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**ABSTRACT**

Advances in our understanding of sensory-motor integration suggest a unique role of the frontal lobe circuits in cognition and behaviour. Long-range afferent connections convey higher order sensory information to the frontal cortex, which in turn responds to internal and external stimuli with flexible and adaptive behaviour. Long-range connections from and to frontal lobes have been described in detail in monkeys but little is known about short intralobar frontal connections mediating local connectivity in humans. Here we used spherical deconvolution diffusion tractography and post-mortem dissections to visualize the short frontal lobe connections of the human brain. We identified three intralobar tracts connecting: i) posterior Broca's region with supplementary motor area (SMA) and pre-supplementary motor area (pre-SMA) (i.e., the frontal 'aslant' tract – FAT); ii) posterior orbitofrontal cortex with anterior polar region (i.e., fronto-orbitopolar tract – FOP); iii) posterior pre-central cortex with anterior prefrontal cortex (i.e., the frontal superior longitudinal – FSL fasciculus system). In addition more complex systems of short U-shaped fibres were identified in the regions of the central, pre-central, perinsular and fronto-marginal sulcus (FMS). The connections between Broca and medial frontal areas (i.e. FAT) and those between the hand-knob motor region and post-central gyrus (PoCG) were found left lateralized in a group of twelve healthy right-handed subjects. The existence of these short frontal connections was confirmed using post-mortem blunt dissections. The functional role of these tracts in motor learning, verbal fluency, prospective behaviour, episodic and working memory is discussed. Our study provides a general model for the local connectivity of the frontal lobes that could be used as an anatomical framework for studies on lateralization and future clinical research in neurological and psychiatric disorders.

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## 1. Introduction

In the last two centuries the role attributed to the frontal lobes has progressively expanded from pure motor execution (Fritsch and Hitzig, 1870; Ferrier, 1875) to more complex functions such as attention and memory (Stuss et al., 1999; Fuster, 2009; Reilly et al., 2011), executive cognition (Fuster, 2009; Krause et al., 2012; Zappala' et al., 2012; Cubillo et al., 2012; Tsermentseli et al., 2012), social behaviour (Shamay-Tsoory et al., 2010; Sundram et al., 2012; Langen et al., 2012) and consciousness (Crick and Koch, 1990; Dehaene et al., 1998). This wide range of abilities relies on multiple networks of fibres composing the intricate anatomy of the frontal white matter (Yeterian et al., 2012; Thiebaut de Schotten et al., 2012). Through long-range projection and association fibres the frontal lobes receive sensory information from subcortical nuclei (e.g., thalamus) and sensory cortices (i.e., visual, auditory, somatosensory, gustatory and olfactory) and respond to environmental stimuli. These connections are also used to exert top-down control over sensory areas (Fuster, 2009). Shorter fibres that mediate the local connectivity of frontal lobes include U-shaped connections between adjacent gyri and longer intralobar fibres connecting distant areas within the same lobe (Yeterian et al., 2012). The anatomy and the functional correlates of these short frontal fibres are largely unknown in man. Therefore, our study aims at using tractography and post-mortem dissections to visualise these short connections of the human frontal lobes.

The short connections of the human brain were described in some detail by Theodor Meynert in the second half of the 19th Century. He attributed to the short U-shaped connections a central role in human cognition and correctly identified them as cortico-cortical short association connections of different lengths:

‘The cortex exhibits on the convexity of each convolution the shape of an inverted U, which is changed in the next adjoining fissure to an upright U (top and bottom of the cortical wave)... The depressed surface of a cortical wave can be easily dissected out as from a smooth medullary groove, which on closer inspection is seen to consist of U-shaped medullary fibres... The U-shaped bundles of the cortex do not necessarily extend simply from one convolution to the one next adjoining, but they may skip one, two, three, or an entire series of convolutions... The shortest *fibrae propriae* lie nearest to the cortex.’ (Meynert, 1885).

Meynert did not specify a pattern of distribution of these fibres and his anatomical observations led him to conclude that such U-shaped connections are ubiquitous in the brain. A decade later Heinrich Sachs produced a detailed atlas of the U-shaped fibres of the occipital lobe where he was able to identify and name prominent short connections organised in larger bundles visible on post-mortem dissections. Among these the U-shaped connections between the upper and lower banks of the calcarine sulcus (i.e., stratum calcarinum) and the dorsal to the ventrolateral occipital cortex (i.e., stratum profundum convexitatis) (Sachs, 1892). Unfortunately, Sachs limited his anatomical investigations to the occipital lobe leaving the mapping of the U-shaped connections of the entire human brain incomplete.

At the turn of the 19th Century, experimental studies in animals (Fritsch and Hitzig, 1870; Ferrier, 1875; Broca, 1861; Bianchi, 1895) and clinical observation in patients with aphasia (Broca, 1861) and epilepsy (Jackson, 1915) attracted the interest of anatomists to the frontal lobe (Catani and Stuss, 2012). In 1906 Cristofor Jakob described a system of longitudinal U-shaped fibres connecting adjacent frontal gyri (Jakob, 1906). He also described a ‘brachial center’ and a ‘facio-lingual center’ in the pre-central gyrus (PrCG) connected to parietal post-central cortex through direct U-shaped connections. It is unfortunate that Jakob’s work on the frontal U-shaped fibres was published in Spanish and had scarce diffusion in the English literature (Theodoridou and Triarhou, 2012).

An original approach to short fibre mapping was made by Rosett who produced an atlas of short connections of the human brain (Rosett, 1933). His method consisted in the immersion of a previously fixed brain in a gas-compressed tank containing liquid carbon dioxide (CO<sub>2</sub>). After quickly opening the valve of the tank the sudden reduction of pressure transforms the liquid CO<sub>2</sub> into a gas. The micro-explosions of the cerebral tissues cause a mechanical separation of the fibres along natural lines of cleavage. With this method Rosett described the main orientation of the short fibres of most the gyri and sulci of the human brain, but he was not able to visualize their entire course and terminal projections.

In more recent years the study of U-shaped connections continued in animals by means of axonal tracing studies. Yeterian et al. (2012) give a comprehensive account of the short frontal lobe connections in monkey. However, the significant differences between species in the anatomy and function of the frontal lobes suggest that probably translating tout court findings from axonal tracing to humans can be not as straightforward as previously thought (Thiebaut de Schotten et al., 2012).

Preliminary diffusion imaging tractography studies have reported U-shaped connections of the frontal lobes in the living human brain (Conturo et al., 1999; Oishi et al., 2008; Lawes et al., 2008; Guevara et al., 2011; Catani et al., 2002). These studies represent an important advancement in our understanding of human connectional anatomy but they need validation.

The present study aims at mapping the architecture of short frontal lobe tracts in the human brain by combining post-mortem blunt dissections (Klingler, 1935) and diffusion tractography based on spherical deconvolution (Dell’acqua et al., 2010; Thiebaut de Schotten et al., 2011a). This combined approach and in particular the use of spherical deconvolution models offers advantages that partially overcome the limitations of classical tractography (Catani, 2007; Thiebaut de Schotten et al., 2011b). The visualization of the tracts as Digital Dejerine maps (see methods section) facilitates the anatomical description of the short U-tracts.

## 2. Methods

### 2.1. MRI acquisition and preprocessing

Diffusion weighted MR data was acquired using a High Angular Resolution Diffusion Imaging (HARDI) acquisition optimized for

spherical deconvolution (Dell'Acqua et al., 2010; Tournier et al., 2004). A total of 70 near-axial slices were acquired from a 29-year-old, right-handed healthy subject on a Siemens Trio 3.0 T equipped with a 32-channel head coil. The acquisition sequence was fully optimized for advanced diffusion-weighted imaging, providing isotropic ( $2 \times 2 \times 2$  mm) resolution and coverage of the whole head. At each slice location, three images were acquired with no diffusion gradient applied, together with 64 diffusion-weighted images in which gradient directions were uniformly distributed in space. The acquisition was peripherally-gated to the cardiac cycle with an echo time (TE) = 85 msec and repetition time (TR) equivalent to 24 RR intervals. The diffusion weighting was equal to a *b*-value of 2000 s/mm<sup>2</sup>. To increase the signal to noise ratio (SNR) the whole acquisition was repeated four times. Raw diffusion-weighted data were up-sampled to  $1 \times 1 \times 1$  mm with a 3rd order *b*-spline interpolation. The four datasets were concatenated and simultaneously registered and corrected for subject motion and geometrical distortions using ExploreDTI (<http://www.exploredti.com>) (Leemans and Jones, 2009). An axial three-dimensional MPRAGE dataset covering the whole head was also acquired (176 slices,  $1 \times 1 \times 1$  mm isotropic resolution, TE = 4.2 msec, TR = 2.3 msec, flip angle = 9°).

In addition to the single dataset, diffusion MRI data were also acquired from 12 right handed, healthy and normal volunteers using a 3T GE Signa HDx TwinSpeed system (General Electric, Milwaukee, WI, USA). Diffusion weighted spin-echo single shot EPI images were acquired with the following parameters: voxel size  $2.4 \times 2.4 \times 2.4$  mm, matrix  $128 \times 128$ , FOV =  $307 \times 307$  mm, 60 slices, 1 NEX, TE 93.4 msec, *b*-value 3000 s/mm<sup>2</sup>, 60 diffusion-weighted directions and seven non-diffusion-weighted volumes, using a spin-echo EPI sequence with an ASSET factor of 2. Peripheral gating was applied with an effective TR of 20/30 R-R intervals. These datasets were acquired to analyze lateralization of tracts related to manual dexterity and language.

## 2.2. Data processing

The diffusion data was then processed using a spherical deconvolution approach based on the damped version of the Richardson Lucy algorithm as described in (Dell'acqua et al., 2010). The high SNR of the data allowed us to apply a relatively low regularisation threshold equal to  $\eta = .02$  without an excessive increase of spurious components in the fibre orientation distributions (FODs). The other parameters for the deconvolution algorithm were: i) a fibre response function equivalent to a tensor of  $[1.5 \ 0.3 \ 0.3] \times 10^{-3}$  mm<sup>2</sup>/s; 200 algorithm iterations and ii) a regularisation geometric parameter of  $v = 8$ . Fibre orientation estimates were obtained by selecting the orientation corresponding to the peaks (local maxima) of each FOD profile. To exclude spurious local maxima, we applied an absolute and a relative threshold. A first "absolute" threshold was used to exclude small local maxima due to noise or isotropic tissue. This threshold is three times the amplitude of a spherical FOD obtained from a grey matter isotropic voxel. A second "relative" threshold of 5% of the maximum amplitude of the FOD was applied to remove the remaining local maxima with values greater than the absolute threshold (Dell'Acqua et al., 2009).

Whole brain tractography was performed selecting every brain voxel with at least one fibre orientation as a seed voxel.

From these voxels and for each fibre orientation streamlines were propagated using an Euler integration with a step size of .5 mm and an angular threshold of 45°. When entering a region with crossing white matter bundles, the algorithm follows the orientation vector of least curvature as described in Schmahmann et al. (2007). Streamlines were halted when a voxel without fibre orientation was reached or when the curvature between two steps exceeded a threshold of 45°.

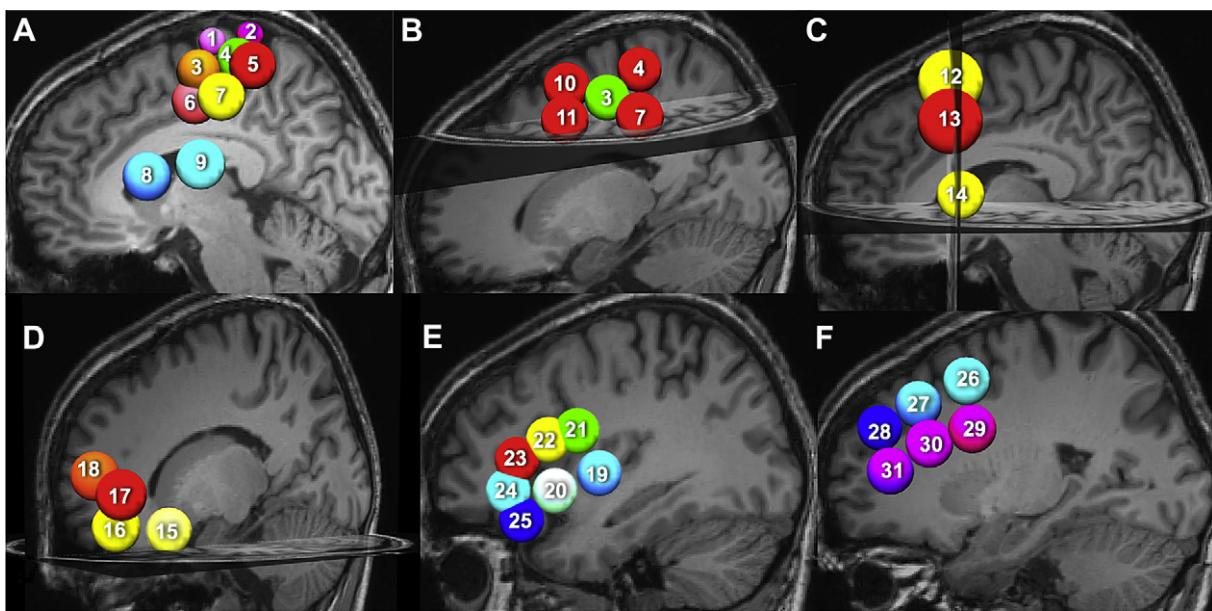
Digital Dejerine Maps were obtained by constraining tractography in non-contiguous brain slices of 2 mm (Axial, Sagittal, Coronal). Tractography was started from 10 seed points randomly placed inside each brain voxel and for each fibre orientation. Streamlines were propagated as in the whole brain tractography following fibre orientations using Euler integration with a step size of .5 mm and an angular threshold of 45°. Tractography propagation was arbitrary stopped after 40 mm. This enhances visualization of the white matter bundles that propagate along the plane of the slice selected. Bundles that are oriented perpendicularly to the surface of the slice are visualized only as dots or very short streamlines. Tractography maps were finally visualized using a lookup table empirically tuned to simulate historical black-and-white anatomical drawings. All data processing was performed using in-house software developed with MATLAB (The MathWorks, Inc., Natick, MA). Visualization was performed using TrackVis ([www.trackvis.org](http://www.trackvis.org)).

## 2.3. Tractography dissections

Virtual dissections were performed in TrackVis using two-ROIs to isolate single tracts (Catani and Thiebaut de Schotten, 2008). Virtual dissections were systematically performed for each sulcus and frontal gyrus following a posterior to anterior order (e.g., central sulcus, pre-central sulcus, etc.). Spheres were used to isolate single tracts as shown in Fig. 1. All tracts presented were dissected on both hemispheres. A lateralization index of the volume of the fronto-parietal U-shaped tracts and premotor connections was calculated using the following formula: (Right Volume – Left Volume)/(Right Volume + Left Volume). Negative values indicate a left lateralization. Two-tails, unpaired samples, t-test was used to assess statistical significance of lateralization indices.

## 2.4. Post-mortem dissections

Post-mortem dissection of white matter fibres was performed according to the technique originally described by Klingler (1935). One right hemisphere was obtained from the autopsy of an 80-year-old healthy woman. The specimen was fixed in 10% formalin solution for at least three months. After removal of the pia-arachnoid membrane and cortical vessels, the hemisphere was frozen at -15 °C for 15 days. The water crystallization induced by the freezing process disrupts the structure of the grey matter (which has a high water content), thus making it easier to peel off the cortex from the brain surface. The freezing process also separates the white matter fibres, thus facilitating their dissection. The specimen was washed under running water for several hours before performing the dissection (Martino et al., 2010).



**Fig. 1 – Placement of the regions of interest (spheres) used to dissect the frontal tracts.** Note that the spheres' colours correspond to those of the tracts shown in Figs. 3–8. A) Regions of interest for the paracentral U-tracts (1 and 2), hand superior (3 and 4), middle (3 and 7) and inferior (5 and 6) U-tracts, and face/mouth U-tracts (8–9). B) Regions of interest for the U-tracts connecting the hand-knob motor region with the postcentral gyrus (3 and 4 for the hand superior and 3 and 7 for the hand middle) and superior (3 and 10) and middle frontal gyri (3 and 11). C) Regions of interest for the frontal aslant tract (FAT) (12 and 14) and the U-shaped tracts connecting the superior and middle frontal gyri (12 and 13) and the inferior and middle frontal gyri (13 and 14). D) Regions of interest for the fronto-orbitopolar (FOP) (15 and 16) and fronto-marginal tracts (FMT) (17 and 18). E) Regions of interest for the fronto-insular tracts (FIT) connecting the posterior insula with the subcentral gyrus (19 and 21) and the anterior insula with the pre-central (20 and 22), pars opercularis (20 and 23), pars triangularis (20 and 24) and pars orbitalis (20 and 25) of the IFG. F) Regions of interest for frontal longitudinal system (FLS) composed of the frontal superior longitudinal (FSL) (26, 27 and 28) and frontal inferior longitudinal (FIL) (29, 30 and 31) tracts.

The superficial anatomy of the brain was studied in detail, with identification of the sulci and gyri. The dissection was then started, with removal of the cortex and exposure of the underlying U-fibres (also known as intergyral or arcuate fibres). The white matter dissection was then completed in a stepwise manner, from lateral to medial. Wooden spatulas were used in the initial step of the dissection, to peel away the brain cortex. Once the U-fibres were identified, the dissection was performed using blunt metallic dissectors with different tip sizes. Care was taken to separate the fibres using the blunt edge of the instrument, thus avoiding the generation of spurious tracts. Metal pins were used to indicate anatomical landmarks and digital pictures were taken during the dissection.

### 3. Results

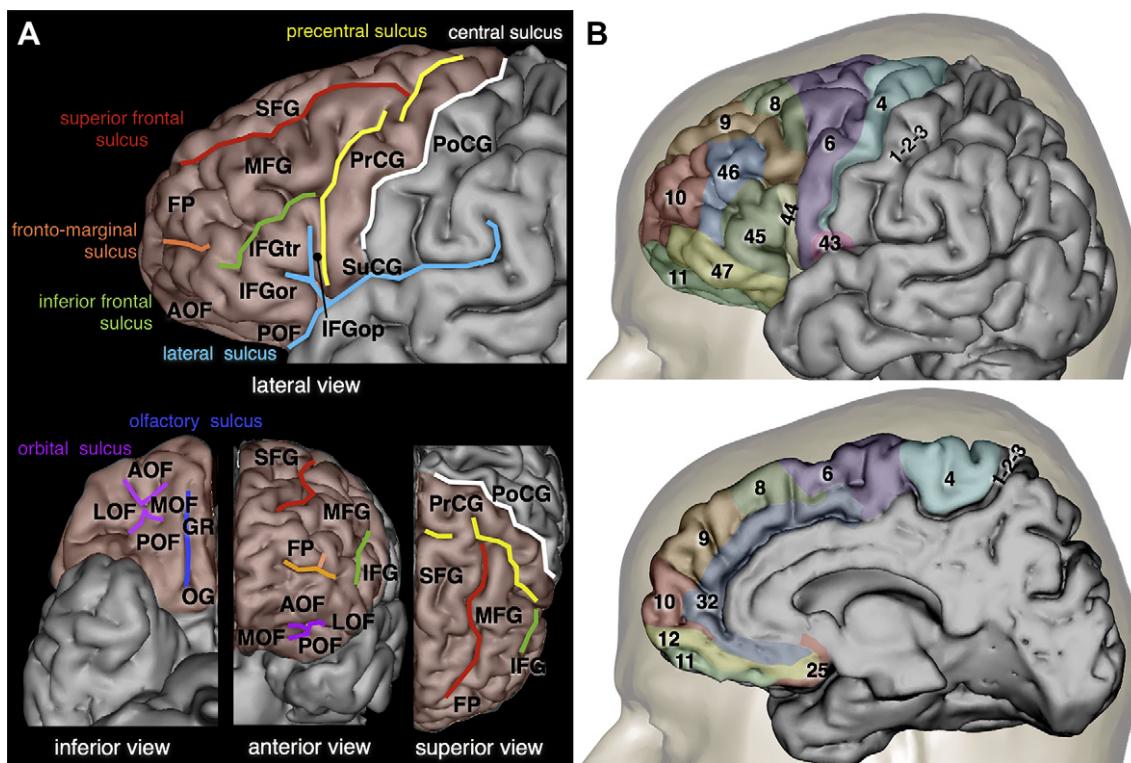
The 3D reconstruction of the frontal lobe surface and corresponding cytoarchitectonic areas according to Brodmann's division (Brodmann, 1909) are shown in Fig. 2. The surface landmarks (i.e., sulci and gyri) and cytoarchitectonic areas (Ono et al., 1990; Catani et al., *in press*) are used to describe the anatomy of the dissected tracts and their projections. Tractography reconstructions of the short frontal lobe tracts are presented in Figs. 3–9, whereas Digital Dejerine maps and post-mortem dissections are shown in Figs. 10–12. A diagram

that summarises the local connectivity and some of the long-range connections of the frontal lobe is presented in Fig. 13.

#### 3.1. Fronto-parietal U-tracts (FPUTs) (central sulcus connections)

A chain of U-shaped connections between the frontal PrCG and the parietal PoCG was identified (Fig. 3). These tracts can be divided into three groups:

- i) The paracentral lobule tract has its convexity oriented medially towards the interhemispheric midline and connects the frontal and parietal portions of the paracentral lobule. This tract connects pre- and post-central regions corresponding to the 'foot' area of the motor-sensory homunculus (purple tract in Fig. 3).
- ii) The hand-knob region contains connections composed of three separate tracts with different orientation; a superior tight U-shaped tract with an anterior-posterior course (green tract in Fig. 3), a ventral tract with an oblique anterior–posterior course (red tract in Fig. 3) and a transverse middle U-shaped tract with a dorsal to ventral course and an upwards concavity (yellow tract in Fig. 3). These three tracts connect pre- and post-central regions corresponding to the hand area of the motor-sensory homunculus.



**Fig. 2 – A)** Surface anatomy and **B)** cytoarchitectonic areas (according to Brodmann, 1909) of the frontal lobe. AOF, anterior orbitofrontal gyrus; GR, gyrus rectus; IFGop, inferior frontal gyrus pars opercularis; IFGor, inferior frontal gyrus pars orbitalis; IFGtr, inferior frontal gyrus pars triangularis; LOF, lateral orbitofrontal gyrus; MOF, medial orbitofrontal gyrus; OG, olfactory gyrus; POF, posterior orbitofrontal gyrus; SFG, superior frontal gyrus; SuCG, subcentral gyrus.

iii) The ventral group of connections is composed of two or more tracts characterised by a more oblique and elongated course compared to the other dorsal tracts of the foot and hand region. These tracts connect pre- and post-central regions corresponding to the face, mouth and tongue area of the motor-sensory homunculus (light and dark blue tracts in Fig. 3).

To investigate the overall local connectivity of the hand-knob region dissections of the U-shaped tracts between pre-central and premotor regions were performed (Fig. 4). A group of four U-shaped tracts connects the hand-knob region to post-central sensory cortex and premotor cortex of the superior and middle frontal gyri. These tracts are circularly arranged around the long projection fibres (green tracts in Fig. 4) of the hand region like the 'petals' of a poppy flower. The concavity of the posterior and inferior 'petals' corresponds to the bed of the central sulcus in the hand region. These two tracts correspond to the superior and middle fronto-parietal connections of the hand-knob region described in the previous section (i.e., hand superior and middle U-tracts). Another two U-tracts connect the PrCG to more anterior premotor cortex. Of these two anterior tracts the superior 'petal' that connects PrCG to the superior frontal gyrus (SFG) passes beneath the junction between the posterior branch of the superior frontal sulcus and the pre-central sulcus (frontal eyefield region). The anterior 'petal' connects the PrCG to the middle frontal gyrus (MFG). The long

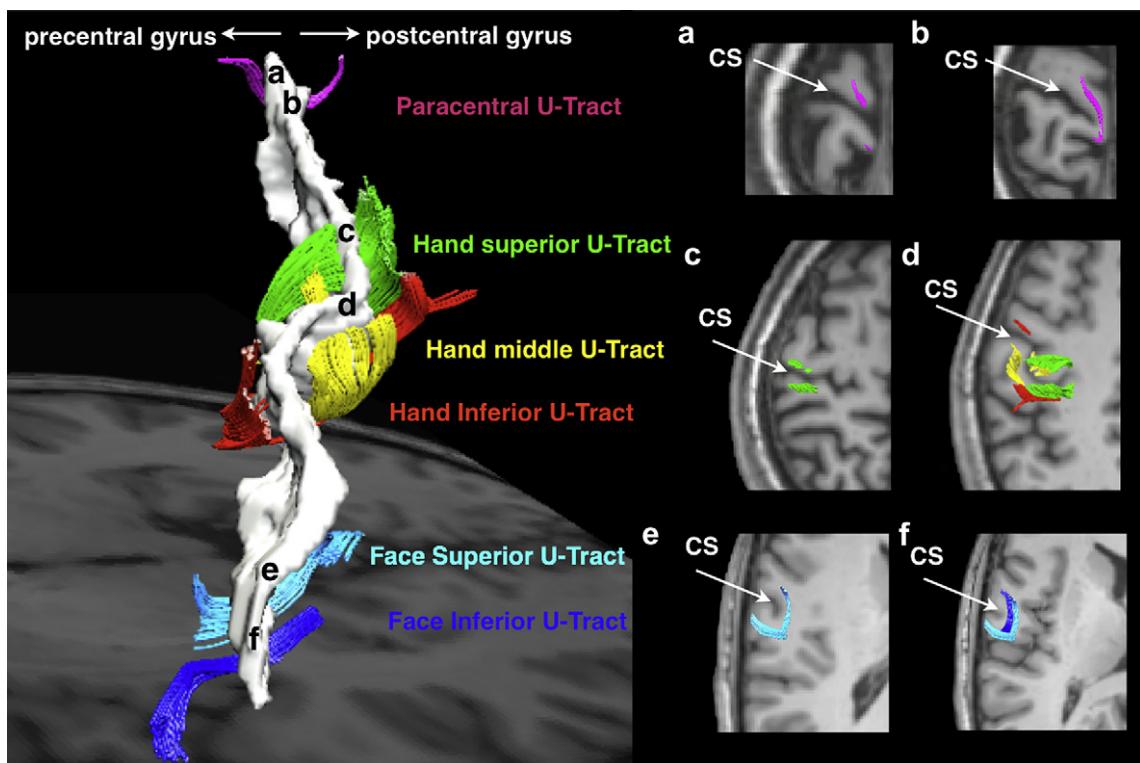
connections of the hand-knob region are surrounded by the short U-tracts and are composed of ascending thalamic projections and descending cortico-striatal (putamen), cortico-pontine and cortico-spinal tracts.

### 3.2. Frontal aslant tract (FAT) and premotor connections

The posterior region of the superior and inferior frontal gyri is interconnected by a direct system of fibres forming the 'frontal aslant tract' (yellow tract in Fig. 5). This tract projects to the anterior supplementary and pre-supplementary motor area (pre-SMA) of the SFG and the pars opercularis of the inferior frontal gyrus (IFG). Some projections reach also the pars triangularis of the IFG and the inferior region of the PrCG. These two regions are also interconnected through U-shaped fibres running superficially to the FAT and projecting to the posterior portion of the MFG (red tracts in Fig. 5). Finally these three cortical regions of the superior, middle and inferior frontal gyri are directly connected to the striatum (caudate and putamen) through a system of radial projection fibres (blue tracts in Fig. 5).

### 3.3. Fronto-orbitopolar (FOP) and fronto-marginal connections

Two prominent intralobar tracts project to the frontal pole (FP) (Fig. 6). The FOP runs on the ventral aspect of the frontal lobe and connects the posterior orbital gyrus to the anterior orbital



**Fig. 3 – Left, lateral view of the short fronto-parietal U-tracts (FPUT) connecting pre-central and post-central gyri. The white region corresponds to the central sulcus (CS). Letters a-f indicate the level of the axial slices on the right panel.**

gyrus and ventromedial region of the FP (yellow tract in Fig. 6). The fronto-marginal tract (FMT) runs beneath the fronto-marginal sulcus (FMS) and connects medial and lateral regions of the frontopolar cortex (red tract in Fig. 6). The cortical regions connected by these short intralobar tracts receive afferent connections through the uncinate and inferior fronto-occipital fasciculi, anterior thalamic projections and send efferent connections to the striatum through the fronto-striatal tracts.

#### 3.4. Fronto-insular tracts (FIT)

A system of U-shaped fibres organised around the peri-insular sulcus connects the inferior frontal and PrCG to the insula of Reil (Fig. 7). The most posterior tracts connect the subcentral lobule to the post-central long insular gyrus (green tract in Fig. 7). Anterior to this tract is a group of four U-tracts connecting the PrCG (yellow tract) and the pars opercularis (red tract), pars triangularis (light blue tract) and pars orbitalis (dark blue tract) of the IFG to the insular gyri anterior to the central sulcus of the insula. The fronto-insular fibres have their concavity always towards the insula.

#### 3.5. Frontal longitudinal system (FLS)

A chain of U-shaped connections that resemble a prolongation of the superior longitudinal fasciculus connects the dorsolateral cortex of the premotor and prefrontal cortex (Fig. 8). Tracts of different length compose this parallel system. Some of these tracts are short and connect adjacent

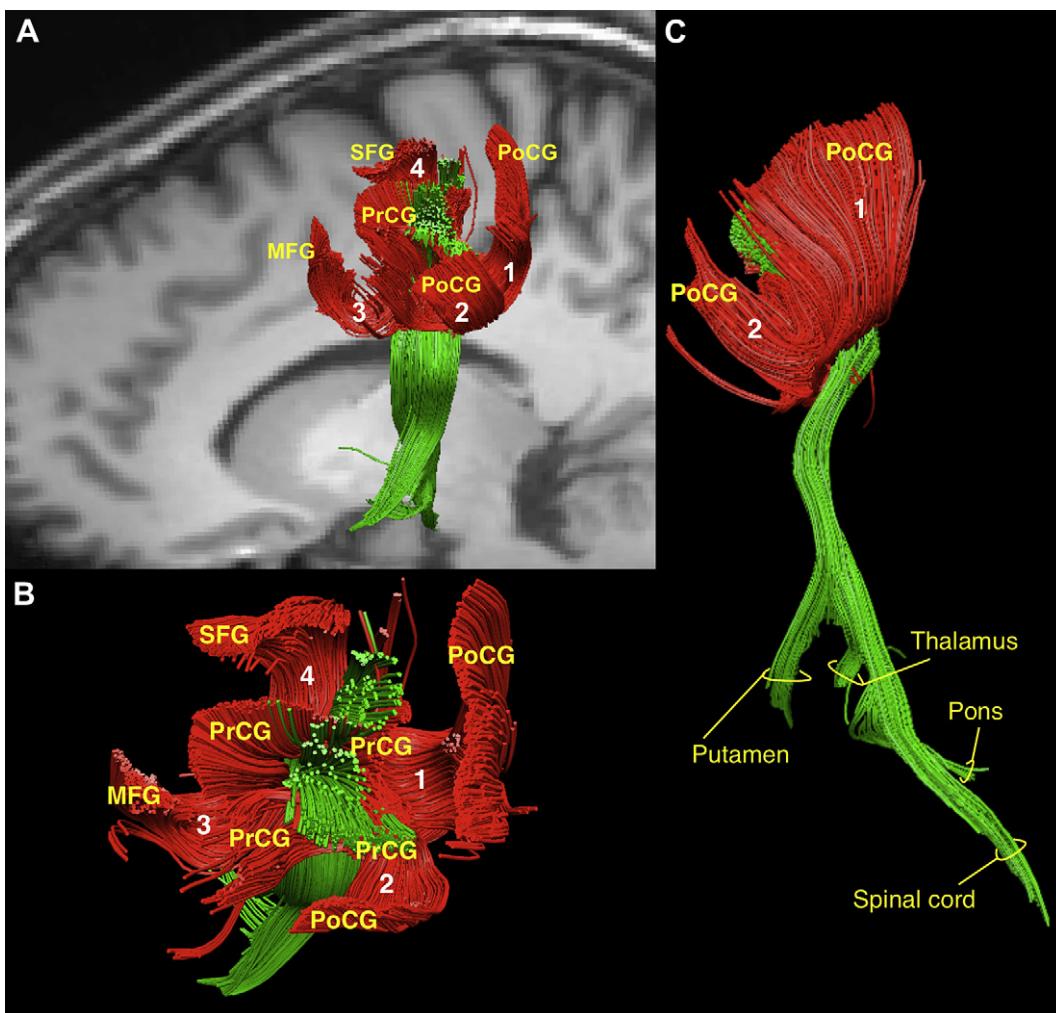
gyri, others connect more distant regions. The majority of these tracts has a longitudinal course and are organised along a direction parallel to the superior and inferior frontal sulci. The superior chain (i.e., frontal superior longitudinal – FSL) connects the PrCG to the ventral part of the SFG and dorsal part of the MFG (light blue tracts in Fig. 8). The inferior chain (i.e., frontal inferior longitudinal – FIL) projects from the PrCG to the ventral part of the MFG and superior part of the IFG (purple tracts in Fig. 8). These two systems converge anteriorly to the same regions of the FP and along their course are interconnected by transversal U-shaped tracts.

#### 3.6. Analysis of the volume asymmetry of the fronto-parietal and premotor connections

A significant leftwards asymmetry was found for the lateralization index of the fronto-parietal U-shaped tracts of the hand region ( $t = -2.932, p = .014$ ) and the FAT ( $t = -3.672, p = .004$ ) (Fig. 9). There were no statistically significant differences in the lateralization pattern of the dorsal ( $t = -1.017, p = .331$ ) and ventral ( $t = -.790, p = .446$ ) fronto-parietal U-shaped tracts and in the connections between superior and middle frontal gyri ( $t = 1.331, p = .213$ ) and middle and inferior frontal gyri ( $t = -1.620, p = .136$ ).

## 4. Discussion

Using a novel tractography approach based on spherical deconvolution and post-mortem blunt dissections, short

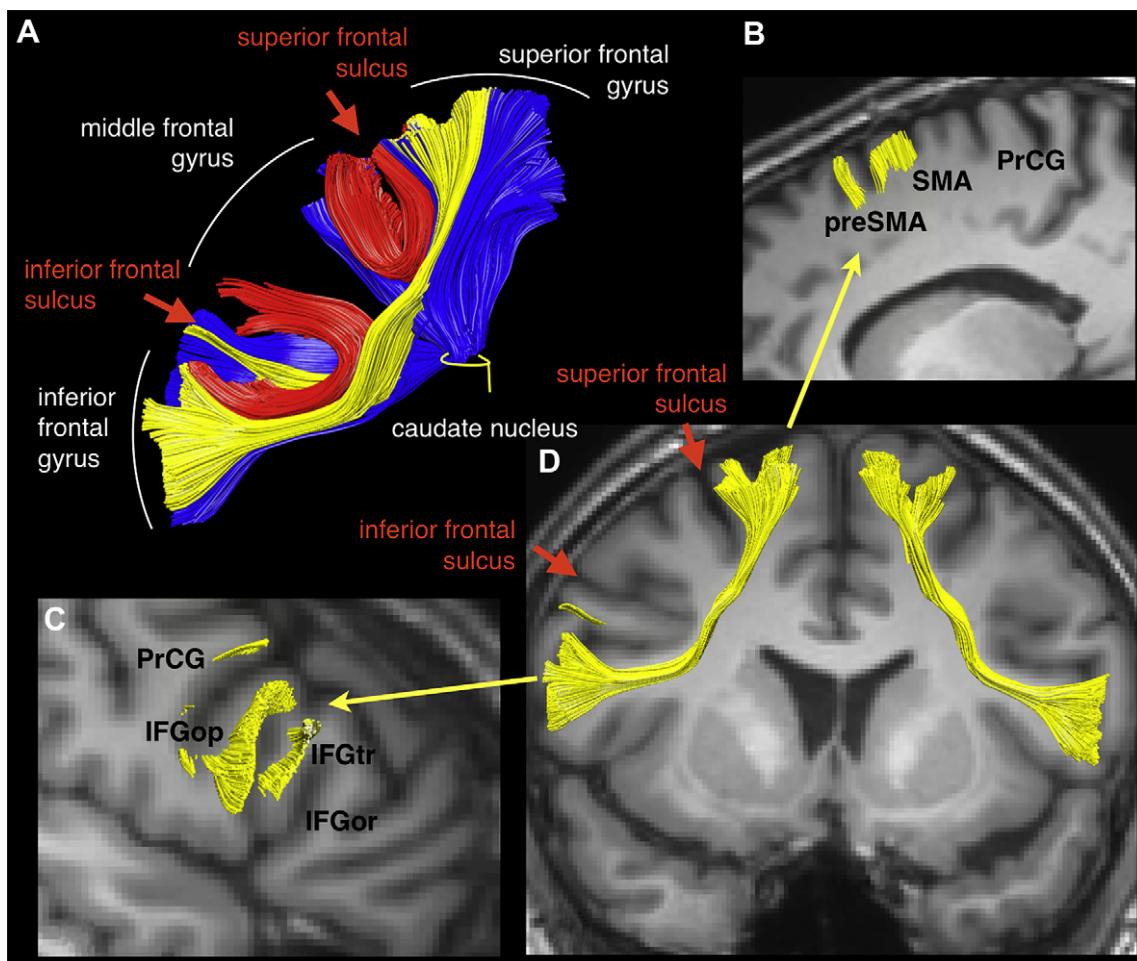


**Fig. 4 – Reconstruction of the short U-shaped (red) and long projection (green) tracts of the hand-knob motor region in the left hemisphere. A) Left lateral view; B) top view C) posterior view.** The connections of the hand region resemble a ‘poppy flower’ with a green stem and four red ‘petals’ (1, posterior; 2, inferior; 3, anterior; 4, superior). The posterior (1) and inferior (2) petals correspond to the fronto-parietal U-tracts (FPUT) between pre-central (PrCG) and post-central (PoCG) gyrus shown in Fig. 3 (i.e. hand superior and hand middle, respectively). The anterior (3) and superior (4) petals correspond to the U-shaped connections between the precentral gyrus (PrCG) and the middle frontal gyrus (MFG) and the MFG and superior frontal (SFG) gyrus, respectively. The ‘green stem’ is formed by ascending thalamo-cortical projection fibres and descending projections to the putamen (cortico-striatal), pons (cortico-pontine) and spinal cord (cortico-spinal tract).

frontal lobe connections of the human brain were identified. Spherical deconvolution has recently been developed to partially overcome the limitations of classical diffusion tensor imaging (Tournier et al., 2004; Dell'Acqua et al., 2007; Dell'acqua et al., 2010). This method has the ability to identify and quantify the orientation of different populations of fibres within a single voxel (Dell'acqua et al., 2010; Tournier et al., 2007). Hence, one of the advantages of tractography based on spherical deconvolution is the possibility of resolving fibre crossing and reducing false negative reconstructions of white matter pathways. This can facilitate the visualization of those connections that are not visible with diffusion tensor tractography (Thiebaut de Schotten et al., 2011a, b).

A preliminary indirect comparison with previous axonal tracing studies in the monkey brain (Schmahmann and Pandya, 2006) and post-mortem human investigations (Lawes

et al., 2008), including our own dissections, suggests that the majority of the short frontal fibres can be easily identified in the living human brain using tractography algorithms applied to acquisitions optimized for spherical deconvolution (Dell'acqua et al., 2010). Some of the large intralobar tracts and the short U-shaped fibres described in our study have also been reported using classical diffusion tensor tractography with both manual and automatic clustering methods (Lawes et al., 2008; Oishi et al., 2008; Guevara et al., 2011). A general feature of the U-shaped tracts is their distribution along the walls and floors of the major sulci of the frontal lobes. For this reason we have used a nomenclature based on the names of the sulci these fibres belong to (e.g., fronto-marginal tract). For other tracts interconnecting distant gyri or projecting to neighbouring lobes (i.e., insula, parietal) the regions of termination of the U-shaped tracts were used instead (e.g., fronto-insular tracts –



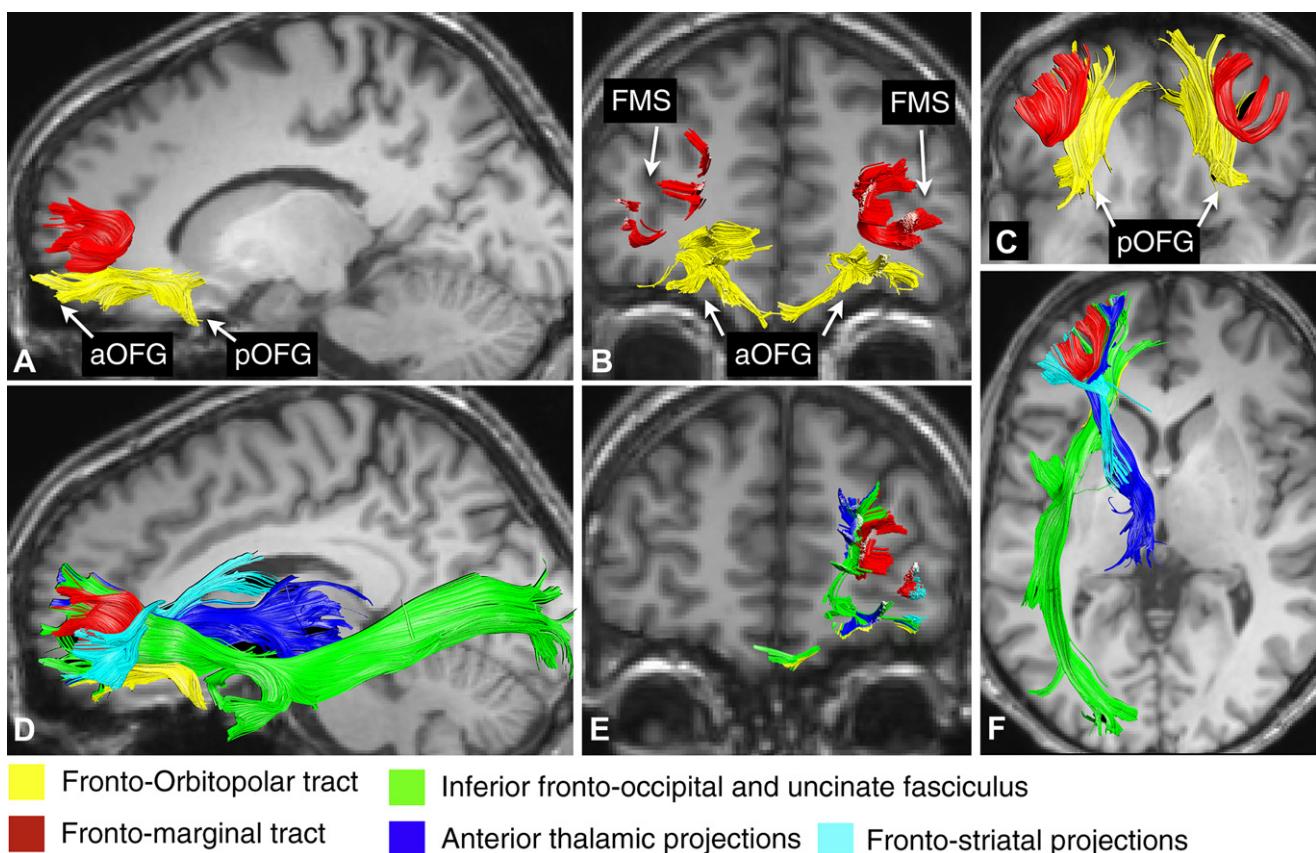
**Fig. 5 – A)** Connections of the premotor regions of the frontal lobe. The frontal aslant tract (FAT) (yellow) connects the **B)** dorsal and medial (supplementary and pre-supplementary motor area, SMA and pre-SMA) cortex of the SFG with the **C)** posterior region of IFG. Red U-shaped tracts connect the superior and middle frontal gyri and the inferior and middle frontal gyri. Blue projection fibres connect the cortical premotor regions with the head of the caudate nucleus. **D)** The frontal aslant is a bilateral tract (for the lateralization analysis see Fig. 9).

FITs). The only exception is the frontal 'aslant' tract that will be discussed below.

Overall the pattern of distribution of these tracts is not homogeneous but rather discontinuous along the course of each sulcus with some regions showing a higher number of interconnecting U-shaped tracts. This observation requires careful interpretation. Current diffusion methods are limited by the dimensions of the voxels and are therefore likely to underestimate the presence of smaller fibres. Hence, the 'absence' of direct U-shaped connections between adjacent gyri (e.g., pre-central and post-central connections are missing in a region between the dorsal paracentral lobule and the hand region as shown in Fig. 3) in the tractography reconstruction should not be interpreted as a complete anatomical absence of axonal fibres. Tractography provides only an indirect indication of the real spatial extension of the tract (i.e., 'volume') and the true anatomical connectivity between regions. Thus while we feel confident to conclude that, in relation to the number of streamlines or the space occupied by these trajectories, some regions are more likely to be interconnected compared to others, we avoid interpreting

the lack of streamlines as indicative of a complete absence of connections.

The exact functional role of the short U-shaped tracts remains to be explained. Overall our study suggests that the distribution of the U-shaped fibres follows a functional division rather than a purely anatomical pattern. The three tracts of the central sulcus, for example, whose distribution and relative volume have a precise correspondence with the homunculus regions (Penfield, 1937), are probably in relation to the importance of sensory information for motor control of skilful movements of the hand, mouth/tongue and foot (Catani and Stuss, 2012). Our post-mortem dissections also suggest that the location of the U-shaped connections has a direct correspondence with some anatomical features of the surface anatomy of the gyri. The orientation and density of the U-shaped of the central sulcus, for example, have a precise correspondence with the presence of protuberances from the wall (i.e., 'buttresses') or the floor (i.e., 'annectant convolutions') of the central sulcus (Fig. 10) (Rosett, 1933). This correspondence could have practical implications for neuroradiologists, for example, or neurosurgeons intending to use surface landmarks



**Fig. 6 – Intralobar and long frontal tracts of the frontal pole shown on sagittal (A and D) coronal (B and E) and axial (C and F) slices. The fronto-orbitopolar (FOP) tract (yellow) connects posterior (pOFG) and anterior (aOFG) orbitofrontal gyri and inferior polar cortex. The fronto-marginal tract (FMT) (red) connects medial and lateral regions of the frontal pole. The frontal pole communicates with posterior cerebral regions and subcortical nuclei through long association and projection fibres visualized in D–F together with the FOP and FMT.**

to identify the underlying U-shaped fibres on conventional radiological images or during surgery.

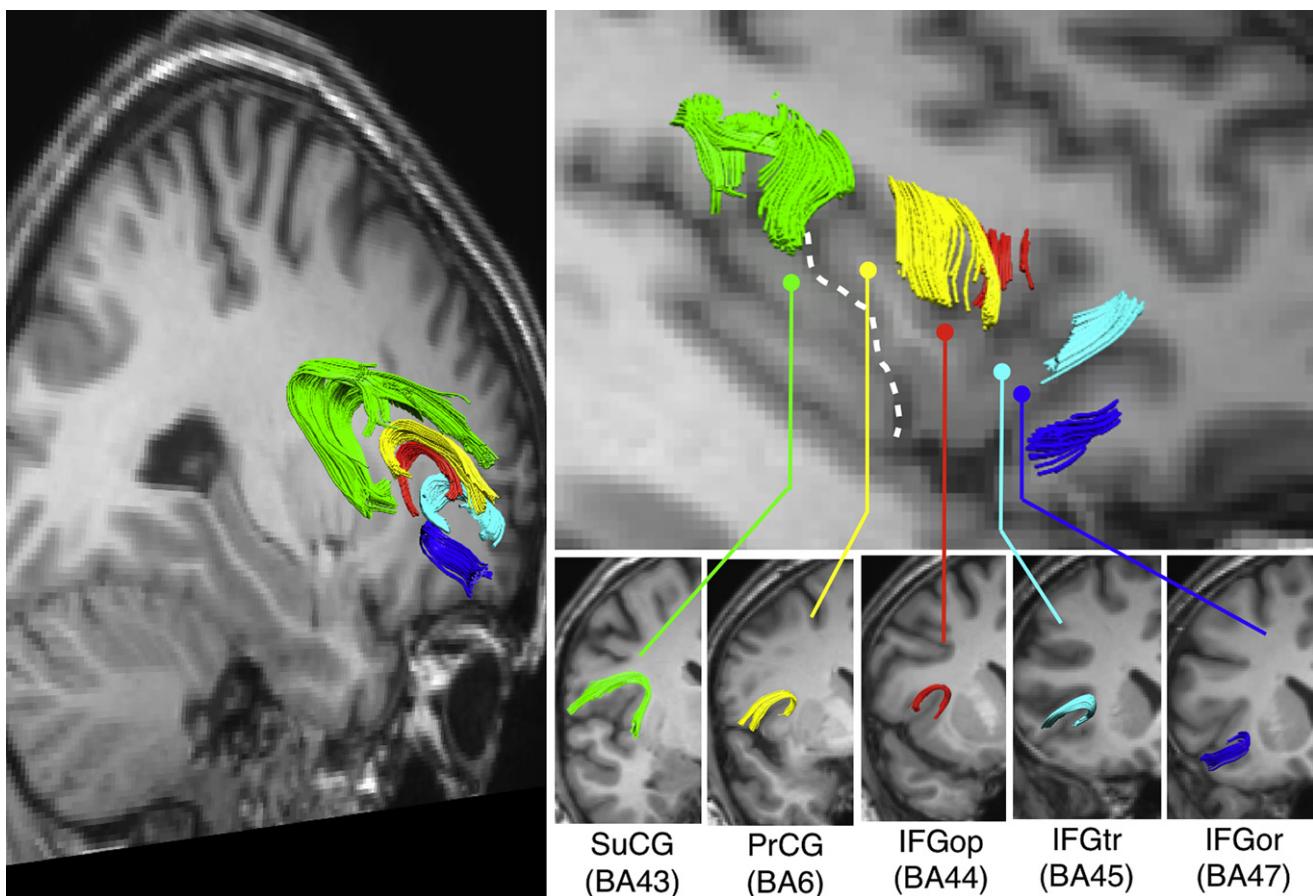
#### 4.1. FPUTs of the central sulcus

Direct connections between post-central sensory and pre-central motor cortex have been previously described in mice (Ferezou et al., 2007), cats (Sakamoto et al., 1987; Sakamoto et al., 1989) and monkeys (Pavlides et al., 1993; Schmahmann and Pandya, 2006). Similar connections have been visualized in the human brain using post-mortem dissections (Rosett, 1933) and diffusion imaging tractography (Conturo et al., 1999; Shinoura et al., 2005; Guevara et al., 2011). It is surprising that direct connections between primary sensory and motor cortices are not considered to play a significant role in current models of sensory-motor integration, for example, in relation to grasping (Grafton, 2010; Davare et al., 2011).

The primary motor cortex receives direct modulatory somatosensory inputs from the thalamus during execution of movements. This input is relayed directly from the ventrolateral thalamic nucleus to the primary motor cortex through the ascending thalamic projections (Fig. 11) (Iriki et al., 1991). Hikosaka et al., 1985 have, however, demonstrated in the monkey that pharmacological inactivation of neurons in the

primary somatosensory area (S1) causes deficits in precision grasping. This suggests that the motor cortex can receive somatosensory thalamic inputs through an alternative pathway relaying in the primary somatosensory cortex. We suggest that the fronto-parietal U-shaped fibres represent the final connections of this alternative indirect somatosensory-motor pathway.

There is some evidence that the direct and indirect somatosensory-motor pathways may have different functional roles. Electrophysiological investigations of the effects of the inputs from S1 to the motor cortex suggest that direct local U-shaped connections from PoCG may play a role in motor learning by facilitating long-term potentiation (LTP) in motor neurons of the primary motor area (M1) (Sakamoto et al., 1987; Iriki et al., 1991). Sakamoto et al., 1987 applied titanic stimulation to areas of the sensory cortex in monkeys and recorded from the corresponding sites in the primary motor cortex, where they found an increased synaptic excitability for periods of up to 90 min after the stimulation. Iriki et al., 1991 were unable to induce LTP in the motor cortex by applying titanic stimulation to the ventrolateral nucleus of the thalamus, which projects directly to motor cortex. From both these experiments we can conclude that sensory connections relayed through S1 (an indirect thalamo-somatosensory-motor route) induce LTP in the motor cortex that helps to consolidate



**Fig. 7 – The fronto-insular system.** This series of U-shaped tracts connect various regions of the frontal operculum with the insular cortex. The insula is divided into anterior and posterior part by the central sulcus of the insula which is indicated by the dash white line. All connections are with the anterior insula except for the connections from the sub-central gyrus (SuCG), which project to the posterior insula. IFGop – pars opercularis; IFGtr, inferior frontal gyrus – pars triangularis; IFGor, inferior frontal gyrus – pars orbitalis.

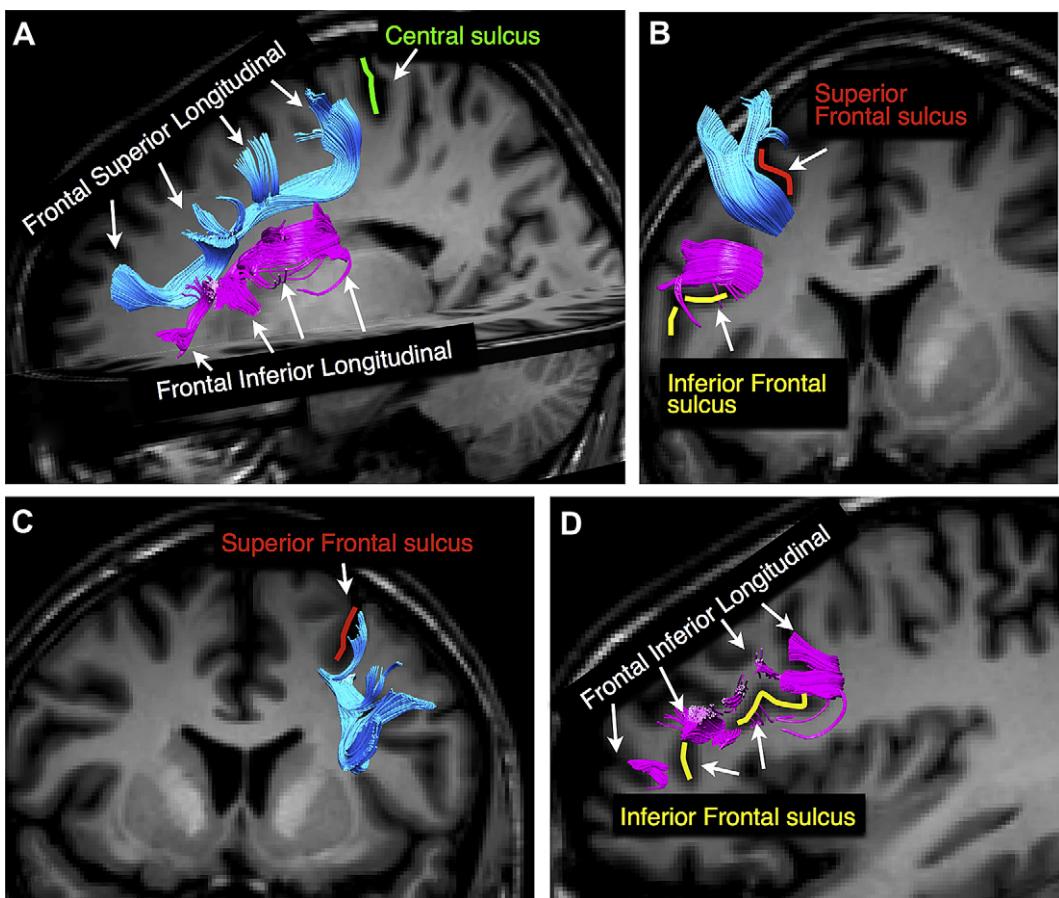
motor schemas and novel movement combinations. Pavlides et al., 1993 have provided further evidence for this hypothesis demonstrating that monkeys with ablated somatosensory cortex were unable to learn new motor skills, but were able to perform skills that had been learnt prior to surgery.

The pre-central and post-central U-shaped fibres are unlikely to convey other type of sensory information (e.g., visual) necessary for motor learning. Indeed, pharmacological inactivation of S1 neurons causes deficits in precision grasping but not in visually guided reaching or hand shaping (Hikosaka et al., 1985). The visual information is processed in the parietal regions posterior to S1 and is conveyed to more anterior frontal regions through the long association fibres of the superior longitudinal fasciculus system (Fig. 11) (Thiebaut de Schotten et al., 2011a, 2012). In the frontal lobe the visual information is used to elaborate complex body movements in the dorsal and ventral premotor regions located in the superior and middle frontal gyri. Our dissections show that the hand region in the PrCG receives direct U-shaped connections from these dorsal and ventral premotor areas. We speculate that the connections from the SFG are part of the ‘reaching’ network and the connections from the MFG belong to the ‘grasping’ circuit (Grafton, 2010; Davare et al., 2011). These U-shaped

connections are likely to carry visual information necessary to coordinate fine-tuning of finger movements with more complex reaching and grasping.

Our dissections also suggest a concentric organisation of the connections of the hand region, where the short association U-fibres are more peripherally distributed and surround the long projection fibres originating from the central core of the white matter of the PrCG. This is in keeping with the observation in the monkey brain of a central ‘cord’ composed of projection fibres surrounded by association fibres (Schmahmann and Pandya, 2006). Thus, it appears that the hand region is a central hub of the sensory-motor system where tactile and visual inputs converge for the online control of a complex cortico-cortical and cortico-subcortical network involving the fronto-parietal cortex, basal ganglia, thalamus, brain stem, cerebellum and spinal cord.

This system adapts dynamically to the task and reorganises with training and after injury. fMRI studies of musicians, for example, show that amateur players recruit a greater area of fronto-parietal cortex compared to professional players (Lotze et al., 2003; Karni et al., 1995). A combined fMRI and DTI study in a patient with a metastatic tumour in the primary motor cortex showed that recovery of motor



**Fig. 8 –** The frontal longitudinal system (FLS) is composed of a frontal superior longitudinal (FSL) (cyan) and a frontal inferior longitudinal (FIL) (purple) tract. These tracts are composed of short and long connections running along the superior and inferior frontal sulci and projecting mainly to the middle frontal gyrus. A) left lateral view; B) posterior view; C) anterior coronal view; D) left lateral view.

function after removal of the tumour and damage to the motor hand region was associated with increased activation of the post-central somatosensory area (Shinoura et al., 2005). Tractography after the operation showed interruption of the U-shaped fibres from the M1 suggesting a possible inhibitory effect of M1 on S1 through the U-shaped fibres of the central sulcus. Release of S1 from inhibitory control can lead to activation of somatosensory area and control of spinal motor neurons through the cortico-spinal fibres originating from extra-M1 cortex.

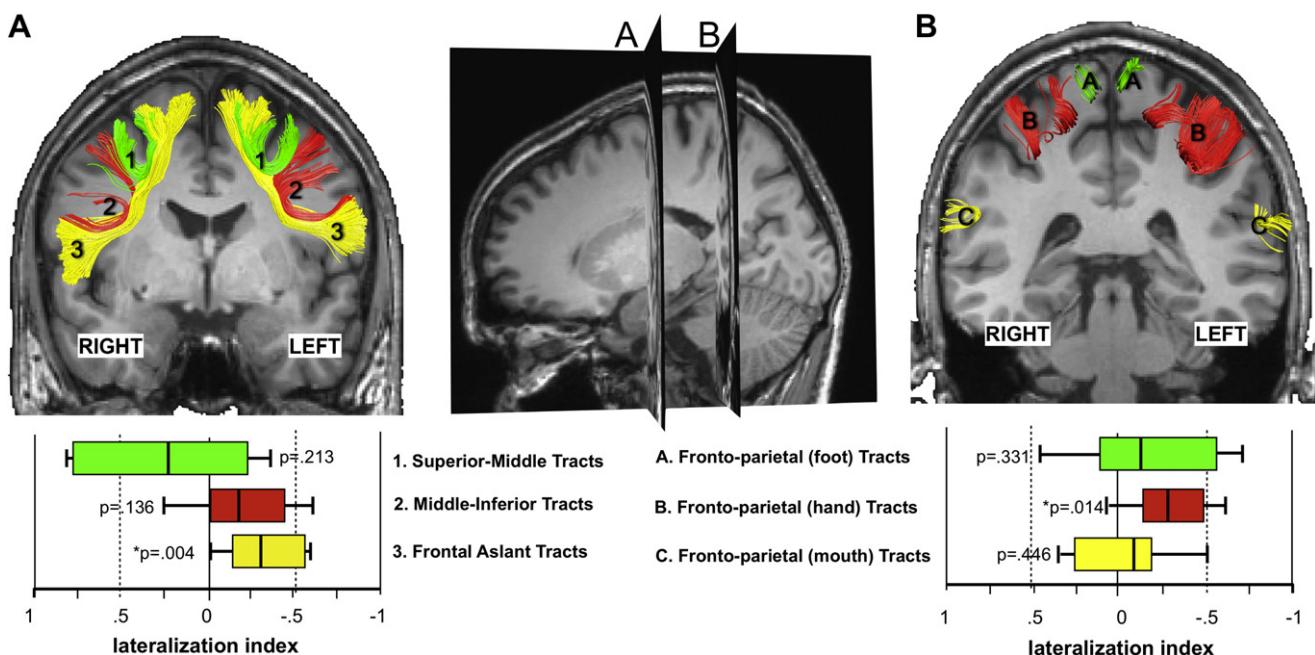
Most of the studies of sensory-motor integration have focused on hand and finger movements, but it is likely that the same conclusions apply to all U-shaped fibres between motor and somatosensory cortices. Our findings suggest, however, a greater volume of U-shaped connections for the hand region compared, for example, to surrounding motor cortex controlling proximal muscles (e.g., forearm). We interpret this finding as evidence of a higher local somatosensory to motor connectivity for those cortical regions controlling muscles involved in finely tuned movements and complex motor skills. This hypothesis is supported by experimental evidence of a greater influence of peripheral somatosensory inputs for movements of the distal muscles (e.g., hand) than proximal muscles (Lemon, 1981). This could also explain the observation of greater volume of the hand region compared to the mouth

and foot region (Fig. 9). The relatively smaller volume of the other two regions suggests the need of progressively minor amount of sensory-motor integration for the mouth and foot regions. Similarly one could argue that if the dominant hand commands a great sensory representation in the contralateral cortex, which allows for finer manipulation and in this case, the learning of more delicate manoeuvres, the lateralization of the U-fibres should correlate with handedness. Our preliminary analysis of the pattern of lateralization showed a left lateralization of the hand U-shaped fibres whereas the dorsal and ventral fibres were symmetrically distributed. The left lateralization may be related to manual dexterity.

Future studies are needed to correlate lateralization of the hand U-shaped fibres with handedness, and the volume of mouth-tongue region with articulatory abilities. Comparative anatomical observations could reveal evolutionary modification of the U-shaped fibres and confirm their role in facilitating the development of complex movements of finger and tongue linked to the emergence of skillful object manipulation and vocalization in the history of human evolution.

#### 4.2. FAT and premotor connections

The posterior regions of the superior and inferior frontal gyri are directly interconnected by a bilateral intralobar tract that



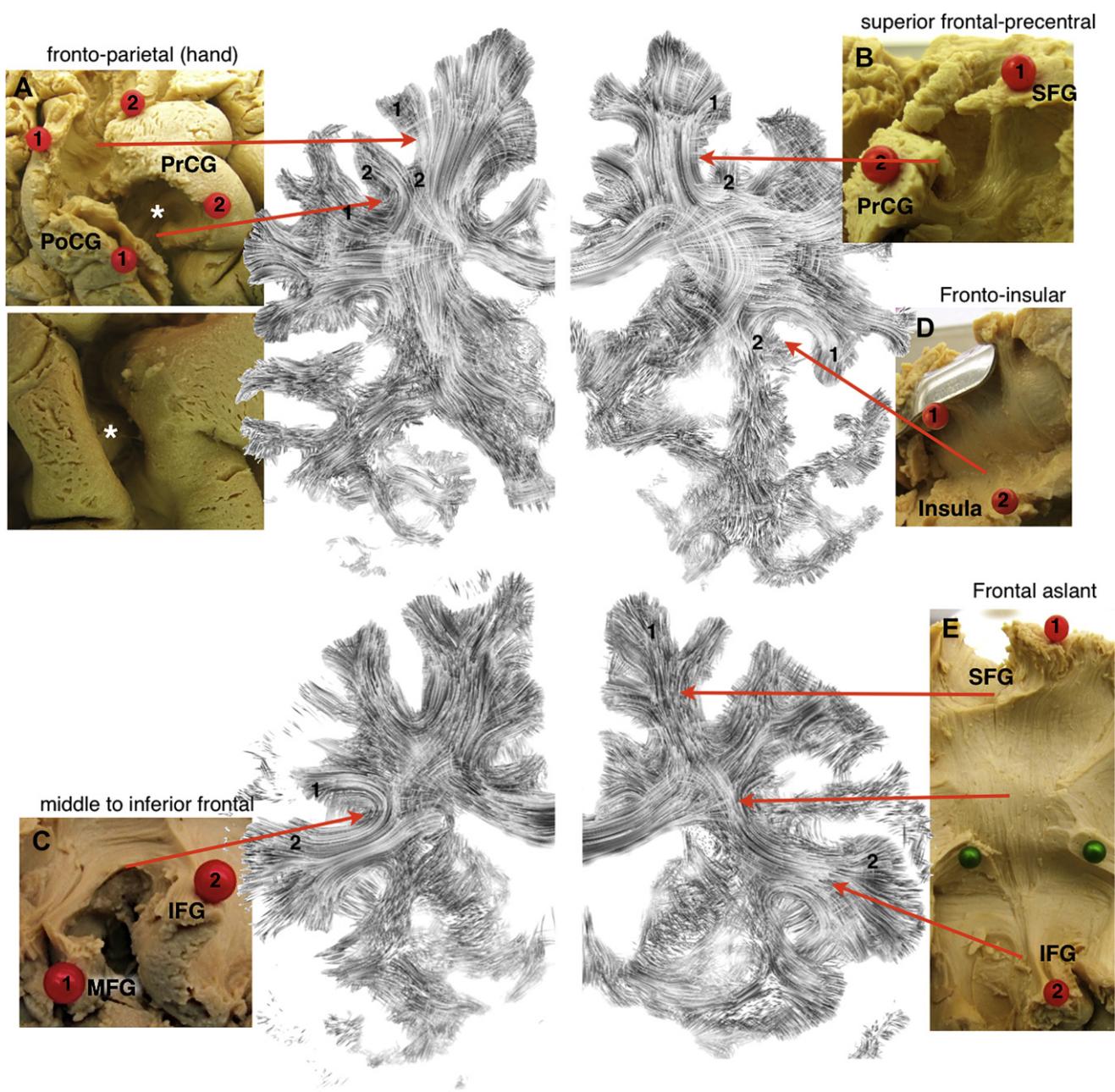
**Fig. 9 – Analysis of the lateralization of the tract volumes.** A) A statistically significant leftward asymmetry was found for the volume of the frontal aslant tract (FAT) (yellow) but not for the connections of the middle frontal gyrus with the superior (1) and inferior (2) frontal gyri. B) Similarly a statistically significant asymmetry was found only for the fronto-parietal U-tracts connecting pre-central and post-central gyri of the hand region (red).

has been previously described in the human brain using tractography (Oishi et al., 2008; Lawes et al., 2008; Ford et al., 2010; Guevara et al., 2011) and post-mortem dissections (Lawes et al., 2008). This tract has an oblique course from the medial-superior to the inferior-lateral region and for this reason we have coined the term frontal ‘aslant’ tract. Similar connections have been described for more anterior regions of the frontal lobe (Guevara et al., 2011; Ford et al., 2010) but we have not been able to dissect these components in our *in vivo* and post-mortem samples. These differences could be related to the methodological approaches used for the elaboration of the diffusion datasets (e.g., probabilistic vs deterministic tractography) or the selection of the regions of interest (e.g., automatic vs manual clustering) as well as the quality and the resolution of the acquired diffusion data.

In our study we also found that the superior and inferior frontal gyri are also connected to the posterior MFG through short U-shaped fibres. In turn each of the three regions connects to the striatum through descending projection fibres. The functions of the cortico-cortical connections of these regions are largely unknown. The medial projections of the FAT reach the anterior supplementary and pre-supplementary areas. Stimulations of these regions produce synergic movements of the eyes, head and arms ‘as though the individual were looking at the hand’ (Penfield and Rasmussen, 1950). Furthermore both medial-superior frontal and superior middle frontal gyri are part of a network for gaze control (Anderson et al., 2011). We speculate that the U-shaped connections between these two frontal gyri are part of an extended network involved in initiating and coordinating complex eye, head and arm movements for reaching actions.

This model could also explain the phenomenon of the ‘anarchic hand’ (i.e., a hand that produces unwanted movements interfering with the desired actions), which has been interpreted as an imbalance between the activity of the supplementary motor area (SMA), responsible for inner-driven actions and for the inhibition of automatic responses, and the lateral premotor cortex responsible for generating movements in response to external stimuli (Goldberg, 1985; Della Sala and Marchetti, 2005). The normal coordination between medial (SMA) and lateral (premotor) frontal activity mediated by the dorsal U-shaped tract is disrupted in patients with ‘anarchic hand’ where the damage to the SMA results in the inability to inhibit the automatic provoked responses (Mushiake et al., 1991; Della Sala and Marchetti, 2005). Similarly ‘utilisation behaviour’ (i.e., a compulsive urge to utilise objects at sight with either hand) (Lhermitte, 1983), often associated with bilateral SMA lesions, has been interpreted as an imbalance between intact premotor cortices, responsive to environmental triggers, and damaged SMA unable to inhibit inappropriate actions (Della Sala and Marchetti, 2005).

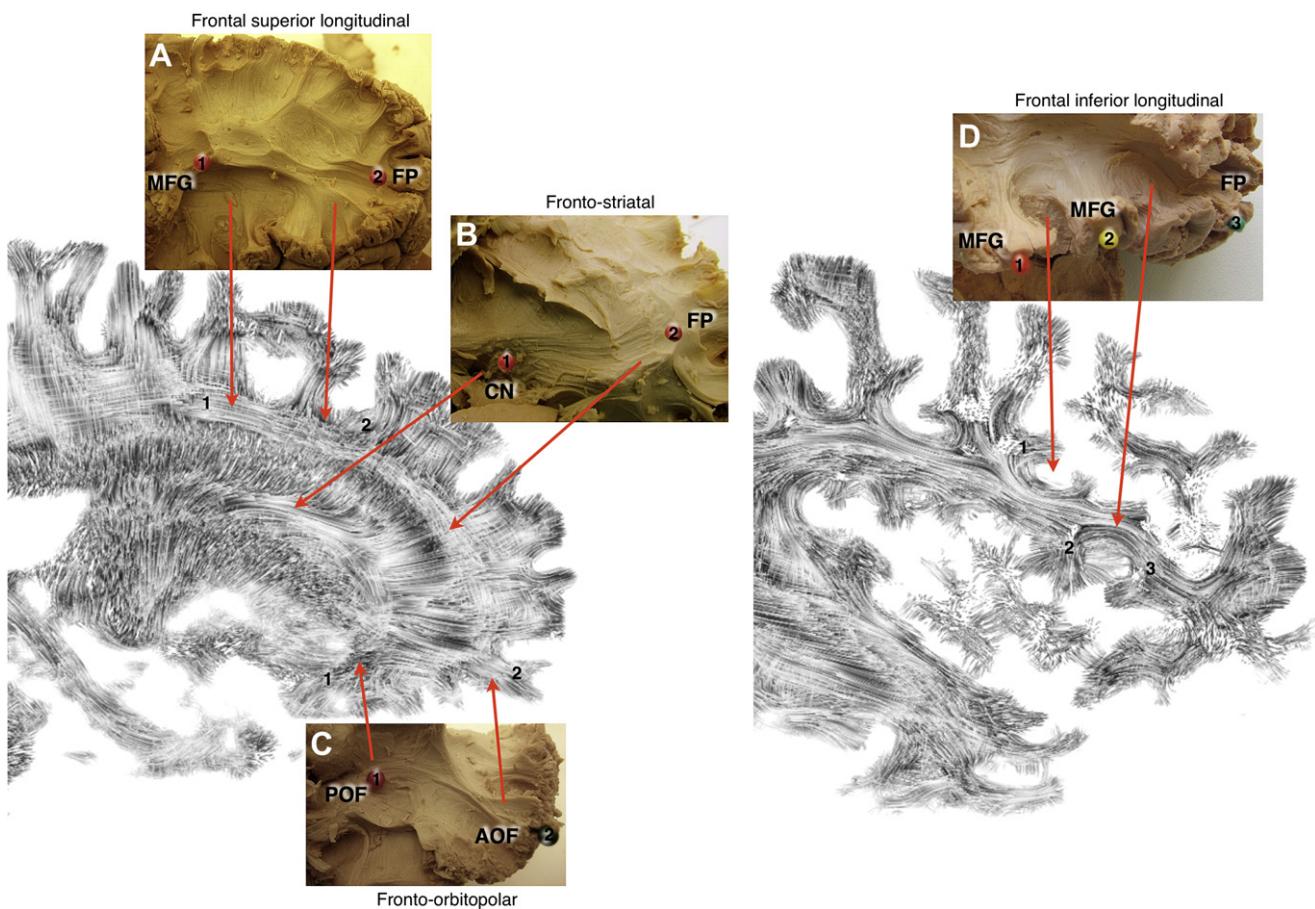
Stimulation of the SMA and pre-SMA also produces both vocalization and arrest of speech (Penfield and Rasmussen, 1950). Patients with lesions of the SMA and pre-SMA present various degrees of speech impairment from a total inability to initiate speech (i.e., mutism) to altered fluency due to ‘stuttering’ and monotonous intonation (Ackermann and Riecker, 2011). Most likely these medial regions of the SFG facilitate speech initiation through direct connections to the pars opercularis and triangularis of the IFG. We were also able to visualize connections between the dorsolateral and medial



**Fig. 10 – Coronal slices of the ‘Digital Dejerine’ maps and post-mortem blunt dissections of the corresponding tracts.**  
**A)** Fronto-parietal U-tracts of the hand region connecting precentral gyrus (PrCG) with post-central gyrus (PoCG). The asterisks in the top left images indicate the correspondence between the presence of protuberances from the wall of the central sulcus and the underlying U-shaped tract. **B)** U-shaped tracts connecting the PrCG with superior frontal gyrus (SFG). **C)** Connections between the middle frontal gyrus (MFG) and inferior frontal gyrus (IFG). **D)** Fronto-insular connections. **E)** The frontal aslant tract (FAT) connecting inferior and superior frontal gyri.

cortical areas and the striatum. These direct connections indicate that cortical areas of the premotor regions rely also on an extensive subcortical loop for the initiation, coordination and performance monitoring of speech and complex limb movements (Fig. 8). Functional imaging studies also suggest that connections between the IFG and the caudate nucleus coordinate activities related to syntactic processing (e.g., recognition of sentences with incorrect sequence of words) (Moro et al., 2001). These activations are left lateralized in

most of the right-handed subjects. This functional lateralization could be related to the anatomical lateralization of the FAT. Furthermore the frequent observation of impaired fluency (Naeser et al., 1989), agrammatism (i.e., impaired syntactic processing) (Alexander et al., 1987) and reduced performance monitoring (Hogan et al., 2006) in patients with deep lesions in the periventricular white matter of the frontal lobes could be explained as a disconnection of the frontal aslant and fronto-striatal tracts.



**Fig. 11 – Sagittal slices of the ‘Digital Dejerine’ maps and post-mortem blunt dissections of the A) frontal superior longitudinal (FSL) system, B) fronto-striatal connections, C) fronto-orbitopolar, and D) frontal inferior longitudinal (FIL) system. CN, caudate nucleus; FP, frontal pole; AOF, anterior orbito-frontal; POS, posterior orbitofrontal; MFG, middle frontal gyrus.**

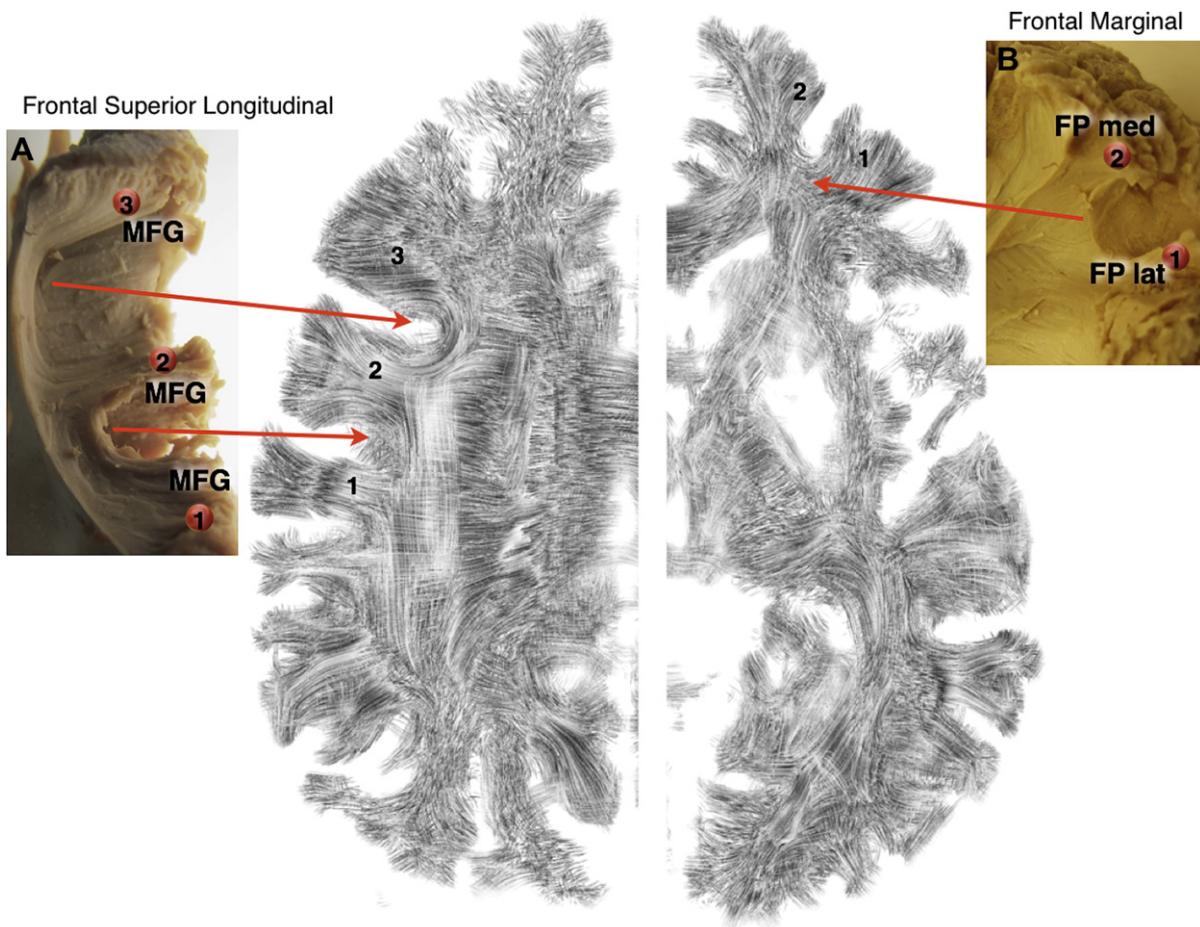
#### 4.3. FOP and FMT

The FOP is the main associative pathway between posterior orbitofrontal cortex and anterior orbitofrontal and polar regions. Similar connections have been described in the monkey brain between areas 10 and 13 (Price, 2007; Yeterian et al., 2012; Thiebaut de Schotten et al., 2012).

The posterior orbital gyrus receives inputs from the limbic regions (i.e., amygdala, hippocampus, nucleus basalis of Meynert, olfactory cortex and insula) and plays an important role in processing olfactory and gustatory inputs and integration of emotions and memories associated with the sensory experience (Rolls, 2002). The anterior orbitofrontal cortex receives auditory and visual inputs from posterior occipital and temporal cortex through the inferior fronto-occipital and uncinate fasciculus (Fig. 6) (Rolls, 2002; Price, 2007; Thiebaut de Schotten et al., 2011a, b). We suggest that the FOP represents a transmodal network for binding memories and emotions with olfactory, taste, visual and auditory inputs. This multi-sensory association and limbic integration could guide more complex cognitive and behavioural functions, such as reward behaviour associated with sensory and abstract reinforcers (e.g., monetary gain and loss) (Kringelbach, 2005) or response inhibition (e.g., go-no-go tasks) (Iversen and Mishkin, 1970).

In humans lesions to the orbitofrontal cortex manifest with a wide range of changes in comportment, such as lack of concern for the present or future, reckless behaviour, altered social manners, and disinhibition (Rolls, 2002; Zappala’ et al., 2012). These patients fail to modify their behaviour on tasks that require changes of strategy in response to changes in environmental reinforcement contingencies (e.g., Wisconsin Card Sorting Test or Iowa Gambling Task) (Bechara et al., 2000). The correlation between the scores on the neuropsychological tests and the severity of behavioural symptoms in their everyday life suggests a common underlying mechanism for both cognitive and behavioural deficits in patients with orbitofrontal lesions (Rolls, 2002).

Our dissections of the frontal pole identified a prominent U-shaped bundle that we named the FMT for its course beneath the groove of fronto-marginal sulcus. The frontal pole is part of the prefrontal region, which corresponds to BA10. It is difficult to identify an equivalent of this area in the monkey brain but in humans it has certainly become the largest area of the prefrontal cortex (Semendeferi et al., 2001; Petrides et al., 2012). The prefrontal cortex is involved in working memory, episodic memory retrieval, mentalizing (Gilbert et al., 2006), monitor self-generated choices (Christoff et al., 2003), allocating attention between simultaneous tasks (Koechlin et al., 1999) and



**Fig. 12 – Axial slices of the ‘Digital Dejerine’ maps and post-mortem blunt dissections of the A) frontal superior longitudinal system (FSL) system and B) fronto-marginal tract (FMT) connecting lateral and medial regions of the frontal pole (FP).**

prospectively coding and deferring goals in multitasking (Burgess, 2000; Koechlin et al., 1999; Volle et al., 2011). Functional neuroimaging and lesion studies suggest that the lateral region of the frontal pole is particularly sensitive to working memory, episodic memory retrieval and attending environmental stimuli, whereas the medial frontal pole region is engaged in self-generated stimuli (i.e., the ‘thoughts in our head’) (Burgess et al., 2007). In particular in the context of the ‘gateway hypothesis’ proposed by Burgess et al. (2007) the role of area 10 is to determine whether signals from the internal (mental) or external (sensory) world dominate ongoing behaviour and cognition.

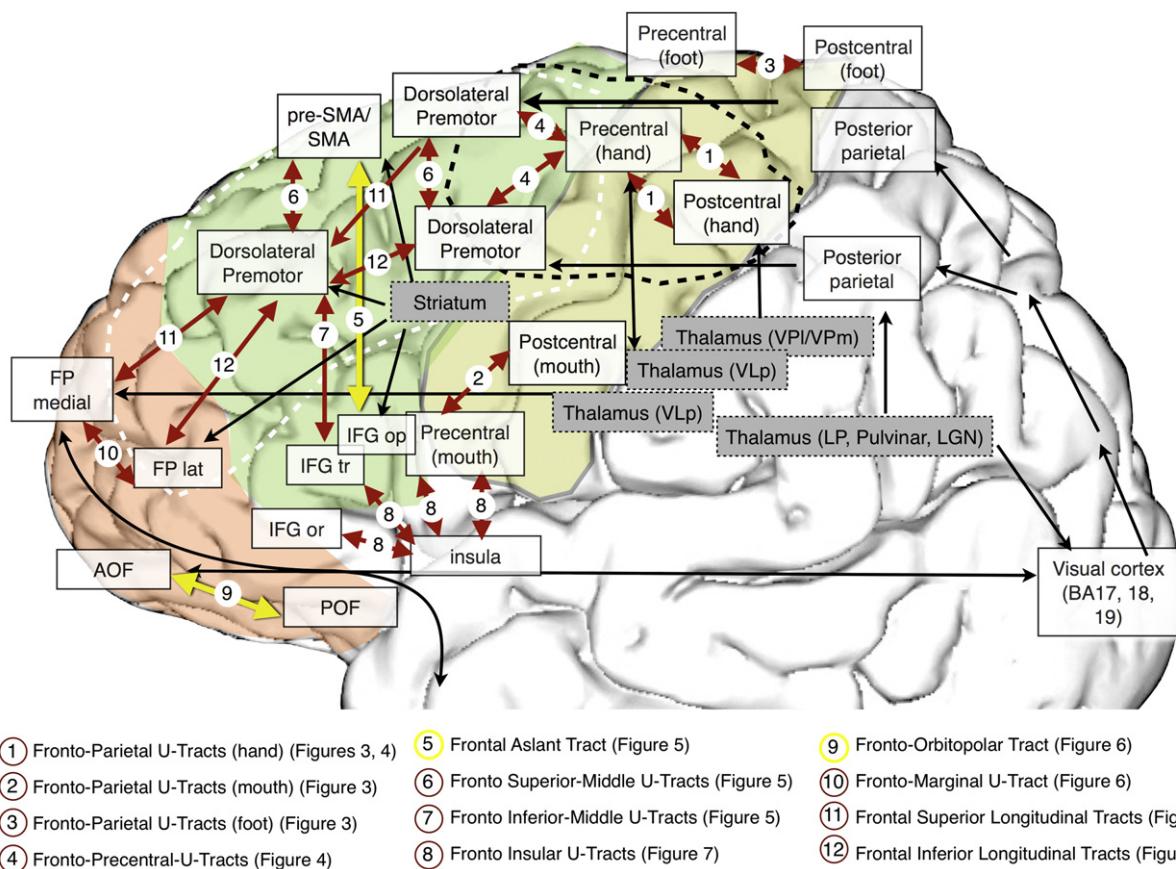
We hypothesise that the activity of the lateral subdivision of the area 10 depends on a three-component network (Fig. 6):

- i) The medial and ventral regions of the frontal pole have reciprocal connections with the thalamus, occipital extrastriate cortex and temporal cortex. These direct connections are probably bidirectional and subserve fast forward access of sensory information to anterior frontal cortex and top-down modulation of early perceptual processes. We speculate that these connections are involved in the encoding and retrieval phase of episodic memory tasks and other tasks involving feedback information (Tsujimoto et al., 2011).

- ii) The most rostralateral cortex of the polar region connects to the striatum and the posterior lateral regions of the motor cortex. This network is likely to play a role in the planning and execution phase of working memory tasks, which involves response selection and monitoring.
- iii) The FMT may represent the anatomical link between these ventromedial and rostralateral regions of the frontal pole.

#### 4.4. FITs

We found a posterior to anterior pattern of distribution of the fronto-insular connections which replicates previous monkey (Mesulam and Mufson, 1985; Yeterian et al., 2012) and human studies (Cerliani et al., 2011). The subcentral region (BA43) is involved in sensory representation of the mouth and taste perception and can be considered an extension of the primary somatosensory cortex. This is the only region of the frontal lobe that shows connections to the posterior insula. The other short fronto-insular connections establish direct communication only with the anterior insula (Fig. 7). The anterior insula receives visceral and sensory (especially gustatory and olfactory) input and integrates it with limbic motivational-emotional afferents. It also sends efferents to subcortical structures involved in alimentary functions (e.g., salivation, gastric



**Fig. 13 – Diagram of the frontal lobe connections.** U-tracts are in red, intralobar frontal tracts are in yellow and the long-range association and projection connections are in black. The different areas outlined correspond to the different functional divisions as following: central sulcus connections (yellow area), hand-knob connections (dashed black line area), premotor connections (green area), prefrontal and orbito-polar (light red area), dorsolateral longitudinal connections (dashed white line area). AOF, anterior orbitofrontal; FP, frontal pole; IFGop, pars opercularis; IFGtr, inferior frontal gyrus pars triangularis; IFGor, inferior frontal gyrus pars orbitalis; LGN, lateral geniculate nucleus; LP, lateroposterior nucleus; POF, posterior orbitofrontal; SMA, supplementary motor area; VLP, ventral lateral posterior nucleus; VPm, ventral posterior medial.

motility). The frontal operculum controls orofacial movements required for non-verbal facial expression, mastication and deglutition, speech articulation, prosody and syntactic and semantic aspects of language. Hence, direct insular inputs to these posterior frontal regions could, for example, provide visceral and emotional information to modulate speech output according to internal states. Conversely frontal projections to the insula could trigger salivation and gastrointestinal motility associated with mastication and swallowing.

Stimulation and lesion studies suggest a functional and anatomical segregation of the FITs (Penfield and Rasmussen, 1950; Mesulam and Mufson, 1985; Dronkers, 1996; Ackermann and Riecker, 2011; Nestor et al., 2003; Augustine, 1996). We speculate that posterior connections between pre-central (BA4 and 6) and insula are involved in integration of taste and visceral (e.g., epigastric discomfort and nausea) sensation with movements associated with mastication, vomiting and facial expression. Connections to the pars opercularis (BA44) of the IFG are likely to be involved in speech articulation, vocalization of emotional states and facial expression. Lesions to these insular connections may result in orofacial and speech apraxia (Dronkers, 1996), flat intonation (motor agraphia), dysphagia

and vomiting. More anterior insular connections to pars triangularis (BA45) and orbitalis (BA47) of the IFG are probably involved in semantic and memory functions associated with taste, visceral sensation and emotions. Lesions to these connections can produce deficits in semantic memory and verbal fluency (Bates et al., 2003; Nestor et al., 2003). It is likely that the insula connections to the different regions of the inferior frontal lobe have some degree of anatomical and functional overlap which we were not able to visualize with our method.

#### 4.5. FLS

The FLS consists of two parallel chains of U-shaped tracts connecting motor, premotor and prefrontal regions. It is composed of a dorsal FSL tract coursing beneath the superior frontal sulcus and a ventral FIL tract running in close proximity of the inferior frontal sulcus. The FLS represents an extension of the superior longitudinal fasciculus connecting fronto-parietal regions (Thiebaut de Schotten et al., 2012). The superior longitudinal fasciculus is composed of three branches, whereas only two chains of connections form the FLS we observed in the frontal lobes. It is possible that this is

related to the limitations of the tractography algorithm that fails to reconstruct small U-shaped connections of the most dorsal region (false negative).

The functions of some of the connections of the FSL tract have been described in the context of the motor premotor connections of the hand-knob region. In general the FLS is likely to play a role in integrating the activity of the different local networks of the frontal lobe, such as, for example coordinating movement planning and execution (carried out by the motor and premotor networks) with an overall goal directed strategy supervised by the FP networks. Lesions to the FLS are likely to manifest with impairment in executive functions, sustained attention and working memory (Stuss et al., 2002; Grafman, 2002).

## 5. Conclusions

In this study we attempted to visualize the intralobar network of the human frontal lobes. The use of spherical deconvolution and post-mortem dissections is a valid approach to overcome some of the limitations derived from axonal tracing studies and classical tensor based tractography. It remains to ascertain whether the representation of some of the tracts is biased by the presence of merging fibres (e.g., callosal) connecting to the same cortical regions of the frontal lobe (Berlucchi, 2012). Furthermore our dissections were performed only on two subjects and need confirmation in a group study. Nevertheless these preliminary findings can be used as framework for understanding heterogeneity of the anatomy of these pathways in larger groups of subjects and correlate their anatomy with cognitive and behavioural performances in healthy population and brain disorders. Future studies are needed to compare these results with other complementary methods that could shed light on some of the functional correlates of these tracts (Matsumoto et al., 2011; Duffau, 2011; Duffau, 2012).

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