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The anatomy of fronto-occipital connections from early blunt dissections to contemporary tractography

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ABSTRACT

The occipital and frontal lobes are anatomically distant yet functionally highly integrated to generate some of the most complex behaviour. A series of long associative fibres, such as the fronto-occipital networks, mediate this integration via rapid feed-forward propagation of visual input to anterior frontal regions and direct top–down modulation of early visual processing.

Despite the vast number of anatomical investigations a general consensus on the anatomy of fronto-occipital connections is not forthcoming. For example, in the monkey the existence of a human equivalent of the 'inferior fronto-occipital fasciculus' (iFOF) has not been demonstrated. Conversely, a 'superior fronto-occipital fasciculus' (sFOF), also referred to as 'subcallosal bundle' by some authors, is reported in monkey axonal tracing studies but not in human dissections.

In this study our aim is twofold. First, we use diffusion tractography to delineate the in vivo anatomy of the sFOF and the iFOF in 30 healthy subjects and three acallosal brains. Second, we provide a comprehensive review of the post-mortem and neuroimaging studies of the fronto-occipital connections published over the last two centuries, together with the first integral translation of Onufrowicz's original description of a human fronto-occipital fasciculus (1887) and Muratoff's report of the 'subcallosal bundle' in animals (1893).

Our tractography dissections suggest that in the human brain (i) the iFOF is a bilateral association pathway connecting ventro-medial occipital cortex to orbital and polar frontal cortex, (ii) the sFOF overlaps with branches of the superior longitudinal fasciculus (SLF) and probably represents an 'occipital extension' of the SLF, (iii) the subcallosal bundle of Muratoff is probably a complex tract encompassing ascending thalamo-frontal and descending fronto-caudate connections and is therefore a projection rather than an associative tract.

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In conclusion, our experimental findings and review of the literature suggest that a ventral pathway in humans, namely the iFOF, mediates a direct communication between occipital and frontal lobes. Whether the iFOF represents a unique human pathway awaits further ad hoc investigations in animals.

1. Introduction

The occipital lobes have been intensively investigated in the last two centuries and many aspects have been clarified with regard to their anatomy and function. Comparative anatomy and neurophysiology studies suggest that the occipital lobes have undergone a complex rearrangement along the phylogeny scale (Rapoport, 1990; Orban et al., 2004). Primary visual areas are relatively smaller in humans with the expansion or addition of associative areas specialised, for example, in face perception (i.e., 'fusiform face area') or word recognition (i.e., 'visual word form area') (Cohen et al., 2000; Epelbaum et al., 2008). It has been proposed that these relatively 'new areas of the human brain' cooperate with more distant regions through long association tracts, whereas evolutionary old areas communicate through short association fibres (Deacon, 1990).

In the human brain a large system of long range associative connections, encompassing the inferior longitudinal fasciculus (ILF), cingulum and inferior fronto-occipital fasciculus (iFOF), mediates fast feed-forward relay of visual input to anterior multimodal temporal, parietal and frontal regions and direct top–down modulation by these regions on early visual areas. The anatomy of the ILF and cingulum has been described in detail both in human and monkey brains, whereas the iFOF has been identified only in humans (Schmahmann et al., 2007; Catani, 2007; Umarova et al., 2010; Yeterian et al., 2012; Thiebaut de Schotten et al., 2012). The controversy further involves a dorsal fronto-occipital fasciculus, namely the superior fronto-occipital fasciculus (sFOF), which has been described in monkey but not in humans (Schmahmann et al., 2007; Thiebaut de Schotten et al., 2012). To further complicate the matter, a dorsal fronto-occipital fasciculus is found in human brains lacking the interhemispheric callosal connection (congenital agenesis), but not in healthy brains. This bundle is often referred to with the eponym 'Probst bundle'. These human–simian discrepancies may be attributed to: (i) methodological limitations of post-mortem and in vivo dissections; (ii) inaccuracy of anatomical terms to indicate the same tracts in different species; (iii) influence of pathological processes on tract development and (iv) true interspecies differences.

In this study we intend to address the following questions: (i) do dorsal fronto-occipital connections described in the monkey and acallosal brains exist in healthy human subjects? (ii) are ventral fronto-occipital connections unique to humans?

To answer these questions we first review the experimental evidence for the existence of dorsal and ventral connections between occipital and frontal lobes in the normal brain, both in animals and humans. Second, we performed tractography dissections of the dorsal and ventral fronto-occipital fasciculus connections using a novel diffusion imaging approach based on spherical deconvolution (SD), which overcomes some of the limitations of the tensor model (Dell'Acqua et al., 2010; Thiebaut de Schotten et al., 2011a, 2011b, 2012; Dell'Acqua and Catani, 2012). Third, we provide dissections of the fronto-occipital connections in subjects with congenital agenesis of the corpus callosum and discuss them in the light of the literature. Finally, the first German–English translation of two seminal papers on the dorsal fronto-occipital connections is provided to clarify current nomenclature. The first of the two is the doctoral dissertation by Onufrowicz (1887) where the term fronto-occipital fasciculus is used to describe, for the first time, a dorsal connection in an acallosal patient. The second paper is Muratoff's (1893) experimental demonstration of a dorsal connection, the subcallosal bundle, in the animal brain.

Our hope is to clarify the anatomy and the history of the fronto-occipital connections and stimulate further functional and anatomical studies.

2. Methods

2.1. *Diffusion tractography of healthy subjects*

A High Angular Resolution Diffusion Imaging (HARDI) sequence optimised for SD was used to acquire 30 datasets from healthy volunteers (aged 23–37 years, 17 males) on a 3T GE Signa HDx (General Electric, Milwaukee, WI, USA). For each subject, a Spin Echo diffusion-weighted echo planar imaging (EPI) sequence was also acquired with the following parameters: voxel size 2.4 × 2.4 × 2.4 mm, matrix 128 × 128, slices 60, NEX 1, TE 93 msec, *b*-value = 3000 sec/mm^2, 60 diffusion weighted directions and seven non-diffusion weighted volumes. Cardiac gating was applied with effective TR of 20/30 R–R intervals (Dell'Acqua et al., in press; Thiebaut de Schotten et al., 2011a, 2011b).

Data were corrected for head-motion and eddy current distortion using the FSL software package (FMRIB Software Library, Release 4.1, The University of Oxford). Fibre orientation distribution (FOD) was estimated using an SD approach based on the damped version of the Richardson–Lucy SD algorithm, which reduces partial volume effects and spurious fibre orientations (Dell'Acqua et al., 2010). Algorithm parameters were chosen as described in Dell'Acqua et al. (2010). Fibre orientation estimates were obtained selecting the orientation corresponding to the local maxima of the FOD profile. To exclude spurious local maxima two mask thresholds were applied to the FOD amplitudes. A first "absolute" threshold (corresponding to three times the amplitude of a spherical

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FOD obtained from a grey matter isotropic voxel) was used to exclude small local maxima due to noise or isotropic tissue. A second "relative" threshold of 5% of the maximum amplitude of the FOD was applied to remove the remaining spurious local maxima with values greater than the absolute threshold (Dell'Acqua et al., 2009, in press).

2.2. *Tractography algorithm*

Whole brain tractography was performed selecting all voxels with at least one fibre orientation. From these voxels and for each fibre orientation the Modified Fibre Assignment by Continuous Tracking (M-FACT) algorithm was used to propagate the streamlines (Descoteaux et al., 2009; Mori et al., 1999).

In regions with crossing white matter bundles the algorithm followed the orientation of least curvature as described by 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°.

2.3. *Delineation of regions of interest (ROIs)*

Three ROIs, delineated on coronal planes, were used to dissect the fronto-occipital connections.

An occipital region was placed on the white matter of occipital lobe posterior to the parieto-occipital sulcus and the temporo-occipital notch. Two anterior ROIs were defined on the white matter of the frontal lobes: a ventral ROI was delineated on the white matter of the external/extreme capsule; a dorsal ROI was placed anterior to the central sulcus on the white matter of precentral gyrus and centrum semiovale. All streamlines between occipital and ventral frontal ROIs were labelled as iFOF. All streamlines between occipital and dorsal frontal ROIs were labelled as sFOF. ROIs are shown in Supplementary material.

2.4. *Percentage overlay maps*

For each individual tractography reconstruction a binary map was computed by assigning each pixel a value of 1 or 0 depending on whether the pixel was visited by at least one tract streamlines or no streamlines. All binary maps were spatially normalised to a standard space of reference (Montreal Neurological Institute – MNI) using FSL linear FMRIB's linear image registration tool (FLIRT) and non-linear FMRIB's nonlinear image registration tool (FNIRT) deformations and summed to produce tract percentage overlap maps (Catani et al., 2007; Thiebaut de Schotten et al., 2011a, 2011b). The percentage overlap maps were displayed on a T1-weighted image from a representative subject for anatomical reference.

2.5. *Diffusion tractography in patients with agenesis of the corpus callosum*

Three datasets were acquired from asymptomatic individuals incidentally diagnosed with partial congenital agenesis of the corpus callosum between 2006 and 2011 across different centres in the UK (Institute of Psychiatry London and University of Cambridge) and Germany (Munich, Klinikum Großhadern, Ludwig-Maximilians-Universität). The datasets from the two English patients (29 years old and 8 years old male) were acquired on a 3T GE Signa System (General-Electric, Milwaukee, WI, USA). High-resolution structural T1-weighted volumetric images were acquired with full head coverage, 196 contiguous slices (1.1 mm thickness, with 1.09 mm × 1.09 mm in-plane resolution), a 256 × 256 × 196 matrix and a repetition time/echo time (TR/TE) of 7/2.8 msec [flip angle 8 degrees, field of view (FOV) 28 cm]. The above diffusion sequence was similar to that used for the healthy subjects except for the number of directions (30 instead of 60). The third dataset from the Munich patient (46 years old female) was also acquired on a 3T GE Signa System (General-Electric, Milwaukee, WI, USA) with a diffusion sequence similar to the one used for the English acallosal brains except for the slightly lower *b*-value (1000 instead of 1300) and anisotropic voxels (.94 × .94 × 2.4). Diffusion data were analysed using ExploreDTI (Leemans et al., 2009) and the analysis consisted of: (i) correcting for eddy current distortion and subject motion (Leemans and Jones, 2009); (ii) diffusion tensor estimation using a non-linear least square method (Jones and Basser, 2004), and (iii) whole brain tractography with a step-size of 1 mm, fractional anisotropy (FA) threshold of .2 to initiate and continue tracking, and an angle threshold of 35° (Mori and van Zijl, 2002). Tractography of the callosal remnants, arcuate fasciculus, cingulum, iFOF and sFOF was performed on TrackVis (Ruopeng Wang, Van J. Wedeen, TrackVis.org, Martinos Center for Biomedical Imaging, Massachusetts General Hospital).

2.6. *Literature review*

A digital literature review was conducted using Internet databases (i.e., PubMed, SCOPUS, and JSTOR). To ensure a thorough search no exclusion criteria were applied and multiple combinations of keywords were used: inferior, fronto, occipital, fasciculus, bundle, tract, pathway, Probst bundle, fronto occipitales Associationsbundel, long association, Muratoff, Onufrowicz, Markfasern, white matter. Additionally, hand-searched original reports from the 19th century were obtained from historical collections of several London-based libraries, such as the Institute of Psychiatry at King's College London, the British library, and the Royal Society in London, as well as several Germany-based university libraries including the Anatomical Institute at Ludwig-Maximilians-Universität in Munich.

Original reports were translated by German (S.J.F., A.D.) and French (M.T.S.) native speakers in collaboration with a native English speaker (J.K.). Anatomical validity of the translations was reviewed by two experts in anatomy (A.D., M.C.). For the canine neuroanatomy, assistance was sought from a veterinarian, and templates indicating the anatomical structures mentioned in the original report are included in the appendix of the translation to facilitate anatomical understanding.

The nomenclature of the original reports was adapted to the Nomina anatomica compiled by the International Anatomical Nomenclature Committee (1989). Both original and currently used terms are indicated in the text (e.g., gyrus fornicatus – cingulate gyrus).

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3. Results

3.1. Literature review: inferior fronto-occipital fasciculus (iFOF)

The first mention of a direct connection between frontal and occipital lobe is included in Burdach's 1822 description of the ILF, a tract connecting the occipital and temporal lobes that was first described by Reil in 1809 as a projection pathway. Burdach not only recognised the cortico-cortical (or associative) nature of the ILF but also described a subcomponent of the tract connecting to the frontal lobe:

> "*In each hemisphere the fasciculus longitudinalis inferior [in the original text: untre Längenbündel] extends along the base of the corona radiata [in the original text: Stabkranz] and [forms] its ventral border. These fibres run uninterruptedly from the occipital pole through the temporal to the frontal pole and thereby form a longitudinal bulge at the inferior base of the cerebrum. It is slightly curved longitudinally, convex laterally and concave medially. It forms an arch superiorly and at the level of the external capsule, and in contrast to the uncinate fasciculus [in the original text: Hakenbündel], it is slightly concave interiorly and convex superiorly. Its fibres originate from the occipital pole and extend anteriorly along the outmost wall of the inferior horn. […] One branch arches underneath the uncinate fasciculus anterior-medially in the temporal pole; the remaining part bends anterior-medially into the insula [in the original text: Stammlappen] where it forms the floor of the external capsule underneath the lentiform nucleus [in the original text: Linsenkern] and thence somewhat arching laterally penetrates the frontal lobe. Here the fibres run superiorly adjacent to the uncinate fasciculus and extend to the lateral cortex of the frontal pole.*" (1822, p. 152).

Burdach's observation of a direct fronto-occipital component of the ILF was largely ignored for almost a century and the term ILF was adopted only for those fibres connecting occipital and temporal lobes. At the end of the 19th century, descriptions of the fronto-occipital connections re-emerged in the French literature. Whilst Adrien Charpy's (1895) description of the fronto-occipital connections was similar to that of Karl Burdach (1822), Jules Dejerine was the first to separate the fronto-occipital fasciculus from the ILF and considered it as a distinct bundle. However, Dejerine's fronto-occipital fasciculus had a different course compared to the occipito-frontal fibres described by Burdach (Dejerine, 1895). In particular, he located the central portion of the fronto-occipital fasciculus above the caudate nucleus and its posterior projections along the ventral surface of the occipital and temporal lobes. Dejerine's textbook was very influential but not everyone agreed with his description. Jean Baptiste P. Trolard (Trolard, 1906; Loukas et al., 2010), for example, whilst agreeing with Dejerine's view that the fronto-occipital fasciculus should be considered as a distinct bundle, gave a description that closely resembled the one of Burdach and Charpy:

> "*[…] so it would exist a proper bundle of fibres, a fronto-occipital fascicle, both frontal and occipital parts being united by a common fasciculus […] placed above the middle portion of the claustrum radiation. It would be possible to gather the uncinate bundle along with the one just described. In our opinion, however, it is best to assign to each its own personality. We ultimately think there are two distinct fasciculi [inferior longitudinal and fronto-occipital fasciculus] in the region just studied, although they both end in the occipital lobe. In support of this view, we will not only report their separation, so easily obtained with our preparation, but we will also insist on their anterior terminations, which are very different. Indeed the blade part belongs to the frontal lobe, while the second belongs to the temporal lobe.*" (1906, p. 446).

In 1909, the Irish-Australian physician Edward Curran was able to replicate Burdach's and Trolard's findings whilst filling a position as anatomy instructor in Chicago (Johnson et al., 1995). Being completely unaware of the work of his German and French predecessors, as it seems, Curran claimed the fasciculus occipito-frontalis inferior (equivalent to the tract today known as iFOF) to be "*a new or hitherto undescribed tract in the cerebrum*" (1909, p. 651). Curran brought the iFOF into the Anglo-American literature and produced its definite description that remains largely valid today:

> "*The fasciculus occipito-frontalis inferior is a large associating bundle of fibres uniting, as its name indicates, the occipital with the frontal lobe. It also contains fibres, which join the frontal lobe with the posterior part of the temporal and parietal lobes. […] From all parts of the frontal lobe the fibres of this fasciculus can be traced converging to a single bundle which swings round the lower external side of the nucleus lentiformis, at which place it appears as a distinct bundle […]. I would emphasize the fact that as it swings to the lower external side of the lenticular nucleus and the external capsule it stands out with striking distinctness and is at once recognized as a separate bundle isolated from the surrounding structures by the directness and compactness of its fibres*" (1909, p. 652).

After Curran, the iFOF has been consistently identified in post-mortem dissections in normal human brains, its existence being reported in at least 44 dissected hemispheres (Davis, 1921; Elliott, 1947; Crosby et al., 1962; Hultkrantz, 1929; Ebeling and von Cramon, 1992; Kier et al., 2004; Fernandez-Miranda et al., 2008; Lawes et al., 2008; Martino et al., 2010, 2011, Fig. 1).

3.2. Literature review: superior fronto-occipital fasciculus (sFOF)

3.2.1. The sFOF in the acallosal brain

Acallosal brains are characterised by the complete or partial absence of commissural fibres (corpus callosum) connecting the two cerebral hemispheres. The absence of callosal fibres is often accompanied by the presence of a prominent dorsal bundle connecting occipital to parietal and frontal regions. As early as 1878, Eichler suggested that a longitudinal ridge, which he was able to appreciate bilaterally in his acallosal patient, was indeed a bundle of callosal fibres that failed to transverse the interhemispheric midline:

> '*In an attempt to interpret our case, it remains without doubt that the longitudinal ridge, whose radiations form the inner white*

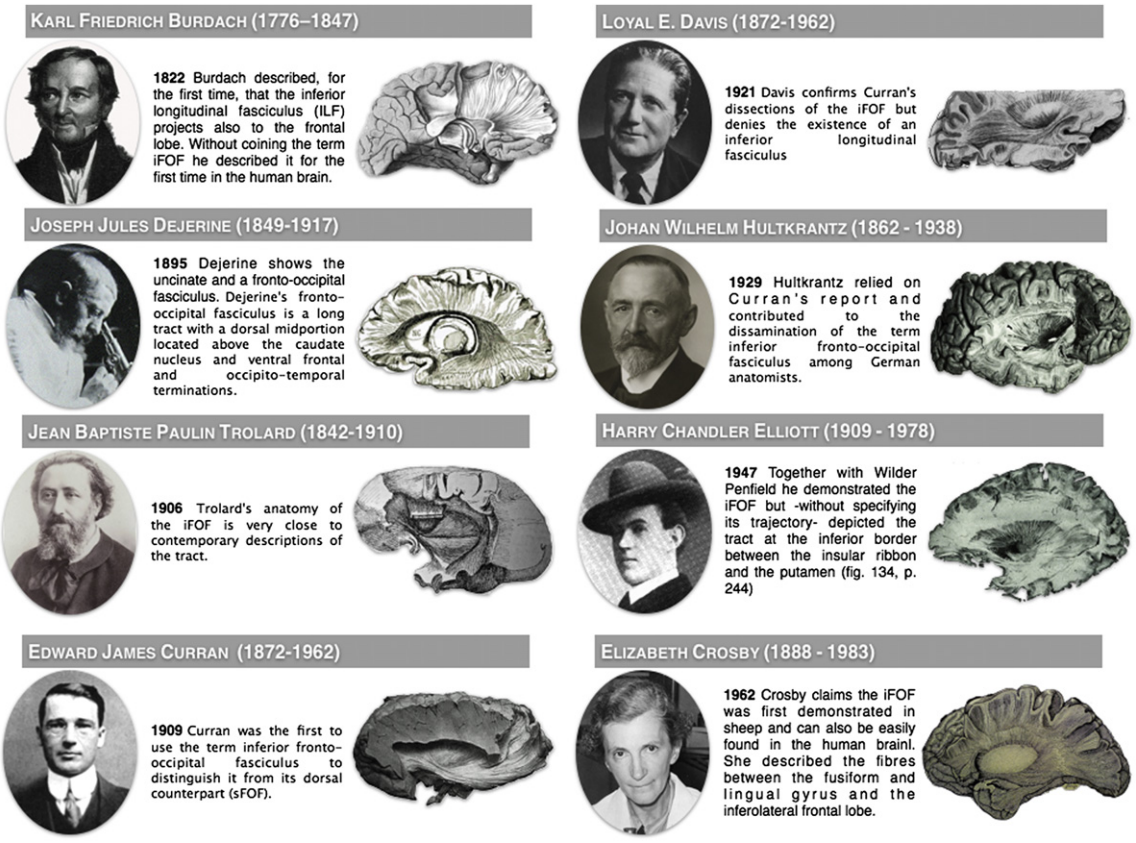

Fig. 1 – Seminal historical contributions to the anatomy of the iFOF in the healthy human brain between 1822 and 1962.

layer of the ventricle, can be considered as rudimentarily developed corpus callosum.' (Eichler, 1878).

Almost a decade later, Wladislaus Onufrowicz, a Ph.D student at the University of Zurich under the supervision of Prof. Auguste Forel, described Eichler's findings in more detail. He published his thesis in the *Archiv für Psychiatrie und Nervenkrankheiten* (1887), which contained a comprehensive review of all 27 single-case reports of acallosal brains published since the year Reil described the first patient in 1812. Onufrowicz gave an accurate account of the *Fronto-occipitales Associationsbündel*, which he claimed to be the equivalent of the arcuate fasciculus in the healthy brains:

'This fibre tract may aptly be called 'Fronto-occipitales Associationsbündel' [associative fronto-occipital fasciculus] or could be referred to as the true fasciculus longitudinalis superior. The ingenious Burdach […] recognised, or rather guessed, this tract and called it the arcuate fasciculus or superior longitudinal fasciculus. Yet neither his [Burdach's] nor Meynert's descriptions of this tract are obvious and it is virtually impossible to prove it [fronto-occipital fasciculus] in the normal brain. We were able to appreciate this tract, located amongst callosal radiations in the normal brain only after comparison with our experiment of nature, in the case of agenesis of the corpus callosum.' (Onufrowicz, 1887).

Onufrowicz hence regarded this fibre system as a normal tract rendered prominent by the absence of the corpus callosum. He thought this tract has hitherto not been identified in healthy brains due to crossing with two major white matter tracts, namely the corpus callosum and the corona radiata (see Appendix 1 for full translation).

The same bundle was also described in an acallosal post-mortem study by Eduard Kaufmann (1887, 1888) who initially disagreed with Onufrowicz's interpretation and suggested that the tract corresponds to the cingulum in the healthy brain:

"On the right hemisphere this [the author refers to the group of fibres he previously described in the left hemisphere] is replaced by […] only one massive bundle, which radiates fibres in all directions. Evidently, this is the association system of the cingulate gyrus [in the original text: gyrus fornicatus]. Due to the missing penetration of the corpus callosum this system is directly abutting superiorly to the wall of the ventricle and is in direct continuity with this structure." (Kaufmann, 1887).

Five years later, Heinrich Sachs, a student of Wernicke, re-examined Kaufmann's specimen and made the important observation that the superior fronto-occipital tract is in fact composed of the callosal fibres that failed to transverse the interhemispheric midline:

"Owing to Mr. Kaufmann's courtesy I was able to re-examine his anatomical preparations. I hereby arrived to the conclusion that this is not indeed an acallosal brain. The fibres of the corpus callosum are all present; they merely do not transverse to the

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contralateral hemisphere but rather remain in the same hemisphere and run anterior-posteriorly. Thereby producing a fronto-occipital bundle in the 'acallosal brain' that is completely absent in the healthy brain." (Sachs, 1892).

This speculation proved to be correct much later as demonstrated by experimental evidence in animals and advanced investigations in humans (Rakic and Yakovlev, 1968; Loeser and Alvord, 1968; Yakovlev and Locke, 1961; Richards et al., 2004; Paul et al., 2007).

In the neuroradiological literature the sFOF, as described in acallosal brains, is associated with the name of Moritz Probst (1867–1923), a German-born Austrian-educated neuropathologist and forensic psychiatrist. It is not clear when and how Probst's name was adopted as eponym for the sFOF. In our review the term 'Probst bundle' is absent from the German literature and it appears for the first time in the English-printed publications of the 1960s: "[…] the composition of the so-called Probst's bundle (longitudinal callosal bundle) will be noted and discussed later. […] Its exact nature has been the subject of much disagreement. […] It is suggested, therefore, that Probst's bundle is composed of […] (1) septal-hippocampal, hippocampal-septal fibres and possible other fornix components; (2) the superior fornix of Elliot Smith; (3) association fibres between various parts of other cortical areas." [Magee and Olson (with Elizabeth Crosby), 1961].

It is possible this adoption was in recognition of Probst' first microscopic description of the tract and for his claim of the tract being uniquely present in the acallosal brain (Probst, 1901). Or, perhaps it is the result of the erroneous adoption of the already existing eponyms in the German literature that indicate two other tracts, one connecting to the reticular formation that was named Probst bundle by Lewandowsky (Peterfi, 1923; Strong and Elwyn, 1943; Truex, 1959; Holmes, 1906), the other connecting the thalamus to the temporal lobe (Ariëns-Kappers et al., 1961; Mettler, 1942).

3.2.2. *The sFOF in the normal animal and human brain*

Whilst the existence of the sFOF in the acallosal brain has never been questioned, the evidence for a similar tract in the normal brain has proved to be more difficult. In the presence of the corpus callosum the sFOF in humans is thought to correspond to the subcallosal bundle described in animals by Muratoff. This tract is a system of fibres running above the caudate nucleus at the corner formed by the internal capsule and the corpus callosum. Muratoff consciously used the term 'subcallosal bundle' to indicate the most distinct feature of this tract (i.e., its midportion lying beneath the corpus callosum) without committing to a clear identification of its terminal projections (see Appendix 2). Muratoff's hesitation was in part related to the crude lesion method he used to study the course of this tract. His method consisted of uni- or bilateral trepanation of the animal skull followed by lesioning of large portions of the brain. After sectioning the brain he was able to follow the trajectory of the degenerating fibres and identify only one of the two cortical end stations (i.e., the one opposite to the lesion).

The development of axonal tracing studies has allowed to describe the anatomy of subcallosal fibres more precisely and to distinguish two different components of the subcallosal bundle in the monkey brain (Yakovlev and Locke, 1961; Schmahmann and Pandya, 2006; Yeterian and Pandya, 2010). The first group consists of fronto-striatal fibres connecting the dorsal and medial aspects of the frontal, parietal and occipital lobes to the caudate nucleus. For this component the eponym Muratoff's bundle had been proposed by Schmahmann and Pandya. The second group includes long association fibres connecting the occipital and the frontal lobe, for which the term fronto-occipital fasciculus continues to apply.

In humans, the fronto-striatal component of the sFOF was originally suggested by Theodor Meynert who used the term 'corona radiata of the caudate nucleus' to indicate that these fibres originate from the frontal lobes and project to the caudate nucleus (1887). The idea of the fronto-occipital fasciculus as an association bundle connecting occipital and frontal regions, as described in the acallosal brain, was extended to the healthy brain by Onufrowicz, Wernicke and Dejerine.

More recently Türe et al. (1997) suggested the existence of a third component of the subcallosal fasciculus formed by ascending thalamo-cortical fibres.

With diffusion tensor imaging (DTI) tractography, all three components of the sFOF have been described (Catani et al., 2002; Wakana et al., 2004; Mori et al., 2005; Makris et al., 2007; Catani and Thiebaut de Schotten, 2012). However, tractography based on the tensor model is prone to artefactual reconstructions mainly due to the inability to separate crossing fibres. The development of SD methods (Dell'Acqua and Catani, 2012) applied to tractography has in part overcome the limitations of the tensor model by allowing the visualization of multidirectional fibre orientations. The use of SD tractography, for example, has been used to dissect and quantify the three branches of the SLF (Thiebaut de Schotten et al., 2011a, 2011b) in humans. In the next section we will present the results of tractography dissections of the fronto-occipital network in healthy and acallosal humans in an attempt to replicate findings from axonal tracing and post-mortem studies.

3.3. *Original data: diffusion tractography of the healthy and acallosal brains*

Two direct fronto-occipital tracts were identified using SD tractography: an inferior pathway connecting ventro-medial occipital and orbito-polar frontal cortex, and a dorsal pathway running between the cingulum and the arcuate fasciculus on the external region of the corona radiata (Fig. 2). The anatomy of the ventral pathway is consistent across all subjects with a >90% overlap along its entire course. The dorsal pathway showed a greater inter-subject variability with a maximum of 66% overlap in its central part.

The ventral pathway corresponds to classical post-mortem descriptions of the iFOF originating mainly from the lingual, posterior fusiform, cuneus and polar occipital cortex. As it leaves the occipital lobe and enters the temporal stem, the iFOF narrows on section and its fibres gather together at the level of the external/extreme capsules just above the uncinate fasciculus. As it enters the frontal lobe its fibres spread to form a thin sheet curving dorsolaterally to terminate mainly in the inferior frontal gyrus. The most ventral fibres continue

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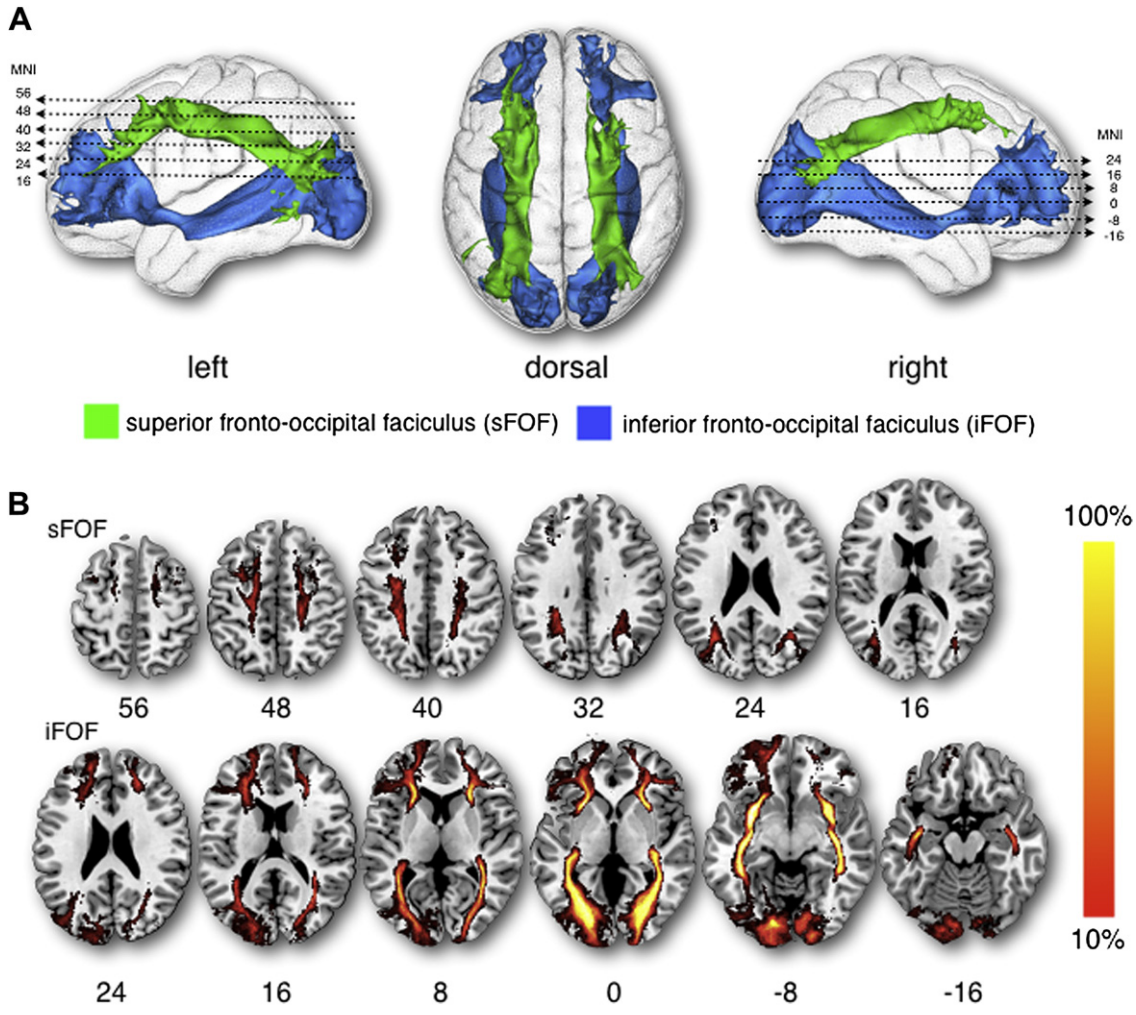

Fig. 2 – SD tractography reconstructions and overlay percentage maps of the dorsal and ventral fronto-occipital fasciculus. (A) 3D reconstruction of the normalised trajectory of the sFOF and the iFOF. MNI coordinates are in correspondence with the MNI slices shown in panel B. (B) MNI-normalised overlay percentage maps of the sFOF (upper panel B, MNI 56–16) and the iFOF (lower panel B, MNI 24 to −16).

anteriorly and terminate in the medial fronto-orbital region and frontal pole.

The dorsal pathway originates from the most anterior and lateral regions of the occipital lobe and projects to the posterior cortex of the superior and inferior frontal gyri after running above the corpus callosum. This tract does neither correspond to the anatomical descriptions of the sFOF nor the subcallosal tract. Direct comparison with recent atlases of white matter connections suggests that this tract corresponds in part to the second branch of the superior longitudinal fasciculus (SLF) (Schmahmann and Pandya, 2006; Thiebaut de Schotten et al., 2011a, 2011b; Makris et al., 2008; Catani and Thiebaut de Schotten, 2012).

Further dissections were performed to clarify the origin and terminations of these fibres running through the subcallosal region. Our dissections show that the streamlines of the 'subcallosal fascicle of Muratoff' connect the frontal lobe to (i) dorsal parietal lobe, (ii) caudate nucleus and (iii) thalamus. None of these streamlines passing through the subcallosal region projected to the occipital lobe.

Neither the ventral nor the dorsal pathways were significantly lateralised to either hemisphere, with the dorsal pathway being slightly larger on the right hemisphere [iFOF: $t(29) = .382$, $p = .705$; sFOF: $t(29) = -1.730$, $p = .094$].

Dissections of the three acallosal brains show the presence of a major dorsal associative pathway connecting occipital, parietal and frontal regions in each hemisphere (Fig. 3B). This tract is separated from the cingulum, arcuate fasciculus and iFOF (Fig. 3C). These three acallosal brains have different degrees of agenesis. Case 1 presented with partial absence only of the anterior body of the corpus callosum (Fig. 3A). In this subject it is possible to visualise the callosal streamlines coursing through the callosal remnants (genu and posterior half of the corpus callosum). In the frontal white matter, corresponding to the subcallosal region of a healthy brain, a longitudinal tract connecting the medial frontal cortex to the thalamus and basal ganglia is visualised. Cases 2 and 3 have a more severe agenesis with callosal remnants of the splenium and genu, respectively (Fig. 3A). In these two cases the subcallosal fasciculus is a prominent tract, which resembles

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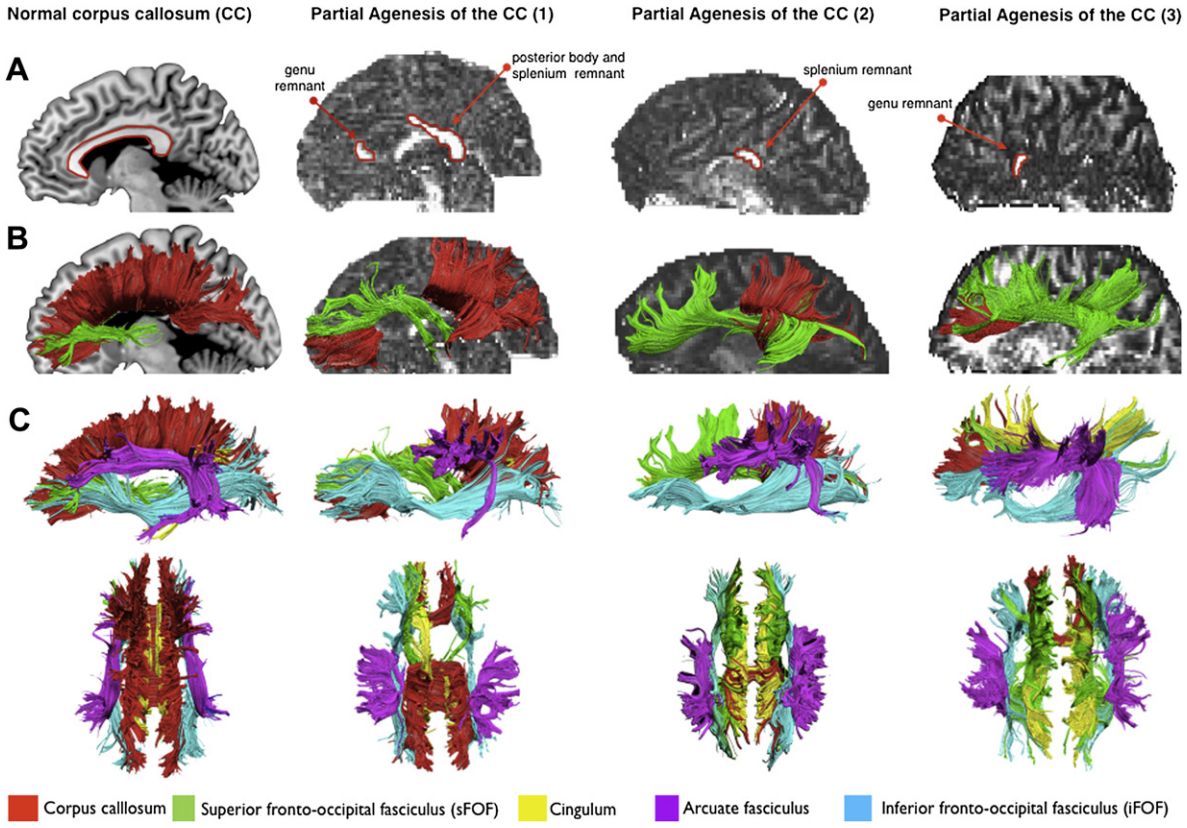

Fig. 3 – Comparison between a healthy and three acallosal brains (1–3) with varying severity of congenital callosal agenesis (absence of corpus callosum, ACC). (A) depicts T1-weighted structural magnetic resonance imaging (MRI) scans of the normal callosal anatomy and acallosal brains. The corpus callosum (CC) and its remnants are delineated in red. (B) shows the virtual in vivo dissections of the (remnants of the) corpus callosum (red) in relation to a subcallosal white matter pathways (green). This demonstrates an increasing prominence of a subcallosal fronto-occipital fasciculus alongside the reduced eminence of interhemispheric callosal fibres. (C) shows the corpus callosum (red) in relation to all major associative white matter pathways, such as the arcuate fasciculus (purple), cingulum (yellow), and the ventral and dorsal fronto-occipital fasciculus (blue, green). The subcallosal tract in the healthy brain and the sFOF in the acallosal brains is clearly a separate tract from the arcuate, cingulum and iFOF.

Onufrowicz's description of the sFOF (see Appendix 1). In these two cases the superior fronto-occipital tract connects the frontal lobe to the parietal, temporal and occipital lobes. Fig. 2C illustrates the tractography reconstruction of all major association tracts in the normal and acallosal brains. The subcallosal tract in the healthy brain and the sFOF in the acallosal brains is clearly a separate tract from the arcuate, cingulum and iFOF.

4. Discussion

In our study we reviewed historical literature and used tractography to clarify the anatomy of the long-range connections between frontal and occipital lobes. Four main results emerge from our study: (i) ventral connections corresponding to classical post-mortem descriptions of the iFOF can be reliably reconstructed in all healthy and acallosal brains; (ii) dorsal fronto-occipital connections can be dissected in vivo in a minority of the healthy brains using SD tractography and are likely to belong to the SLF system; whereas the subcallosal tract (or Muratoff bundle) is a complex system of projection fibres (thalamo-frontal and fronto-striatal) without fronto-occipital associative connections; (iii) in acallosal brains the uncrossed callosal fibres form a large association tract that connects the frontal to parietal, temporal and occipital lobes. For this tract we propose to use the name of Onufrowicz as eponym (i.e., Onufrowicz' bundle instead of Probst or Sachs–Probst bundle).

4.1. *Ventral fronto-occipital fasciculus*

Despite several post-mortem and in vivo dissection studies have reported positive findings, the existence of the iFOF in humans has been questioned in recent years on the basis of axonal tracing studies in the monkey brain: *'There is no convincing support in the experimental literature for connections between inferior occipital regions and the orbitofrontal or ventrolateral prefrontal cortices, and our own observations in the monkey also do not document an 'inferior FOF''* (Schmahmann and Pandya, 2007, p. 373).

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According to these authors the experimental literature is not persuasive as it is primarily based on blunt dissections or in vivo tractography, which are both prone to a number of limitations, including generating the presence of false positives (i.e., non-existing tracts) and false negatives (i.e., absence of truly existing tracts). The SD tractography we used to visualise the fronto-occipital network can in part overcome these limitations (see Dell'Acqua and Catani, 2012, for discussion), although validation is still required. Also it is important to consider that axonal tracing studies are limited in exploring the connections of ventro-medial occipital regions due to limited accessibility. For example the atlas of Schmahmann and Pandya (2006) does not contain information on the connections of the regions equivalent to the human projections of the iFOF. Based on the results in monkeys, Pandya favoured the extreme capsule as containing long ventral association tracts rather than the external capsule (Pandya and Kuypers, 1969). Our view is that, in addition to the extreme capsule tract described by Schmahmann and Pandya, humans have a longer subset of connections reaching the most posterior occipital regions. This enlargement in the human brain might be related to the phylogenetic expansion of the frontal and occipital lobes (Deacon, 1990).

Indirect evidence in support of the existence of an iFOF in humans can be found in studies using other methods, such as electrophysiology and functional imaging.

Rudrauf et al. (2008) employed magnetoencephalography (MEG) to describe the activity within the ventral visual processing tasks involving emotional material and found an activity latency of 100 msec between early visual areas (V2–V3–V4) and the orbitofrontal and ventro-medial prefrontal cortex. This short time interval is highly suggestive of a signal transmission through long-range monosynaptic association fibres along the inferior fronto-occipital connections. Similarly, short activity latency was shown in electroencephalography (EEG) (Barceló et al., 2000; ffytche and Catani, 2005) and cortical recording (Kawasaki et al., 2001) studies of visual percepts.

Although supportive of the existence of the iFOF, the above methods cannot be seen as a direct anatomical validation for blunt and in vivo virtual dissections. This short latency could, in fact, result from a parallel processing route between the lateral geniculate nucleus and the occipital lobe. Further studies are also necessary to clarify whether the iFOF runs throught the extreme capsule or extends into the external capsule.

In conclusion, both post-mortem and multimodal in vivo studies have consistently reported evidence for the existence of an iFOF in humans. The lack of a similar connection in the monkey brain, suggests that the iFOF may represent a tract unique to the human brain (Catani, 2007).

4.2. *Dorsal fronto-occipital connections*

The sFOF has been extensively described in the monkey brain using axonal tracing methods. In humans there are fewer post-mortem studies, which deny the existence of an equivalent bundle in the human brain (Meynert, 1887; Türe et al., 1997). Tractography studies based on DTI were likewise unable to visualise a dorsal fronto-occipital bundle although the majority of studies reported direct connections between frontal lobe and parietal regions (Catani et al., 2002; Wakana et al., 2004; Mori et al., 2005; Makris et al., 2007). The absence of the sFOF on tractography reconstruction could represent a false negative due to the limitations of the tensor model. Tractography based on deconvolution has recently been used to show tracts, such as the SLF, that were described in the monkey but not in DTI tractography studies (Thiebaut de Schotten et al., 2011a, 2011b). Our dissections of the sFOF based on SD tractography showed the presence of tracts between occipital and frontal lobes, which are clearly distinct from the iFOF. These tracts run lateral and dorsal to the corpus callosum and are likely to represent longer branches of the SLF system. Our conclusion is that even with SD tractography, that facilitates reconstructions of pathways not visible with DTI methods, we were not able to visualise a human equivalent of the sFOF in the healthy brain. These results are in accordance with blunt post-mortem dissections.

A second finding from our SD tractography dissections is the identification of a subcallosal tract connecting the frontal lobe to subcortical structures such as the caudate nucleus and the thalamus. This projection tract corresponds to Muratoff's bundle that can be easily identified both in animals and humans. The descending component of Muratoff's bundle belongs to an extended fronto-striatal system, which includes tracts running outside the 'subcallosal region'. Similarly the thalamo-frontal component of the Muratoff's bundle belongs to the anterior thalamic peduncle, a much larger ascending projection system that projects to the entire frontal cortex. Although Muratoff's bundle seems to have some distinct anatomical features (e.g., composed mainly of poorly myelinated fibres compared to other projection fibres) it remains to be established whether it deserves to be considered as a distinct bundle. Whether the Muratoff bundle is an entity on its own or more likely an integrated part of the abovementioned striatal and thalamic projection systems awaits further investigation.

4.3. *Onufrowicz's bundle in the acallosal brain*

Our dissections in three acallosal brains, with varying severity in the expression of the pathology, suggest an inverse relationship between the remnants of the corpus callosum and the fibres of the 'sFOF'. The volume of the 'sFOF' appears more prominent in the most severe cases of callosal agenesis, whereas in partial acallosal brains and in normal brains progressively disappears (Fig. 3). Furthermore our dissections show a clear separation between the 'sFOF' and the arcuate fasciculus, which indicates that Onufrowicz's interpretation of the sFOF being equivalent to the arcuate/SLF, was probably incorrect.

Recently, Schmahmann and Pandya (2006) suggested adding the name of Sachs to that of Probst in recognition of his insightful suggestions on the true callosal nature of the sFOF. We suggest that if an eponym should be used, which is rather questionable, the names of Eichler and especially Onufrowicz should have a priority before those of Sachs and Probst. In Appendix 1, we report the first integral translation of the

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paper by Onufrowicz to draw attention to his seminal contribution and for future reference in the Anglophone literature.

5. Conclusion

Our in vivo dissections based on SD tractography support the presence of a bilateral ventral pathway directly connecting occipital and frontal lobes. This tract corresponds to the classical descriptions of the iFOF derived from blunt post-mortem dissections and recent DTI findings in the human brain, which has not been described in the animal brain. We also found a dorsal pathway running in the outermost region of the corona radiata. This pathway was identified in only two-thirds of the subjects and its trajectory does not correspond to the classical descriptions of the sFOF derived from axonal tracing studies in animals. It is possible that the dorsal pathway we identified is part of the SLF, a lateral system of fibres connecting dorsal regions of the occipital, parietal and frontal lobes. Future studies are needed to establish whether the iFOF is a bundle unique to humans; this includes for example Marchi's staining in the human brain and additional experiments with axonal tracing in monkeys investigating connections from ventromedial occipital regions.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.cortex.2012.09.005.

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