementary motor area, and precuneus. These routes connect regions that

have been acknowledged to be highly involved in the initiation of motor activity, executive functions and the default mode network. Therefore, the study of its functional aspects must go beyond its participation in the limbic system and in the cortical processing of emotions.

In the left hemisphere, fractional anisotropy was associated to cognitive inhibition, and voxel count was associated with flexibility processes. In the right hemisphere, voxel count and volume were associated with nonverbal memory reproduction. The findings suggest the participation of transcingular direct frontoparietal pathways on executive functions and visuospatial memory.

Our understanding of the structure and function of the white matter bundles has evolved considerably over the last two decades. In addition to its classical participation in the limbic system, the cingulum has been identified as the anatomical substrate of a connective system for several areas involved in higher functions. These recent observations have had a direct influence on how we have and will interpret disconnection syndromes. As the cingulum is a multilayered tract, an important avenue for future research is to distinguish the functional roles of the different layers. More than simply a fiber bundle, it should be now perceived as the primary interconnecting apparatus of the medial aspects of the cerebral lobes.

## **5- Perspectives of future collaborations with the host laboratory**

The ex-fellow and the host researcher continue to work together on research projects, especially in the field of ex vivo imaging, fiber dissection, and cerebral vascularization. After his fellowship IL Maldonado was hired by the Tours University Hospital and remained working in the iBrain research unit, Inserm U1253. Fiber dissection and magnetic-resonance imaging continue to be among his most used methodological tools.

## **6- Scientific production in the framework of the fellowship**

### **6.1- Published article**

Maldonado IL, Parente de Matos V, Castro Cuesta TA, Herbet G, Destrieux C. The human cingulum: From the limbic tract to the connectionist paradigm. *Neuropsychologia*. 2020 Jul;144:107487.

### **6.2- Article in press**

Maldonado IL, Destrieux C, Ribas ESC, Guimarães BSAB, Cruz PP, Duffau H. Composition and organization of the sagittal stratum in the human brain: a fiber dissection study. *Journal of Neurosurgery*. *In Press*.

### **6.3- Submitted articles**

Cuesta TAC, Matos VP, Andersson F, Brachet M, Destrieux, Maldonado IL. Trans cingular dorsal frontoparietal connections: a study of diffusion imaging and neuropsychological testing in elderly. *Neuropsychology*. Under review.

Cuesta TAC, Matos VP, Destrieux C, Maldonado IL. Comparative connectivity in human and non-human primates. *Journal of Primatology*. Submitted.

### **6.4- Book chapters**

Maldonado IL, Zemmoura I, Destrieux C. Middle longitudinal fasciculus in the human brain from fiber dissection. In: Turgut M, Yurttas C, Tubbs RS, editors. *Island of Reil (insula) in the human brain : anatomical, functional, clinical and surgical aspects*. Cham: Springer; 2018. p. 71–5.

Maldonado IL, Zemmoura I, Destrieux C. Gross anatomy of the Human Insula. In: Turgut M, Yurttas C, Tubbs RS, editors. *Island of Reil (insula) in the human brain : anatomical, functional, clinical and surgical aspects*. Cham: Springer; 2018. p. 15–22.

Destrieux C, Maldonado IL, Terrier L-M, Zemmoura I. Surgical anatomy of the insula. In: Turgut M, Yurttas C, Tubbs RS, editors. *Island of Reil (insula) in the human brain : anatomical, functional, clinical and surgical aspects*. Cham: Springer; 2018. p. 23–37.

### **6.5- Conference abstracts**

Human Brain Mapping 2020

- HotRY, Popov A, Beaujoin J, Perez G, Poupon F, Maldonado IL, Mangin JF, Destrieux C and Poupon C. Ex vivo mapping of the cyto- and the myeloarchitecture of the human cerebral cortex using ultrahigh field MRI (7T and 11.7T).

- Smirnov M, Serres B, KERdilles G, Barantin L, Zhornyk V, Maldonado IL, Destrieux C. Towards an accurate identification of vascular territories in the human brain.

Maldonado, I. L.; Destrieux, C. Characterization of limbic system connectivity through fiber dissection and diffusion imaging techniques, *LE STUDIUM Multidisciplinary Journal*, 2019, 3, 64-88

<https://doi.org/10.34846/le-studium.170.02.fr.01-2019>

6-6- Lectures and workshops in international conferences

May 22-25, 2019. Surgery Follows Function. White Matter Dissection Course & Symposium. Graz, Austria.

- Cerebral Network System - Lateral Aspect
- Cerebral Network System - Medial Aspect
- White Matter Dissection Unit - Hands-On.

April 12-13, 2019. 6ème Journée de Neurochirurgie d'Oran, Oran, Algérie.

- *Anatomie intrinsèque de la substance blanche cérébrale*

January 30-31, 2019. World Federation of Neurosurgical Societies Anatomy Committee, Hands-On Cadaveric Course, Manipal, India.

- Intrinsic anatomy of the human brain
- Limbic lobe & related white matter tracts. Anatomy and surgery - 3D Lecture
- Medial Aspect white matter fiber tracts dissection

May 31- June 1, 2018 WMTours2018: Dissection and imaging of white matter tracts – Neurosurgical applications

Tours – France

- Autoradiography. Contributions to the understanding of white matter anatomy
- Step by step dissection of the arcuate fasciculus. Hands-On Workshop
- Step by step dissection of the ventral pathway. Hands-On Workshop.

September 21-23, 2018, The Cerebral White Matter – Functional Anatomy and Surgical Approaches, Cochabamba – Bolivia

- General organization of the hemispheric white matter.
- The cerebral white matter – Hands-On Cadaver Dissection.

### 6-7 Organization of a scientific meeting

5-7 December 2018. Frontiers in connectivity. Exploring and Dissecting the Cerebral White Matter

Lectures / workshops performed by the fellow:

- Tumor infiltration and white matter fibers
- General anatomy of the human cerebral white matter with fiber dissection
- Step-by-step dissection of the dorsal stream (Hands-on Workshop)
- Step-by-step dissection of the ventral stream (Hands-on Workshop)

Maldonado, I. L.; Destrieux, C. Characterization of limbic system connectivity through fiber dissection and diffusion imaging techniques, *LE STUDIUM Multidisciplinary Journal*, 2019, 3, 64-88

<https://doi.org/10.34846/le-studium.170.02.fr.01-2019>

- Step-by-step dissection of the optic radiations and tapetum (Hands-on Workshop)

- Morphology of the medial aspect of the cerebral hemisphere and limbic system

- Dissection of the medial aspect the cerebral hemisphere and limbic system (Hands-on Workshop)

### 6-8 Participation in educational website

Anthropotomia, e-manuel de dissection. Ed.: Destrieux C. Home page: <http://anthropotomia.univ-tours.fr/>; Central Nervous System page: <https://anthropotomia.univ-tours.fr/v2/en/central-nervous-system/>

### 6-9 Other publications during the period of residence

Lechanoine F, Janot K, Herbreteau D, Maldonado IL, Velut S. Surgical Thrombectomy Combined with Bilateral Decompressive Craniectomy in a Life-Threatening Case of Coma from Cerebral Venous Sinus Thrombosis: Case Report and Literature Review. *World Neurosurg.* 2018 Dec;120:485–9.

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