

### Singularity of the white matter structural connectivity of the human brain compared to the chimpanzee brain Maëlig Chauvel

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## Singularity of the white matter structural connectivity of the human brain compared to the chimpanzee brain

Singularité de la connectivité structurelle de la substance blanche du cerveau de l'Homme comparée à celle du chimpanzé

#### Thèse de doctorat de l'université Paris-Saclay

École doctorale n° 575, electrical, optical, biophysics and engineering (EOBE). Spécialité de doctorat: Physique et imagerie médicale. Graduate School : Sciences de l'ingénierie et des systèmes. Référent : Faculté des sciences d'Orsay

Thèse préparée au sein de l'unité de recherche BAOBAB (Université Paris-Saclay, CEA, CNRS) sous la direction de Cyril POUPON, Directeur de recherche.

Thèse soutenue à Paris-Saclay, le 27 mars 2023 par

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9.1	Picture Pr. Jane Goodall, one of the pioneers of primatology, and a chimpanzee.	
	Picture credits: Jane Goodall Institute/Michael Neugebauer	177

### Acronyms

- **AC** Anterior Commissure
- ${\bf ADC}\,$  Apparent Diffusion Coefficient
- **AF** Arcuate Fasciculus
- **ANTs** Advanced Normalization Tools
- ATL Anterior Temporal Lobe
- ${\bf B}{\bf A}\,$ Brodmann Area
- ${\bf CC}\,$  Corpus Callosum
- $\mathbf{CGv}/\mathbf{CGd}$  Cingulum ventral/dorsal
- ${\bf CNS}\,$  Central Nervous System
- ${\bf CPCT}$ Cortico-Ponto Cerebellar
- ${\bf CSD}\,$  Spherical DeConvolution
- ${\bf CSF}$ Cerebro-Spinal Fluid
- ${\bf CST}\,$  Cortico-Spinal Tract
- **DARTEL** Diffeomorphic Anatomical Registration Through Exponentiated Lie Algebra
- ${\bf DBSCAN}$  density-based spatial clustering
- ${\bf DISCO}$ DIffeomorphic Sulcal-based COrtical
- **DNA** DeoxyriboNucleic Acid
- $\mathbf{DTI}$  Diffusion Tensor Imaging
- **DSI** Diffusion Spectrum Imaging
- $\mathbf{DW}$  Diffusion Weighting
- $\mathbf{DWMB}\,$  Deep White Matter Bundle
- **EPI** Echo Planar Imaging
- ${\bf F}{\bf A}$ Fractional Anisotropy
- ${\bf FAT}\,$  Frontal Aslant Fasciculus
- $\mathbf{FO}$  Fronto-Orbital
- FOV Field Of View

 $\mathbf{FX}$  Fornix **GFA** Generalized Fractional Anisotropy **GP** Globus Pallidus GM Grey Matter HARDI High Angular Resolution Diffusion Imaging **HCP** Human Connectome Project **IFOF** Inferior Fronto-Occipital Fasciculus IFG Inferior Frontal Gyrus **ILF** Inferior Longitunal Fasciculus L Lunate **MD** Mean Diffusivity MFC Medial Frontal Cortex MLF Middle Longitunal Fasciculus **MPFC** Medial prefrontal cortex **MRI** Magnetic Resonance Imaging **MSME** MultiSlice MultiEcho sequence **dMRI** diffusion Magnetic Resonance Imaging **ODF** Orientation Distribution Function **PC** Posterior Commissure PCA Principal Component Analysis **PCGS** ParaCinGulate Sulcus **PCPM** Point Cloud Pattern Mining **PET** Positron Emission Tomography **PFC** PreFrontal Cortex PGSE Pulsed Gradient Spin Echo **PNS** Peripheral Nervous System **PT** Planum Temporale **QBI** Q-Ball Imaging  $\mathbf{RBW}$  read bandwidth **RF** Radio Frequency **ROI** Region Of Interest SE Spin Echo

SLF Superior Longitudinal Fasciculus
SN Substancia Nigra
STN Subthalamic Nuclei
STS Superior Temporal Sulcus
SWMB Superficial White Matter Bundle
SyN Symmetric Normalization
TE Echo Time
TR Repetition Time
Unc Uncinate
VVS Ventral Visual Stream
WM White Matter
YNPRC Yerkes National Primate Research Center

### Résumé de la thèse

#### Introduction

Suite aux découvertes faites grâce aux fossiles et à l'avancée des techniques d'investigations en génétique notamment, nous savons que l'espèce humaine est le fruit d'une évolution longue et complexe. Tenter de comprendre la singularité du cerveau de l'Homme implique deux approches complémentaires : examiner les caractéristiques ancestrales et non ancestrales de sa propre évolution et/ou procéder à des comparaisons avec d'autres espèces.

Parmi les hominidés (l'ordre phylogénétique auquel l'Homme appartient), l'espèce vivante la plus proche de l'Homme génétiquement est le chimpanzé, avec lequel l'Homme partage un ancêtre commun ayant vécu il y a environ 6 millions d'années. La proximité phylogénétique entre le chimpanzé et l'Homme interdit leur utilisation en recherche clinique pour des raisons éthiques évidentes. Cependant, l'existence d'outils de neuroimagerie non invasifs, comme l'imagerie par résonance magnétique (IRM), a permis de mettre en place des études visant à comprendre les structures cérébrales du cerveau du chimpanzé. L'exploration du modèle de plissement cortical du cerveau du chimpanzé à l'aide de l'IRM anatomique ou plus récemment l'exploration de sa connectivité structurelle profonde à l'aide de l'IRM de diffusion (IRMd) en sont des exemples.

L'IRM de diffusion est désormais un outil bien établi pour explorer la microstructure du cerveau par l'observation de l'anisotropie du mouvement brownien des molécules d'eau présentes dans les tissus. À ce jour, elle reste la seule méthode permettant d'explorer *in vivo* la connectivité anatomique du cerveau. L'anatomie du cerveau et sa connectivité sont intimement liées. Les grandes fonctions cérébrales résultent de la connexion des régions corticales et/ou de la substance grise profonde via des faisceaux de fibres axonales peuplant la substance blanche cérébrale. Cela permet l'établissement de réseaux fonctionnels.

L'un des grands défis des neurosciences, du point de vue de l'évolution, est de construire et de comparer des modèles de ces réseaux fonctionnels (aussi appelés connectomes) entre espèces. C'est dans ce projet que s'inscrit cette thèse. Le travail présenté ici vise principalement à comprendre les caractéristiques communes et les différences entre la connectivité anatomique du cerveau du chimpanzé et celle du cerveau de l'Homme.

Afin de répondre à cette problématique, un atlas des faisceaux de substances blanches du cerveau du chimpanzé *in vivo* a été établi, grâce à une cohorte de chimpanzés (comprenant des données IRM anatomiques et de diffusion) provenant du centre de conservation "Yerkes National Primates Research Center (YNPRC, Atlanta, Université d'Emory)" et partagée par le Pr. William Hopkins (MD Anderson cancer center, Department of comparative medicine, Bastrop, Texas), dans le contexte de la chaire d'excellence Blaise Pascal. Dans un but comparatif, un atlas de la substance blanche du cerveau de l'Homme a été établi grâce à une cohorte de 39 sujets humains (comprenant aussi des données IRM anatomiques et de diffusion). Les atlas des deux espèces comprenent : un nouvel atlas de la connectivité profonde ainsi que de la connectivité superficielle de la substance blanche.

La création de ces atlas résulte d'une pipeline d'analyse de données issues de l'IRM de diffusion utilisant des algorithmes avancés de clustering de fibres, adaptés aux deux espèces.

La seconde contribution de cette thèse consiste en l'étude comparative de la morphologie des

faisceaux de substance blanche profonds et superficiels, grâce à une autre approche de clustering fondée sur l'algorithme dit "isomap" originellement développé pour l'étude de la morphométrie sulco-gyrale.

Enfin, la dernière contribution de cette thèse est l'étude du faisceau fronto-occipital inférieur (aussi dit "IFOF") chez le macaque Fascicularis grâce à l'utilisation de l'IRM à très haut champ (11.7 Tesla), permettant l'exploration de la connectivité structurelle d'un faisceau controversé chez cette espèce.

### Singularité de la connectivité structurelle de la substance blanche du cerveau du chimpanzé comparée à celle de l'Homme

Les données d'IRM anatomiques et de diffusion ont été traitées à l'aide d'une pipeline Python dédiée à chacune des deux espèces, en utilisant la toolbox C++ Ginkgo du CEA/NeuroSpin, disponible sur le site https://framagit.org/cpoupon/gkg.

**Cohorte des sujets chimpanzés** Nous avons eu la chance d'avoir accès aux données d'un groupe de 39 chimpanzés *in vivo* composé de 23 femelles et 16 mâles, scannés entre 9 et 35 ans (moyenne = 19 ans) et hébergés au sein du Yerkes National Primate Research Center (YNPRC, Atlanta). Ces données ont été obtenues à l'aide d'une IRM 3 Tesla (un balayage anatomique à haute résolution 3D pondéré en T1 (séquence MPRAGE) d'une résolution isotropique de 0,625 mm, temps d'écho TE/temps de répétition TR = 4.38ms/2600ms; et cinq scans d'IRM pondérés en diffusion utilisant une séquence EPI (écho-planar) à écho de gradient pulsé (PGSE) 2D (TE/TR=86ms/6s à b=1000s/mm<sup>2</sup> le long de 60 directions de diffusion et 5 images de référence pondérées en T2 b=0 s/mm)).

Toutes les procédures ont été effectuées conformément aux protocoles approuvés par le YN-PRC et le Emory University Institutional Animal Care and Use Committee.

Toutes les images pondérées en T1 des 39 cerveaux de chimpanzés ont été recalées sur un template de cerveau du chimpanzé (version actuelle : https://www.chimpanzeebrain.org/). Ce modèle, nommé Juna.Chimp, est publié avec une résolution spatiale adaptée à notre projet et correspond à la taille d'un cerveau standard de chimpanzé (de l'antérieur au postérieur =106mm ; de haut en bas = 72mm ; de gauche à droite = 87mm). Il comprend également une parcellisation corticale dont 76 régions d'intérêt correspondant aux zones corticales de l'atlas DAVI 130 ont été sélectionnées (38 par hémisphère) pour le futur développement de l'atlas des faisceaux superficiels.

Les cartes individuelles des fonctions de distribution de l'orientation locale (ODF) ont été générées avec le modèle analytique Q-ball à l'ordre SH=6 des harmoniques sphériques avec un facteur de régularisation Laplace-Beltrami  $\lambda = 0,006$ . Un algorithme de tractographie déterministe régularisé pour l'ensemble du cerveau (1 graine/voxel, pas avant de 0,4 mm, angle d'ouverture de 30°, seuil GFA inférieur = 0,15). Cela a généré les tractogrammes individuels des 39 chimpanzés, composés de plusieurs millions de streamlines.

Cohorte des sujets humains Concernant l'Homme, Nous avons utilisé des scans d'IRM anatomiques et de diffusion provenant d'une cohorte de 39 sujets humains sains issus du Human Connectome Project (HCP, release : http://www.humanconnectomeproject.org/) comprenant 23 femmes et 16 hommes, scannés entre 22 et 35 ans. Pour chaque sujet, une série de séquences d'IRM pondérées en diffusion (IRMd) ont été réalisées sur un système d'IRM 3T utilisant une séquence EPI multibande 2D spin-echo single-shot (résolution spatiale isotrope de 1. 25 mm, TR/TE = 5500/89,50 ms) sur b=1000/2000/3000 s/mm2 pour 90 directions de diffusion et 6 images de référence non pondérées en diffusion (b=0s/mm2). Les données ont été prétraitées avec des étapes de correction des courants de Foucault et des artefacts de susceptibilité.

En ce qui concerne les données de l'Homme, comme pour les chimpanzés, nous avons conçu une pipeline d'analyse pour le traitement des données d'IRM pondérées en diffusion à partir de la toolbox Ginkgo. Trois étapes consécutives ont été réalisées pour chaque sujet : le recalage des données vers un espace commun (le modèle asymétrique non linéaire MNI ICBM 2009c) ; calcul des fonctions de distribution de l'orientation de la diffusion (ODF) avec le modèle analytique Q-ball ; calcul d'une tractographie du cerveau entier avec un algorithme déterministe régularisé (paramètres : 1 graines/voxel, angle d'ouverture : 30°, plage de longueur des fibres : 1,25 - 300 mm, pas : 0,3 mm, SH : 6,  $\lambda$  : 0,006).

**Clustering** Comme les méthodes de reconstruction des fibres peuvent produire des millions de strealines par sujet, l'établissement d'atlas de faisceaux de matière blanche à partir d'un groupe de sujets est une tâche difficile d'un point de vue informatique en raison de la grande taille des matrices de connectivité impliquées au niveau du groupe. C'est pour cela que pour chacune des deux espèces, une stratégie de clustering en deux étapes, similaire à celle proposée dans [P. Guevara, Cyril Poupon, et al. 2011], a été utilisée pour construire des clusters de faisceaux de fibres pertinents à l'échelle de la population. Cette stratégie est basée sur une première étape de clustering établissant des clusters de fibres au niveau du sujet (dit clustering intra-sujet, voir les étapes sur la figure 6.3). Une deuxième étape vise à regrouper, pour chaque individu, les ensembles de fibres obtenus précédemment afin de créer des faisceaux de matière blanche représentatifs de la connectivité structurelle de la population (dit clustering inter-sujet, voir les étapes sur la figure 6.4).

**Création des atlas** Les faisceaux issus des étapes de clustering ont été séparés en deux groupes en fonction de leur longueur moyenne par rapport à un seuil choisi empiriquement et établi à partir de l'histogramme des longueurs de fibres à l'échelle de la population. Les groupes de faisceaux dont la longueur était inférieure à ce seuil étaient considérés comme "superficiels", tandis que ceux dont la longueur était supérieure à ce seuil étaient considérés comme "profonds".

Les faisceaux de fibres de la substance blanche profonde obtenus mesuraient entre 50 et 133 millimètres de long pour les chimpanzés et entre 90 et 300 millimètres de long pour les humains. Les faisceaux profonds n'ont pas nécessité la définition de régions d'intérêt pour être sélectionnés, ils ont été établis à partir du regroupement de faisceaux du clustering suite à une inspection visuelle confirmée par deux neuro-anatomistes indépendants.

#### Atlas des faisceaux profonds du cerveau chimpanzé

Les 46 faisceaux de substance blanche profonde identifiés pour les chimpanzés sont : le faisceau fronto-occipital inférieur, le faisceau longitudinal moyen, le faisceau arqué, le frontal aslants, le faisceau unciné, le fornix, les cingulums (dorsal et ventral), les fibres ascendantes et descendantes motrices et somato-sensorielles (tractus cortico-spinal et radiations thalamo-corticales), le corps calleux, la commissure antérieure, le faisceau visuel ventral, les radiations optiques et certains faisceaux du cervelet (fibres hypothalamiques et subthalamiques, les fibres parallèles, le faisceau cortico-ponto-cerebelleux). Afin d'éliminer toute spécificité liée à des effets de latéralisation putatifs (comme pour le tractus cortico-spinal par exemple), l'atlas des faisceaux de matière blanche établi a été en outre symétrisé par rapport aux deux hémisphères pour sa future application sur de nouvelles cohortes de sujets.



Figure 1: Un nouvel atlas des faisceaux de substance blanche profonds du cerveau du chimpanzé basée sur la méthode de tractographie régularisée par streamline déterministe et représentée sur un maillage 3D du template anatomique. Les 46 faisceaux de substance blanche sont montrés avec des couleurs différentes.

#### Atlas des faisceaux courts du cerveau chimpanzé

Après avoir écarté manuellement les groupes de fibres présentant des trajectoires artéfactuelles, les groupes de faisceaux ont été fusionnés en utilisant un critère de distance, afin d'obtenir des ensembles finaux de faisceaux superficiels pertinents d'un point de vue anatomique. Les faisceaux superficiels ont ensuite été nommés en utilisant l'atlas Juna.Chimp contenant la parcellisation "Davi130" pour les chimpanzés. Chaque faisceau de fibres reliant deux régions A et B s'est vu attribuer un nom suivant la syntaxe A\_B\_Id (Id correspondant à l'indice du faisceau dans l'ensemble de tous les faisceau reliant les parcelles A et B).

111 paires de régions corticales dans l'hémisphère gauche et 116 paires de régions corticales dans l'hémisphère droit présentent des connexions, correspondant à 422 faisceaux de substance blanche (agrégeant 76 845 fibres issues des tractogrammes individuels) pour l'hémisphère gauche, et 400 faisceaux de substance blanche (agrégeant 74 091 fibres issues des tractogrammes individuels) pour l'hémisphère droit (voir figure 2). Des connexions ont été trouvées pour l'ensemble des 38 régions corticales composant l'atlas Davi130.



Figure 2: Un nouvel atlas des faisceaux de substance blanche superficiels du cerveau du chimpanzé, composé de 822 faisceaux. a) 422 faisceaux connectant 111 paires de régions corticales pour l'hémisphère gauche et b) 400 faisceaux connectant 116 paires de régions corticales pour l'hémisphère droit ; c) superposition 3D de tous les faisceaux de l'atlas sur la surface piale du template Juna.Chimp; une couleur différente est attribuée à chaque faisceau; d): zoom sur 3 faisceaux superificiels.

#### Atlas des faisceaux profonds du cerveau de l'Homme

Pour établir une comparaison pertinente entre l'homme et le chimpanzé, nous avons soigneusement fait correspondre les pipelines de post-traitement des données ainsi que les cohortes. 45 faisceaux profonds de substance blanche ont été identifiés (voir figure 4).



Figure 3: Un nouvel atlas des faisceaux de substance blanche profonds du cerveau de l'Homme basé sur la méthode de streamlining déterministe régularisé et représenté sur un maillage 3D du template anatomique. Les 45 faisceaux de substance blanche sont montrés avec des couleurs différentes.

#### Atlas des faisceaux courts du cerveau de l'Homme

Suivant la même méthodologie que pour le cerveau du chimpanzé, nous avons constitué un atlas du cerveau de l'Homme. Les atlas de Desikan (atlas humain) et de Davi130 (atlas chimpanzé) ne présentant pas exactement des régions corticales homologues, nous avons dû redéfinir davantage l'atlas de Desikan et proposer un nouvel atlas cortical partageant le même nombre d'aires corticales que l'atlas DAVI 130 du chimpanzé. Pour ce faire, nous avons utilisé un outil (Voi) permettant le découpage et la définition de 76 régions corticales (voir figure 4).



Figure 4: Parcellisation corticale des cerveaux du chimpanzé et de l'Homme: (qauche) parcellisation corticale du cerveau du chimpanzé où les 38 régions de l'hemisphère gauche sont montrées, (droite) parcellisation corticale du cerveau de l'Homme où les 38 régions de l'hemisphère gauche sont montrées, elles sont dessinées sur le template MNI. Abbreviations : the anterior/middle/posterior superior frontal gyrus (aSFG/mSFG/pSFG); the anterior/ posterior middle frontal gyrus (aMFG/pMFG); the anterior/middle/posterior inferior frontal gyrus (aIFG/mIFG/pIFG); the medial lateral orbitofrontal cortex (mOFC/ lOFC); the superior, middle, inferior precentral gyrus (sPrCG / mPrCG / iPrCG); the Paracentral Lobule (PCL) ; the anterior and posterior insula (alns / plns) ; the anterior/posterior superior temporal qyrus (aSTG/pSTG); the anterior/posterior middle temporal qyrus (aMTG/pMTG); the anterior/posterior inferior temporal gyrus (aITG, pITG); the anterior/posterior fusiform gyrus (aFFG/pFFG); the superior/middle/inferior postcentral gyrus (sPoCG/mPoCG/iPoCG); the superior parietal lobule (SPL); the supramarginal gyrus (SMG); the angular gyrus (AnG); the Precuneus (PCun) ; the cuneus (Cun) ; the Lingual Gyrus (LG) ; the superior/middle/inferior occipital gyrus (sOG / mOG/iOG); the entorhinal Cortex (EnC); the parahippocampal gyrus (PHC).

Sur la figure 5 est représentée une vue d'ensemble de l'atlas des faisceaux superficiels du cerveau humain, avec la matrice circulaire des connexions entre les régions corticales pour les hémisphères gauche et droit. Au total, 1365 faisceaux superficiels ont été trouvés entre toutes les paires de régions.



Figure 5: Un nouvel atlas de la connectivité superficielle du cerveau de l'Homme. (Haut): Matrices de connectivité des faisceaux pour les hémisphères gauches et droit ; (bas) Representation de tous les faisceaux de l'atlas, avec une couleur représentant chaque faisceaux, sur la droite, quelques exemples de faisceaux trouvés superposé à la surface piale du template humain avec le sillon traversé associé.

### Etude comparative de la morphologie des faisceaux de substance blanche entre les cerveaux du chimpanzé et de l'Homme

Après la création des atlas de faisceaux superficiels et profonds pour le chimpanzé et l'Homme, le nouvel objectif fut d'essayer d'établir une comparaison pertinente des faisceaux de substance blanche superficiels et profonds entre les deux espèces. Pour ce faire, nous avons utilisé l'algorithme "isomap". En effet, cette méthodologie inspirée par l'article de Sun et al. 2017 est généralement utilisée pour étudier la morphologie des sillons cérébraux. Il permet de caractériser les formes en identifiant, et en capturant, la variabilité morphologique d'un ensemble de données et permet de quantifier les spécificités individuelles relatives à ces caractéristiques morphologiques. La valeur ajoutée de ce travail a été d'améliorer la précision de l'évaluation de la forme des faisceaux de matière blanche en utilisant la méthode PCPM (point cloud pattern mining) décrite dans Pascucci et al. 2022.

#### Comparaison morphologique des faisceaux superificiels, analyse visuelle

Afin de pouvoir comparer la connectivité superficielle entre le cerveau de l'Homme et celui du chimpanzé, nous avons d'abord utilisé une approche visuelle puis une approche géométrique. Ceci afin de tenter de surmonter tout biais lié à des préjugés subjectifs.

Des recherches antérieures menées sur les faisceaux de substance blanche superficielle chez l'Homme ont mis en évidence l'existence de formes alternatives aux fibres en forme de U bien décrites (voir figure 6). Etant donné que peu d'éléments sont connus à propos de ces fibres, leurs formes sont également mal connues et semblent être naturellement liées à la gyrification corticale. La question est de savoir s'il existe une diversité dans les formes des faisceaux de substance blanche chez le chimpanzé et si elle est partagée avec l'Homme.



Figure 6: Différentes formes de faisceaux superificiels trouvées chez l'Homme de Labra Avila 2020.

**Chez le chimpanzé -** La plupart des SWMB du cerveau du chimpanzé ont pu être regroupées en cinq groupes de formes spécifiques (voir figure 7, A.). Globalement, deux types principaux de formes de faisceaux superficiels ont été observés : 1) les faisceaux à bords recourbés et 2) les faisceaux à bords plats.

Alors que les faisceaux à bords recourbés semblent être présents dans tous les lobes du cerveau, les faisceaux en forme à bords plats sont plus ou moins restreints à la partie ventrale du cerveau, à l'exception de certaines sous-parties du corps calleux qui ont été considérées comme des faisceaux superficiels. Les faisceaux à bords plats mis à part, les faisceaux aux bords recourbés peuvent être divisés en 2 sous-groupes principaux : 1) les faisceaux coudés et 2) les faisceaux en U.

En effet, ces deux catégories, que l'on ne retrouve pas dans les mêmes proportions, présentent deux types de morphologies différentes. Les fibres coudées correspondent à des fibres en "V", qui ressemblent étrangement à celles que l'on trouve dans les faisceaux superficiels de l'Homme. En observant chaque faisceau à l'aide du viewer "Anatomist", les plus anguleuses semblaient être

situées sur le lobe frontal et le lobe temporal et apparaissaient comme une minorité. L'extrémité des faisceaux en forme de "V" présente parfois un aspect en éventail.

Dans le groupe des fibres en U, différents types de fibres ont été observés et regroupés en 3 sous-groupes selon que les bords des fibres étaient plus ou moins fermés. Les fibres en forme de C sont appelées ainsi en raison de leurs bords fermés, dirigés vers l'intérieur du centre de gravité du faisceau, comme la lettre "C". Elles sont peu représentées dans le cerveau mais sont présentes dans tous les lobes. Ce sont également les faisceaux dont la longueur des fibres est la plus petite. Le deuxième groupe est celui composé de la majorité des faisceaux et est appelé "fibres en forme de U" car elles ressemblent à la lettre "U". En effet, elles possèdent des bords recourbés mais moins fermés que les fibres C. Elles peuvent être considérées comme des faisceaux de "longueur moyenne". Le troisième et dernier groupe de formes est celui des faisceaux "Open-U". Ce groupe est composé de faisceaux ressemblant à la lettre "U", mais contrairement au groupe précédent, ils présentent des bords plus ouverts. Les faisceaux qui composent ce groupe sont les plus longs. Les faisceaux Open-U et les faisceaux V sont parfois très difficiles à distinguer.

**Chez l'Homme -** Le même type de classification que celle du chimpanzé peut être avancé, avec toutefois quelques variations. En effet, on retrouve les deux groupes principaux de faiceaux (recourbés et plats). En revanche, parmis les faisceaux plats, un type de faisceaux apparaît comme ayant une forme de "L". Les faisceaux ayant cette forme sont notamment situés près de l'insula. Elle semble être présente exclusivement chez l'Homme. Parmis les faisceaux à bords recourbés, on retrouve les formes en "C", "U" et "Open-U" mais aussi la forme "6".



Figure 7: Ratio des différentes formes de faisceaux superificiels des cerveaux du chimpanzé (à gauche) et de l'Homme (à droite).

#### Comparaison morphologique des faisceaux superificiels : analyse géométrique

Nous avons utilisé le pipeline PCPM (point cloud pattern mining) décrite dans Pascucci et al. 2022, sur un grand ensemble de données, comprenant 844 faisceaux de fibres pour le chimpanzé et 1365 faisceaux de fibres pour l'Homme. Afin de réduire ce large volume d'information à analyser par l'algorithme, chaque faisceau a été réduit à un "centroïde", qui est une fibre représentative de tout le groupe.

L'ancienne classification visuelle et empirique donnait déjà des indices sur les groupes de formes attendus et confirmait l'existence de diverses formes de faisceaux superficiels tels que les faisceaux en U, en V, et plats. Il a également été observé une symétrie dans la distribution de ces formes entre les deux hémisphères. L'utilisation de l'algorithme basé sur les isomaps a confirmé cette observation.

Nous avons appliqué une réduction de la dimensionnalité de l'espace à N dimensions en utilisant l'algorithme isomap avec un paramètre de nombre de voisins maintenu inférieur à 5. Une analyse des résultats basés sur ces dimensions nous a conduit à ne considérer que 2 dimensions en conservant suffisamment d'informations pour les étapes ultérieures de clustering consistant en l'identification de clusters dans l'espace réduit par isomap en utilisant un algorithme k-means. Cette étape a été suivie d'une inspection visuelle des résultats en augmentant le nombre k de clusters jusqu'à l'observation de clusters morphométriquement pertinents.



Figure 8: Analyse géométrique des faisceaux superficiels à l'aide de l'isomap entre l'Homme et le chimpanzé

Ces résultats nous renseignent sur la présence de deux formes de faisceaux principales : ouverte et fermée chez les deux espèces. En revanche, les faisceaux avec la forme plus fermée (bords recourbés) (partie supérieure de la figure, en bleu) sont plus grandement distribués à travers le cerveau de l'Homme par rapport au chimpanzé.

Dans le cas d'une analyse plus fine des formes moyennes présentes parmi les faisceaux superificiels (partie inférieure de la figure), on observe des formes allant de la plus plate à la plus ouverte chez les deux espèces. Chez l'Homme, les formes en "U", "Open-U" et "C" sont clairement identifiées, chez le chimpanzé on distingue uniquement des faisceaux en "U" et "Open-U".

En complémentarité avec l'inspection visuelle menée précédemment, il existe donc des différences de formes moyennes de ces faisceaux entre les deux espèces et au sein de ces espèces.

#### Comparaison morphologique des faisceaux profonds

Pour tenter d'analyser les points communs et les différences entre les morphologies des faisceaux profonds de substance blanche des cerveaux humain et chimpanzé, des étapes successives de traitement des données ont été nécessaires, et sont résumés ci-dessous :

- Le calcul d'un espace commun entre les deux templates Homme et chimpanzé afin d'obtenir des données comparables, en utilisant les toolbox "DISCO" et "DARTEL" de *Brainvisa*.
- l'application des atlas des faisceaux profonds du chimpanzé et de l'homme sur chaque cohorte de sujets respectives grâce à l'outil "Advanced fiber labeling" de la toolbox Gingko;
- le calcul des *alpha-shapes* des faisceaux issus de l'application de l'atlas, pour chaque sujet. En effet, une fois l'atlas appliqué et les faisceaux récupérés chez tous les sujets, la quantité d'informations est colossale, avec des millions de streamlines, composées par une multitude de points. Une commande de la toolbox ginkgo a été développée pour calculer l'enveloppe de chaque faisceau de matière blanche profonde. Cela qui reste suffisant pour décrire sa morphologie et réduit considérablement la taille de la représentation à quelques centaines de points.

Ici, deux exemples sont montrés : l'étude de la morphologie du faiceau arqué (figure 9) et du frontal aslants (figure 10).



Figure 9: Analyses géométrique du faisceau arqué entre l'Homme et le chimpanzé. En haut, à gauche : formes des faisceaux provenant des atlas des deux espèces, au centre : les formes moyennes des faisceaux contruites par l'isomap et recalées dans l'espace commun, sur la droite : l'histogramme des différentes dimensions de l'embedding. En bas : l'axe isomap provenant de l'embedding selon la dimension 1.

Pour ce faisceau, la différence morphologique entre les deux espèces est si importante que l'algorithme n'apporte pas d'information supplémentaire, en revanche, il permet de se rendre compte de la bonne séparation entre des morphologies différentes.



Figure 10: Analyses géométrique du faisceau frontal aslants entre l'Homme et le chimpanzé. En haut, à gauche : formes des faisceaux provenant des atlas des deux espèces, au centre : les formes moyennes des faisceaux contruites par l'isomap et recalées dans l'espace commun, sur la droite : l'histogramme des différentes dimensions de l'embedding. En bas : l'axe isomap provenant de l'embedding selon la dimension 1.

Pour le frontal aslants, alors qu'aucune différence morphologique marquée n'était observée à l'oeil nu, l'algorithme permet de mettre en évidence une différence d'ouverture du faisceau entre les deux espèces : plus ouvert chez l'Homme que chez le chimpanzé. Cela est potentiellement lié à la différence du nombre de sillons traversés entre les deux espèces par ce faisceau.

### Etude du faisceau fronto-occipital inférieur chez le macaque fascicularis à l'aide de l'imagerie par résonnance magnétique à trés haut champs (11.7T)

Le faisceau fronto-occipital inférieur, également appelé IFOF, est l'un des principaux faisceaux d'association peuplant le cerveau humain. Ce faisceau de substance blanche est l'un des plus longs et des plus épais présents dans le cerveau et est impliqué dans divers réseaux cognitifs supérieurs. Parmi ses fonctions figure le traitement du langage. Plus précisément, ce faisceau semble être impliqué dans la production de la parole ce qui en fait un faisceau de choix, en conjonction avec le fascicule arqué, pour l'étude de l'émergence du langage chez l'homme.

Il est généralement admis que le développement de l'IFOF chez l'homme a joué un rôle clé dans l'acquisition de la parole au cours de l'évolution. Pendant longtemps, l'IFOF a été considéré comme spécifique à l'homme parce qu'il ne pouvait pas être identifié de manière précise chez les primates non humains comme les macaques.

L'intérêt croissant de la communauté scientifique pour les sciences de l'évolution et l'acquisition du langage a conduit à un regain d'intérêt pour le lien existant entre les faisceaux de matière blanche et les fonctions qu'ils supportent ainsi que pour leur comparaison entre les différentes espèces de primates. Cependant, peu d'études ont abordé la morphologie et l'anatomie du faisceau fronto-occipital inférieur entre les cerveaux de l'homme, du chimpanzé et du macaque.

Ce chapitre vise à combler cette lacune et présente une étude expérimentale du faisceau fronto-occipital inférieur dans le cerveau du macaque, et plus précisément de l'espèce "*Macaca Fascicularis*" scannée en utilisant des données IRM à ultra-haut champ à 11,7 Tesla pour le cartographier à haute résolution.

Le cerveau *ex-vivo* utilisé pour cette étude a été prélevé sur un macaque femelle de 3 ans de l'espèce *Macaca Fascicularis* par l'unité iBrain de l'INSERM U1253 (Université de Tours, France). Il a été scanné par une IRM préclinique de l'institut NeuroSpin (CEA, Gif-sur-Yvette) dans le cadre d'un protocole d'imagerie approuvé par le Comité Local de Protection des Animaux.

Le cerveau du sujet a été scanné à l'aide d'un système d'IRM Bruker Biospin 11,7 T et d'une bobine volumique de 60 mm avec un protocole d'imagerie comprenant un balayage MSME 3D pondéré en T2 à 100µm, un balayage MSME 2D pondéré en T2 à 180µm et un balayage d'IRM de diffusion (dMRI) multibande utilisant une séquence EPI PGSE segmentée 3D à b=1500/4500/8000s/mm<sup>2</sup> le long des directions 25/60/90 (TE/TR=24/250ms, 33 segments, résolution isotrope de 250µm).

Après correction des artefacts d'imagerie (tels que les courants de Foucault, les artefacts de susceptibilité), les données d'IRMd ont été utilisées pour calculer des cartes ODF analytiques Q-ball (ordre SH 6, facteur de régularisation Laplace-Beltrami de 0,006) à partir desquelles une tractographie déterministe régularisée du cerveau entier a été réalisée (1 graine/voxel, pas avant 60µm, angle d'ouverture 15°, seuil GFA 0,04) pour obtenir le tractogramme du cerveau.

De manière similaire à l'approche précédemment décrite, un algorithme de clustering hiérarchique des fibres a été appliqué au tractogramme pour créer une représentation parcimonieuse composée de petits faisceaux de matière blanche (chacun peuplé de quelques dizaines de fibres et représenté par une fibre appelée centroïde) subdivisés en deux ensembles correspondant aux 2 hémisphères, puis classés selon leurs plages de longueur.

#### Inferior fronto-occipital fasciculus reconstruction

Pour chaque hémisphère, deux ROIs ont ensuite été délimitées manuellement au niveau de 2 plans coronaux distants : un premier ROI correspondant à la partie moyenne du lobe frontal et un second ROI correspondant à la partie antérieure du lobe occipital. Les faisceaux passant par les deux ROIs ont ensuite été sélectionnés pour identifier les deux IFOFs cibles gauche et droite.



Figure 11: Resultats issus du pipeline d'analyse des données IRM du macaque. Haut : résultats du clustering, milieu : faisceaux composant le corps calleux, les deux hémisphères et le cervelet, bas : faisceau fronto-occipital inférieur chez le macaque.

Les IFOFs gauche et droit du macaque semblent tous deux prendre naissance dans le cor-

tex frontal supérieur. Ces faisceaux passent ensuite en profondeur dans le lobe temporal et se terminent dans le lobe occipital. En traversant le lobe temporal, les extrémités postérieures semblent se diviser en deux sous-parties différentes, l'une se connectant au lobe occipital supérieur et l'autre atteignant le lobe occipital inférieur.

Les IFOFs du macaque semblent être beaucoup plus fins que ceux de l'Homme et du chimpanzé. Le tracé des faisceaux est similaire, sauf dans la zone frontale. En effet, les extrémités frontales des IFOFs atteignent principalement le cortex frontal supérieur alors que chez l'Homme et le chimpanzé elles atteignent principalement le cortex frontal moyen et inférieur.

Les données de diffusion et anatomiques à haut champ ont permis de reconstruire les faisceaux fronto-occipitaux inférieurs gauche et droit du macaque. Ce résultat contredit les études précédentes qui n'ont pas réussi à reconstruire ces faisceaux chez le macaque, et qui supposent leur présence comme étant exclusive chez l'Homme.

Les trajets des IFOFs et les régions traversées observées sont assez similaires à ceux des humains, avec des connexions particulièrement fines dans les zones frontales. Ceci est cohérent avec des études précédentes suggérant que le lobe frontal pourrait être associé à des fonctions cognitives supérieures, absentes dans le cerveau du macaque.

#### **Conclusion - Contributions**

## Création d'un nouvel atlas complet in vivo de la substance blanche du cerveau du chimpanzé

Un premier atlas de connectivité structurelle profonde et superficielle du cerveau du chimpanzé a été conçu à partir d'acquisitions d'IRM anatomiques et pondérées en diffusion à 3T sur une cohorte de 39 sujets. Cet atlas est composé de 46 faisceaux de matière blanche profonds et de 822 faisceaux de matière blanche superficiels étiquetés qui reflètent la structure complète de la matière blanche. L'atlas des faisceaux de matière blanche superficiels et l'atlas des faisceaux de matière blanche profonds présentés dans cette thèse sont entièrement disponibles aux adresses suivantes :

- https://zenodo.org/record/7147503 Ginkgo Chauvel's left and right superficial white matter atlas of the chimpanzee brain;
- https://zenodo.org/record/7147789 Ginkgo Chauvel's deep white matter atlas of the chimpanzee brain.

Ce travail a été soumis au journal NeuroImage et est en cours de revision.

## Création d'un nouvel atlas complet *in vivo* de la substance blanche du cerveau de l'Homme

Un nouvel atlas de connectivité structurelle profonde et superficielle du cerveau humain a été construit à partir d'une cohorte de 39 sujets. Pour pouvoir établir une correspondance pertinente avec l'étiquetage cortical du chimpanzé, un nouvel atlas cortical humain a été construit à partir de la base de données HCP. Il a permis d'étiqueter 45 faisceaux de substance blanche profonds et 1365 faisceaux de substance blanche superficiels.

Les atlas des faisceaux de matière blanche profonds et superficiels présentés dans cette thèse sont entièrement disponibles aux adresses suivantes :

- https://doi.org/10.5281/zenodo.7308510 Ginkgo Chauvel's deep white matter atlas of the human brain;
- https://doi.org/10.5281/zenodo.7308606 Ginkgo Chauvel's superficial white matter atlas of the human brain.

#### Morphologie comparative des faisceaux superficiels de matière blanche entre le cerveau du chimpanzé et le cerveau humain

A partir d'une exploration visuelle des atlas des deux espèces, nous avons observé des formes communes (fibres en U, fibres en Open-U, fibres en C, fibres en V, fibres plates) et des formes propres au cerveau humain (fibres en L, fibres en 6).

Grâce à l'algorithme de l'isomap, on peut observer que dans le cerveau humain comme dans celui du chimpanzé, deux morphologies principales se distinguent, avec des fibres présentant des bords fermés et des bords plats. Ces formes moyennes plus finnement analysées montrent cinq groupes de formes moyennes en fonction de leur degré d'ouverture et de courbure.

On observe ainsi que les formes des faisceaux superficiels sont proches entre les deux espèces, néanmoins leur organisation diffère. Chez l'Homme, les faisceaux en U sont plus nombreux et plus uniformément répartis que chez le chimpanzé. Le cerveau humain semble aussi composés de faisceaux superificiels de morphologies plus variées, traduisant une possible organisation sulcigyrale plus riche.

## Morphologie comparative des faisceaux profonds de matière blanche entre le cerveau du chimpanzé et le cerveau humain

L'application des atlas de faisceaux longs chez les deux espèces a permis de mettre en évidence des différences de connectivité et de morphologie assez facilement repérables. C'est notamment le cas quant à la trajectoire des fibres des faisceaux : cortico-spinaux, cortico-ponto-cérébelleux ou arqués. L'utilisation de l'algorithme isomap, a permis de confirmer ces résultats, mais aussi d'apprécier plus finement d'autres différences morphologiques chez des faisceaux tels que le faisceau unciné ou le frontal aslants. Les plus grandes différences morphologiques obsvervées au niveau des faisceaux profonds de substance blanche semblent liées à des grandes fonctions singulières à l'Homme telle que la bipédie et une forme de language parlé développée.

Deux articles portant sur les analyses morphologiques des faisceaux superficiels et profonds entre les espèces Homme et chimpanzé sont en préparation.

## Étude du faisceau fronto-occipital inférieur (IFOF) chez le macaque Fascicularis

La dernière contribution de cette thèse est l'étude de l'IFOF, exploré pour la première fois chez le macaque Fascicularis. Ce faisceau, longtemps considéré comme absent chez le macaque, semble lié à la voie ventrale du langage. Les travaux de cette thèse ont montré que ce faisceau était présent dans le cerveau du macaque, et que sa trajectoire globale était la même que chez le chimpanzé et l'Homme. Ce faisceau semble cependant plus fin que pour les deux autres espèces et présente des connections frontales différentes. Cela peut être lié à l'évolution des régions frontales chez les primates et aux capacités cognitives sous-jacentes dans ces aires telles que : la planification, le raisonnement, la résolution de problèmes, le contrôle des impulsions et la régulation des émotions.
# Chapter 1

# **General Introduction**

# 1.1 Context and motivations

The term singularity is defined as "an exceptional feature that distinguishes itself, whether it is good or bad". To what extent are we singular as humans? There are two different spectrum by which we can try to answer this question, and there is no simple answer. Our place in the animal reign is incontestable, in both the fascinating and terrible aspects. If we look at ourselves through the prism of the history, without trying to go far back in time, we observe that we are driven by primitive behaviors : violence, territorial wars, male expression of superiority, extreme predating, self destruction. Paradoxically, if we look at ourselves by the prism of human cognitive abilities, we are singular by our creativity, by our developed language faculties, by our adaptation to hostile environment, by our empathy, and by our incredible curiosity that leads sometimes to existential questions that tried to be answered in hundred paper manuscripts.

If we are not sure of what makes us singular, we are as unable to furnish a good definition of the human intelligence and uniqueness. This is the idea behind the work presented here, even if it may represent only one single piece of the puzzle.

Humans are the fruit of a long and complex brain evolution. A way to better appreciate the ancient or evolved Homo sapiens brain characteristics relies on comparative investigations with homologous species. Because the Human kind phylo-genetically separated from the Pan kind (common chimpanzee) around 7 to 10 million years ago, chimpanzees remain our closest living hominidae relative, making it a pertinent model for brain neuro-evolution studies. Contrary to the macaque species, few studies have been performed in vivo on chimpanzees due to its proximity with humans which pushes ethical committees to prevent their use for research.

Understanding the singularity of the primate brain is an exciting field of research aiming at better understanding the factors driving the high level cognitive abilities of these rare species that fascinate us. Recent advances in MRI have recently made it possible to bring out new perspectives to compare the Chimpanzee and Human brains.

This thesis project is intended to focus mainly on understanding the common features or differences between the anatomical connectivity of the chimpanzee brain and the human brain.

# 1.2 Thesis organization

This thesis is made of two parts. The first one is the background part that reviews the general frame of the primate brain evolution (Chapter 2), the human brain anatomy as it is known nowadays (Chapter 3) as well as the methods and results of the exploration of the non-human primate brain, and especially the chimpanzee brain (Chapter 4). The last chapter of this part (Chapter 5), aims to introduce the basic principles of diffusion imaging, from the basic physic principles to its interest in the study of the cerebral white matter connectivity.

The second part dives into the exploration of the singularity of the structural connectivity of the chimpanzee brain, compared to the human brain.

In order to better appreciate these common or different traits, new atlases of deep (long) and superficial (short) white matter fiber bundles have been created for both the human and the chimpanzee brains (Chapter 6). The chimpanzee white matter bundle atlas was established thanks to a cohort of 39 chimpanzees (with anatomical and diffusion MRI data) stemming from the Yerkes National Primates Research Center (YNPRC, Atlanta, Emory University) shared by the Pr. William Hopkins (MD Anderson cancer center, Department of comparative medicine, Bastrop, Texas). The human white matter bundle atlas was built relying on a cohort of 39 subjects (with anatomical and diffusion MRI data), intentionally matching the chimpanzee cohort in terms of number of subjects and gender.

The two species atlases were built following a dedicated diffusion MRI processing pipeline using an advanced fiber clustering algorithm adapted for the two species.

Following the creation of these novel atlases, a comparative study of the morphology of deep and superficial white matter bundles between chimpanzee and human brains was conducted (Chapter 7). The choice was made to use the isomap algorithm, usually applied to sulci investigations, with the help of the developed pipeline from Dr. Marco Pascucci (BAOBAB Unit, NeuroSpin, CEA). The use of this algorithm was different regarding deep or superficial white matter bundles.

The final chapter of this thesis (Chapter 8) concerns the investigation of one of the major association white matter fiber bundles called the "inferior fronto-occipital fasciculus", in the *Macaca Fascicularis* species. This subject was obtained from the collaboration with the Pr. Christophe Destrieux from the university of Tours and was scanned at ultra-high field MRI (11.7 Tesla).

# Part I Background

# Chapter 2

# Evolution of the primate brain

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Figure 2.1: Evolution of the hominid brain, from [Roberts 2018]

### 2.1 Introduction

This chapter presents the background concerning the evolution of the primate brain, necessary to understand the scope of the thesis. A first part presents the primate lineage and the evolutionary theories depicting the rich and fascinating diversity of the primates and their evolution, leading to the human species. The second part focuses on brain evolution, starting from what is known concerning vertebrates and primates. This section ends with the presentation of the different methods used to explore the neuro-evolution of primates, notably the use of fossils, the endocast investigations, and the possible cognitive implications behind this brain evolution.

# 2.2 Primate lineage and evolutionary theories

### 2.2.1 Primates evolution

**Evolution and adaptation** Two concepts have to be integrated to understand the diversity of the primates : adaptation and evolution.

A simple way to speak about evolution is to say that our world is highly creative when it comes to conceiving or modifying organisms.

The evolution is the process by which organisms change over the course of time and generations and one ancestor can engender many descendants. The evolution is responsible for species specialisation and can be driven by natural selection or genetic drifts.

The adaptation has for consequences the variability of an individual in physical characteristics. Most of the times, the adaptations are related to a physical feature that is needed in the environment of the individual for a particular function. It explains that some primates display long and strong arms adapted for bracing the trees of the forest, some have grasping hands and feet with a particular pattern of toe placements. Others, like the Capuchin, possess a tail that can also grasp the trees branches.

**Species** The teeming population on our planet has forced scientists to develop methods of classification. The first and most intuitive one consists in classifying the individuals with respect to their most shared characteristic. This system is still used today since it was created by Carl Linnaeus. The Latin language is used for this classification relying on phenotypes, and every species is attributed a unique two-word Latin identifier comprising genus and species (ex : *Homo sapiens*). "Species" is the consecrated term that is used to describe the organization of distinct spread and variations of organisms. Nowadays, more than 500 primate species from 16 different families are known [Estrada et al. 2017].

The primate family tree, although starting from a common ancestor (around 80 million years ago), displays a high diversity of phenotypes that were classified using DNA evidence and fossil records. Even if the current advanced DNA and fossils records coupling analyses are sharp, they can only provide an estimate of the date of the split between different cousins, with sometimes multiple millions of years.



Figure 2.2: Phylogenetic tree of the diversity of the primates [Gilbert, Lehman, and Fleagle 2006]

The heterogeneity of primates started with the split between the Strepsirrhines and Haplorrhines around 68 million years ago [Finstermeier et al. 2013]. The Strepsirrhines can be subdivided into two subgroups corresponding to the Lemuriformes and the Lorisiformes, whereas for Haplorrhines, the subgroups are more diverse, with a first split between the Tarsier and Anthropoids around 64 million years ago. The Anthropoids order can further be subdivided into the American monkeys and the Afro-Eurasian primates. 32 million years ago, this branch split in its turn to give birth to the order of the Afro-Eurasian monkeys (Colobinae and Cercopithecinae) and to the order of the Apes, further composed of the "small apes" (Hylobatidae) and great apes (Hominidae). If humans do share very common phenotype features with small apes, one of the major distinctions is the fact that the great apes do not display a tail.

Primates are very heterogeneous in their characteristics, whether it is the skull or the soft tissues. This is due to the adaptation to their different environments. Some particular features are common to all :

• strong and powerful arms and shoulders, important for brachiation, allowing a high degree of movement,

- binocular visual system, with a color vision,
- grasping hands and feet, with opposable thumb,
- some primates would have a tail that would also help them in grasping or equilibrium, while others like the great apes don't have this characteristic.

**Diversity of primates** The order of the primates is highly various.

In the world as it is known now, the non-human primates territories are quite limited. This can be explained by climate and tectonics that influences the primates' evolution and migration [Gilbert, Lehman, and Fleagle 2006]. Unfortunately, today, the most striking cause of primates dispersal, extinction and reduction of their territories is the expansion of their cousin's territories *e.g.* the modern human primate [Estrada et al. 2017]. As can be seen in (Figure 2.4), the primates occupation is concentrated in the lower hemisphere of the globe.



Figure 2.3: The geographic distribution of primates today compared to that during the two warmest times of the past 55 million years: the Eocene Climatic Optimum, and the mid-Miocene Climatic Optimum [Gilbert, Lehman, and Fleagle 2006]



 $\label{eq:Figure 2.4: Geographical occupation of nowadays non-human primates, freely adapted from website "https://slidetodoc.com/introduction-to-the-living-primates-what-is-a/"$ 

**The great Apes : Hominids** The great apes or hominids (hominidae) consist of eight species : the three orangutan (Pongo) species (the Bornean, Sumatran and Tapanuli orangutan), two gorilla species (the eastern and western gorilla) and two chimpanzee (Pan) species (the chimpanzee and the bonobo) as well as the last of the living Homo sapiens. While the orangutan and the gorillas separated from the other apes 15 and 8 million years ago, the last common ancestor of humans and chimpanzees lived until about six million years ago [Mittermeier and Wilson 2013].

#### 2.2.2 Human evolution in the primates order

If humans are classified in the order of the great apes, it is instinctively admited that this species stand out from the others.

A crucial difference between homo species and the other great apes is bipedal posture. Indeed, this implies strong modification of the skeleton, including the spine, the legs, the pelvic bones, the emplacement of the toes and the postural place of the skull. The other great apes, such as chimpanzees and orangutans, move by knuckle walking most of the time.



Figure 2.5: The great apes skeletons from [Roberts 2018]

Research on the thin frontier that separates us from the great apes is quite recent. The split between chimpanzees and humans species occurred around 6 million years ago.

Each decade brought new discoveries about what was considered to be a human trait and finally appeared to be common with other great apes. Indeed, the use of tools which was long considered as being proper to human intelligence, and described as an adaptive use of what it present in nature being diverted for a particular purpose, has been significantly challenged. Chimpanzees for example use grass stems or sticks to extract the termites from the ground. They also use leaves as sponges to drink the water in holes.

However, the Human species "Homo" have been thought a fascinating process of evolution. The first piece of evidence of the "birth" of the Hominid drives us back 7 million years ago. While nowadays the Homo sapiens species is the only one present, millions of years ago more than one Homo species cohabited.

It may be hard to understand this by looking at a modern human and a chimpanzee, but humans are genetically closest to them as they are to gorillas. Indeed, the Homo genetic patrimony differs from the one of the chimpanzee of about one percent, which is a lot, from a genetic point of view, but few at the scale of species evolution. One of the main challenges of paleoanthropology is understanding what the common ancestor of humans and chimpanzees looked like. This is why the tracing of the way from this common ancestor to the modern human have relied on genetics and fossil records.

From the fossils investigation, it appears that the first hominin appeared in Africa between 8 and 6 million years ago.



Figure 2.6: Hominin genealogy from Hominid phylogeny from The Tangled Bank link : https://evolution.berkeley.edu/what-are-evograms/the-emergence-of-humans/

Starting with the fact that humans are apes, the different hominin identified along with their existence in time are depicted on Figure 2.6. By looking at the branch deriving towards *Homo Sapiens*, a series of sequential and crucial changes along the way through evolution can be observed :

- the adaptation for bipedal walking, a change in dentition by having smaller canine teeth. It occurred around 7 million years ago, with *Sahelanthropus Tchadensis* species, the oldest known of hominids, which is the only specimen of this genus. His fossil was found in Chad, and was first known by the name "Toumai". With *Orrorin Tugenensis* and *Ardipithecus*, they form the group called the "very early hominins";
- enlarged cheeks, teeth and jaws, evolved approximately 5 million years ago with Australopithecus, who got extinct around 2 million years ago. He is considered as the first "early hominin". His genus is particularly important since our modern genus "Homo" seems to have evolved from the Australopithecus about 2 million years ago. This species is key in the comprehension of our evolution since it possesses both characteristics from non-human great apes and modern humans : the sexual dimorphism was more pronounced than for

modern humans, males were 50 percent larger than females (as for gorillas and orangutans), its brain size compared to its body size was smaller than modern humans. However, *Australopithecus* was biped and displayed comparable footprints as modern humans [Website n.d.]. The *Australopithecus* taxon was abundant since different versions of the genus were found. One famous *Australopithecus* kind *afarensis* that was discovered in the Afar region of Ethiopia is the commonly known "Lucy", which has nowadays the most complete Australopithecus fossil record;

The Human modern genus named "Homo" first appeared between 2.5 and 3 million years ago. Their fossils depict a number of features closer to the modern human than the non-human primates, such as the enlargement of their brains, and less prograthic jaws;

- greater enlargement of the brain, verticalisation of the face, disappearance of the snout, fingers capable of precision grip, development of the construction and use of simple tools made of stones with *Homo Habilis* which means *skilled man*, due to the tool-use of the species between 3 and 2 million years ago. Stone tools were often discovered close to their fossils. While depicting modern human features, *Homo Habilis* retained some phenotypes of the previous hominin species such as long arms;
- approximately 1.8 million years ago, appeared the *Homo Erectus*, believed to have for origin East Africa and to be the first to migrate out of Africa (fossils of the same genus were found in India, Java, China and Europe). This species are believed to have lived until 50,000 years ago and show an increasing number of features close to the ones of the modern humans, with a sexual dimorphism, less prominent than the previous species (males are 20 to 30 percent larger than females, close to the feature of modern humans), smaller jaws and cheeks, elongation of the legs and arched feet (walking for long distances, running), enlargement of the brain which reaches 775–1,100 cubic centimeters (1,130–1,260 for modern humans). This species is believed to be the first one to have used fire. *Homo Erectus* means : the man who stands upright.

The birth of Homo sapiens :

- some species are believed to have evolved from *Homo erectus*, with a progressives increase of brain size to reach a size similar to the one of modern humans (1,200 to 1,400 cubic centimeters). It is the time of the sophistication of tools, especially for hunting with *Homo Heldelbergensis*, *Homo Rhodesiensis* and *Homo Neanderthalensis* around 500,000 to 1 million years ago. Some of these species were still there 30,000–10,000 years ago. By looking at the time frame, this implies that they coexisted at the same time as the modern humans, but were anatomically slightly different due to a thick skull, a prominent brow ridge, and a receding chin;
- large brain, small face and rounded skull, development of art and symbolic thought, developed language with *Homo sapiens*, meaning the *thinking man*.

# 2.3 Brain evolution

### 2.3.1 Neuro-evolution of vertebrates

Historically, it was believed that individual brain growth was largely dependent on the demands from the living environment.

In his pioneer studies about brain evolution, Jerison noted that primates have significantly larger brain sizes related to their body size than other vertebrate species [Jerison 2012]. He also noted that different groups in different taxonomic classes - including mammals, birds, amphibians and reptiles - had different body to brain size ratios.

This implicit relation between brain size and body size has theoretically long been considered as related to species intelligence. More objective and scientific studies have then demonstrated that this assumption was not true.

A second assumption related to brain size and folding was that folding degree also reflects the species intelligence. This hypothesis should be taken with caution : while it is not meaningless, it however rises the question of what is intelligence ? Considering the cortical folding of the brain, the dolphin or the elephant display a more folded brain than humans (see figure 2.7). Maybe the concept to be taken into account is not intelligence but intellectual capabilities, which reflects more the natural and variability of gifts from nature attributed to certain species, of which others are devoid.

Researchers have been investigating what could be the particular environmental features driving the brain size of the primates and have found correlations with ecological and lifehistory variables [Tim H Clutton-Brock and Harvey 1980], [Harvey, T. Clutton-Brock, and Mace 1980], [Eisenberg and Wilson 1981] and the correlation with the evolution of "complex" behaviors [Egan and Funk 2006]

Some studies have also focused on the size of some particular parts of the brain. Indeed, between different species, there may not be a huge difference in brain size, however the brain may rearrange differently. If it is assessed that the brain is composed of different areas, corresponding to distinct brain functions, it is not surprising to find diversity between different species of the same brain size. This seems to give insights to the species cognitive differences, whether in birds [Lefebvre et al. 1997] and bats [Pitnick, Jones, and Wilkinson 2006], or primates [Reader and Laland 2002].



Figure 2.7: Large brains appear several times in the mammalian radiation. Example species are illustrated for each major mammalian group. The mammalian radiation is based on the findings of [Murphy, Stanyon, and Stephen J O'Brien 2001] and [Kaas 2013]. Brain images are from the University of Wisconsin and Michigan State Comparative Mammalian Brain Collections (www.brainmuseum.org).

### 2.3.2 Fossil records and evolution of the primate brain



Figure 2.8: The primate brains, and relative brain size cross-species comparison. a) 34 threedimensional digital brain reconstructions from the brain catalogue [Heuer et al. 2019] b) body size and weight comparison across apes c) brain and body weight scatter plot comparison [Jerison 2012]. Note that the red circle indicates human primates who deviate from the linear relationship existing between body and brain weight. Image taken from [Friedrich et al. 2021]

#### 2.3.2.1 Brain expansion

The study of the differences in the primate brain size has been a subject of intense interest in the scientific community [Powell, Isler, and Barton 2017]. Evolutionary increases in brain size is assumed to bring enhanced cognitive abilities [Healy and Rowe 2007]. The enhancement of brain size of species is a hard subject of investigation, and can be explained by different causes and yield various interpretations, whether ecological or social [Barton 2006].

Ecological causes imply the living environment of the species with the effect of diet [DeCasien, Williams, and Higham 2017], home range size, terrestrially and activity period. All of these can have different impacts on the brain, in terms of information, memory, visual and olfactory processing.

Social causes suggest that the variation in terms of brain size is due to social interactions, in the cognitive demand in managing relationships inside a group of individuals [Humphrey 1976] [Dunbar 1992].

**Bones of the skull - endocasts -** Human fossils are very rare, and a well preserved cranial specimen even remarkable. The first investigations that were made to try to understand the history of the primate human brain evolution were based on fossil records, using endocasts [Holloway and De La Costelareymondie 1982]. The endocasts are known to contain "imprints" of brain folding and vascular network. Indeed, they provide a 3D rendering of the brain anatomy that typically embed "imprints" left by the different sulci and veinous system on the surface of the endocast [Falk 1980], although they cannot provide information about deep brain structures.



Figure 2.9: 3d rendering of the investigation using endocasts processing. The cranial box contains imprints of the brain sulcation. Using dedicated research tools, it is possible to reveal the brain casting, source : https://www.ameliebeaudet.com/research/brain-evolution/. In this case, the brain studied is one Australopithecus Africanus specimen

Different studies made on endocasts revealed that the total brain volume varied during primate evolution [Tobias 1971], [Holloway 1973].

During 3.5 million years of *Homo* evolution, the brain size increased from 450 cm3 (*Australopithecus*) to 1350cm3, with a prefrontal cortex (involved in planification) being larger compared to other species [Brodmann 1909, Deacon 1990].

The human brain is approximately 3.5 times larger than the one of chimpanzees, and can be grossly represented as a scaled-up great ape brain [Schoenemann 2006], [Herculano-Houzel 2012]. However, it remains an over-simplistic interpretation if we consider the real complexity of the human brain in terms of shape [Aldridge 2011], degree of gyrification [Rilling and Insel 1999], or sulcal pattern [Gardner 1950].

The observations that can be made using endocasts are nevertheless pretty incomplete since it is not possible to draw any conclusion about the inner structure of the different brains. However, endocasts remain the only available investigative tools to explore the anatomy of species that are now extinct. Still, they allow the analysis of the endocranial characters and volumes [Xiujie, L. Wu, Norton, et al. 2007], and allow to draw advanced observations and hypotheses.

First, by looking at the brain of extinct hominids and the current human brain, changes in gross cerebral morphology appear obvious. The difference between endocranial capacity and the actual modern human brain is about 5 percent. The absolute brain size is usually expressed by the measure of weight and volume. "Sahelanthropus Tchadensis", considered as the possible oldest hominid, present on Earth between 7 and 6 million years ago displayed a cranial capacity of about 400ml (close to the actual chimpanzee, of the genus Pan). The cranial volume of "Australopithecus" was quantified between 400 to 500 ml, for "Homo Habilis" the cranial volume is 510 to 725 mL ; for "Homo Erectus" the cranial volume is between 600 and 1251 ml, which implies an increase of 25 to 40 percent. The "archaic" Homo Sapiens (Homo Heldelbergensis, Homo Rhodesiensis and Homo Neanderthalensis) displayed brain sizes between 1100 and 1500 ml, which is close to the modern Homo genu brain volume. (between 1300 to 1750ml). The idea that the hominid brain linearly increased in volume is wrong. Indeed, studies suggest that brain size has decreased : during the Holocene period, the European cranial volume decreased by 95 to 65 ml for males and 74 to 106 ml for females.

If endocasts bring out information about the gross anatomy of the hominid brain in size/volume, it is now possible to investigate some finer details of certain brain regions when they can be relatively well identified on the endocast. Indeed, some brain reliefs and folds such as the coronal suture, the lambdoidal suture and the lateral sulcus give good indication of the position of the different brain lobes.

For example, the investigation driven on the frontal lobe, has shown that the frontal lobe of "Australopithecus" is larger than the one of the common modern apes, opposite to the occipital lobe [Falk, Redmond Jr, et al. 2000]. With evolution, the frontal lobe shape tends to be tall, spherical and large. The underlying frontal lobe morphological rearrangement, especially in what concerns Broca's language area [Grimaud-Hervé 1997] is key to understand the possible trajectories of developments of the modern human major cognitive functions.

With evolution, the parietal lobe tends to be wider and taller [Grimaud-Hervé 1997]. However, only few hypotheses exist concerning this particular lobe since the reliefs of the brain do not print very well and leave few imprints on the skull.

The occipital lobe seems to decrease in surface as brain size increases. This process is described as being the result of the progressive rotation of the "posterior complex" under the cerebral mass [Falk, Redmond Jr, et al. 2000], [Xiujie, L. Wu, Norton, et al. 2007]. This implies that early hominid had a bigger, posterior located, occipital lobe with a developed primary visual cortex, a pattern that can still be seen nowadays in great apes such as gorillas or chimpanzees. Indeed, marking the frontier of the visual cortex, a controversial sulcus called "lunate sulcus" due to its shape, imprints.

As for the occipital lobe, the cerebellum followed the morphological dynamic brought by the brain rearrangements. While appearing posterior in early hominids, this structure slowly moved under the occipital lobe, and then the parietal lobe across time with evolution.

#### 2.3.2.2 Cognitive implications

It is nowadays well accepted that the human brain is asymmetric. The increase of the brain complexity in time, notably its folding, is allegedly accompanied by the development of hominid cognitive abilities such as language and tool-use. The observed enlargement of the frontal lobe known to be the siege of higher cognitive functions such as planification, voluntary motor coordination, and language is then not surprising and could be explained by a growth of the different human cognitive functions. Another interesting point is that the acquisition of higher cognitive abilities such as language or handedness resulted in the asymmetry of our brain. This asymmetry of structures has been observed on endocasts from *Australopithecus*, *H. Habilis*, *H. Erectus*, *Neanderthals*, and *H. Sapiens*.

# 2.4 Conclusion

The diversity of the primates is staggering, especially if one keeps in mind that their populations, and especially the one of the great apes, are constantly decreasing. However, one species of primate stands out after thousands of years of evolution : the one of the genus *Homo*. The last and only living species of humans is called Homo Sapiens, the thinking man. Each new discovery made on the evolution of the non-human primate brain opened the way to new questions, gathering together neuroscientists, anthropologists, archaeologists, primatologists or behaviorists for decades of research. Trying to understand our own evolution is far from obvious. This is why the scientific community relies not only on the study of fossils, but also on the characteristics of the human's closest living primates. In order to be able to rely on concrete and relevant elements of comparison, several criteria of classification were elaborated: phylogenetic trees, studies of the shape of the skulls, and studies based on behavior. There will always be a part of mystery in the humankind evolution, *Australopithecus* or *Homo Erectus* to name a few, were not predetermined to evolve and *Homo Sapiens* is only a branch of a once very diverse humanity. It is this process of change to which our species has been subjected that has shaped its brain as it is known today.



Figure 2.10: Drawings in the Lascaux caves, dated at around 17,000 years ago.

# Chapter 3

# The human brain anatomy

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Figure 3.1: The human brain skull, sketch of Leonardo Da Vinci (1452-1519)

# 3.1 Introduction

This chapter presents the global organisation of the human brain as is most recently known. There are hundred possible ways to describe the human brain, from the macroscopic scale to the microscopic scale.

This chapter attempts, in a first part, to describe the macroanatomy of the human brain, with sections concerning the protective structures of the brain, the ventricular structures, and the organisation of the brain lobes and their functions. Another part aims to describe the gray matter, firstly with regards to the cortex, and secondly with regards to the deep structures such as the diencephalon, the basal ganglia, the brainstem and the cerebellum. This chapter then addresses the brain white matter with deep and superficial white matter structures. The second part of this thesis aims to describe the microanatomy of the human brain with the description of the brain cyto-architectural components : neurons and glial cells.

# 3.2 Brain architecture

### 3.2.1 Brain lobes and functions

The nervous system is composed of the central nervous system (CNS) which goals are to integrate, analyse and create an appropriate answer to our environment, and of the peripheral nervous system (PNS) which goal is to transport the information. The PNS is composed of the motor nervous system (for skeleton muscles) and and autonomous nervous system (cardiac smooth muscles and glands). The CNS is composed of the brain and the spinal chord, and controls many of the body's functions including sensation, movement, awareness, decision making and memory.

### 3.2.1.1 Gross anatomy organisation

The largest part of the brain is known as the cerebrum, responsible for cognitive functions that neuroscientific community has been aiming to map accurately for centuries.

**Protecting the brain -** The brain is enclosed in a skull, using protective structures known as the meninges. The meninges are 3 membranes, ensuring a mechanical and infectious protection of the brain including :

- the dura mater : from the Latin words meaning "hard mother", superior layer of the meninges found directly under the bones of the skull. It is composed of dense connective tissue, with an essentially mechanic role of protection;
- the arachnoid mater or the arachnoid membrane : the second layer of the meninges, a transparent membrane looking like a spider's web made up of collagen and elastic fibers. In this space circulates the cerebrospinal fluid (CSF) and blood capillaries;
- the pia mater: from the Latin for "soft mother", is the innermost layer of the meninges. This membrane follows the brain surface in all convolutions and ensures the passage of nutrients from the vessels of the subarachnoid space by diffusion.



Figure 3.2: Meninges scheme and organisation, freely adapted from website "https://slideplayer.com/slide/8354135/".

These protective structures do not only provide a mechanical protection but also a chemical protection from foreign elements. The entire CNS is immersed in a liquid substance called cerebrospinal fluid (CSF), forming a supplemental layer of protection for the brain from potential damages and participating to the glymphatic system allowing brain tissues to eliminate biological waste.

**Ventricular structures** - The brain owns four cavities called "ventricles", filled with CSF, allowing the inner nutrition of the brain. The CSF is secreted by the choroid plexuses, a set of cells hosted inside the ventricles.

- 1st and 2nd ventricles (lateral): symmetric and paired, they supply the brain hemispheres with CSF; they follow the inner structure of the brain thanks to their anterior temporal/occipital horns;
- 3rd ventricle : supplies the base of the brain, in the diencephalon;
- 4th ventricle : supplies the cerebellum.

These ventricles are all connected to one another : between the 1st and 2nd ventricles and the third ventricle by the inter-ventricular foramen; between the third and fourth ventricles by the aqueduct of Sylvius (see figure 3.3).



Figure 3.3: Organisation of the brain ventricles, on frontal and lateral views, adapted from website "https://quizlet.com/239148256".

**Lobes of the brain** - The cerebrum is divided in two parts, left and right, called "hemispheres", composing 85 percents of its weight. These hemispheres are quasi symmetrical and each hemisphere is divided in sub-regions called "lobes" referring to the bones of the skull that cover them. They are also delineated using surrounding sulci. Even if a complete detailed functional mapping of each lobe is not available yet, the knowledge of their functional role and of the localisation of functional areas has significantly progressed since the introduction of brain imaging tools (see figure 3.4):

- the frontal lobes : responsible for higher cognitive functions such as planification, decision making, problem-solving, attention, emotional and behavioral control, personality. They are also involved in speech production and body movement. Particular areas to note in the frontal lobe are the motor cortex for body movements ; the prefrontal cortex for executive functions (problem-solving) and Broca's area involved in language functions, speech production;
- the parietal lobes : process the entirety of the sensory information. The motor system and sensory system are close from one another, on each side of the Rolando scissure. Their proximity allows a good communication;
- the occipital lobes : quasi exclusively devoted to visual processes such as visual interpretation, object and facial recognition, distance perception;
- the temporal lobe : responsible for hearing, language comprehension, learning and memory. A particular area of the temporal lobe is Wernicke's area, involved in language comprehension.

Two other great structures can be considered as lobes :

• the insular lobe or insula is a cortical region hidden in lateral view by the temporal lobe. This region is involved in taste analyse and in visceral functions, • the limbic lobe is subdivided into two limbic lobes: the superior limbic lobe (lobus limbicus superioris) and the inferior limbic lobe (lobus hippocampi or lobus limbicus inferioris).



Figure 3.4: Functional areas of the cerebral cortex. Adapted from https://dana.org/article/neuroanatomy-the-basics/

The brain also includes a vast vascular system. This network will not be described further since it is not of major interest for this thesis.

#### 3.2.2 Gray matter

#### 3.2.2.1 The cortex : cortical folding and brain mapping

**The Cortex** - The cortex is the main part of the brain as it represents 80 percent of the total volume of the encephalon and covers a surface of  $2500 \ cm^2$ . The cortex is subdivided into two structures : the neocortex and the allocortex. The neocortex contains six layers of "gray matter" with specific cellular arrangements and is the tissue observed while looking at the external surface of the brain. This neocortex is specific to mammals and is the most recent developed cortical structure on an evolutionary point of view. The allocortex is older and possesses three to four cortical layers. It is not proper to mammals as it can be found in birds and reptiles. The allocortex plays a fundamental role in emotional processes and memory.

The cortex composing the neocortex is a thin neural tissue of a few millimeter thickness (between 1 and 4.5 for the adult brain [Fischl and Dale 2000]) that recovers the brain hemispheres. Anatomically, the cortex is folded in order to be able to fit in the cranium. This implies that humans are a gyrencephalon species, in opposition with lissencephalon species such as rats or mice that display a smooth cortex. The folds consist of many deep grooves called sulci and raised areas called gyri. On its surface, the brain is composed of different cortical areas. A cortical area

is defined as the set of gyri and sulci of a same lobe, ensuring a proper function. Highly visible gyral differences pushed neuroanatomists to propose maps of the cortex.

In 1543, the anatomist and physician André Vésale published the first atlas of the brain. Then in the middle of the 19th century, the German neurologist Franz Joseph Gall introduced the notion of "phrenology" that attempts to explain the localization of brain functions using the shape of the skull, supposed to undergo deformations during brain development. This work marks the beginning of research on the localization of certain functions in the cerebral cortex. Thus, at the end of the 19th century, the physician, neuroanatomist and French anthropologist Paul Broca discovered the speech center that now bears his name by studying the brains of aphasic people deprived of speech.

The beginning of the 20th century was marked by a growing interest in the construction of anatomical and functional atlases of the human brain. In 1909, the German neurologist Korbinian Brodmann was the first to link brain function and structure at the cellular level, and he established the first atlas of functional areas based on the architecture of the cells. By studying brain slices taken from deceased people, he showed that the cortex is divided into several layers and defined 52 areas to which are attributed specific functions such as motor skills, vision or hearing. Several neuroanatomists proposed new atlases built from similar methods, for example Alfred Campbell in 1907, Constantin von Economo and Georg Koskinas in 1925, the Russian School with Semen Sarkisov in 1949, and Percival Baley and Gerhardt von Bonin in 1951.

New advances in neuro-imaging, such as PET scans and MRI, brought new methods of brain atlas conception, and facilitated the transition from paper to digital brain atlases such as, in 2006, the Desikan atlas [Desikan et al. 2006], in 2010, the Destrieux atlas [Destrieux et al. 2010] and the Glasser atlas in 2015 [Glasser et al. 2016].



Figure 3.5: Different brain maps, A. Brodmann 52 cortical areas from [Brodmann 1909], adapted from [Nieuwenhuys and Broere 2020], B. Desikan-Killiany cortical atlas from [Desikan et al. 2006], C. Destrieux cortical atlas from [Destrieux et al. 2010], lateral view on the left and medial view on the right

Despite the controversy, Brodmann's areas remain the best known and most frequently cited cytoarchitectural organization of the human cortex, these areas are corresponding to primary or secondary (associative) areas :

- primary areas : they are in direct link (afferent or efferent) with the different body structures, handling the basis functions (sensory, primary motor area, auditory, visual). They consist in areas 1,2,3 (primary somatosensory cortex), area 4 (primary motor cortex), area 17 (primary visual cortex), area 22 (primary auditory cortex);
- secondary areas : they must be associated to primary areas to work. They are used to plan, program and understand. They allow the contextualisation of information.

**The sulcal pattern -** The brain convolution called "sulci" are a relatively recent subject of investigation in research. Indeed, in the human brain, despite the fact that every brain is different and displays its own morphology, some particular sulcation features are common to all brains. This allowed brain neuro-anatomists to name and to explore the putative links between the inter-individual sulcation variations and neurological disorders [Borne et al. 2021].



Figure 3.6: Organisation of the brain sulci, from Dojat, Pizzagalli, and Hupé 2018, F.C.L.a: anterior lateral fissure; F.C.L.p: posterior lateral fissure; F.C.L.r.asc: amending remus of the lateral fissure; F.C.M.ant.: calloso-marginal anterior fissure; F.C.M.post.: calloso-marginal posterior fissure; F.Cal.ant.-Sc.Cal.: calcarine fissure; F.Coll.: collateral fissure; F.I.P.: intraparietal sulcus; F.I.P.Po.C.inf.: sup. postcentral intraparietal sup. Sulcus; F.P.O.: parieto-occipital fissure; INSULA: Insula; Occipital: occipital lobe; S.C.: central sulcus; S.Call.: subcallosal sulcus; S.Cu.: cuneal sulcus; S.F.inf.: inferior frontal sulcus; S.F.inf.ant.: anterior inferior frontal sulcus; S.F.int.: internal frontal sulcus; S.F.inter.: intermediate frontal sulcus; S.F.marginal.: marginal frontal sulcus; S.F.median.: median frontal sulcus; S.F.orbitaire.: orbital frontal sulcus; S.F. polaire.tr.: polar frontal sulcus; S.F. sup.: superior frontal sulcus; S.Li.ant.: anterior intralinqual sulcus; S.Li.post.: posterior intra-lingual sulcus; S.O.T.lat.ant.: anterior occipito-temporal lateral sulcus; S.O.T.lat.int.: internal occipito-temporal lateral sulcus; S.O.T.lat.med.: median occipito-temporal lateral sulcus; S.O.T.lat.post.: posterior occipito-temporal lateral sulcus; S.Olf.: olfactory sulcus; S.Or.: or bital sulcus; S.Pa.int.: internal parietal sulcus; S.Pe.C.inter.: intermediate precentral sulcus; S.Pe.C.median.: median precentral sulcus; S.Pe.C.sup.: superior precentral sulcus; S.Po.C.sup.: superior postcentral sulcus; S.Rh.:r hinal sulcus; S.s.P.: sub-parietal sulcus; S.T.i.ant.: anterior inferior temporal sulcus; S.T.i.post.: posterior inferior temporal sulcus; S.T.pol.: polar temporal sulcus; S.T.s.: superior temporal sulcus; S.T.s.ter.asc.ant.: anterior terminal ascending branch of the sup. temp. sulcus; S.T.s.ter.asc.post.: posterior terminal ascending branch of the sup. temp. sulcus.

#### 3.2.2.2 Deep gray structures

During brain neuro-development, the inner structures of the brain grow sequentially over time (see figure 3.7). Around 25 days of fetal development appears the neural tube, that gives birth, at around 40 days, to the forebrain, midbrain, hindbrain and spinal cord. The forebrain is the precursor structure of the telencephalon and diencephalon, that respectively further differentiate into the cerebral hemispheres and thalamus/hypothalamus after 50 days of development. The hindbrain is later differentiated into the cerebellum, pons and medulla. All structures are in place after 100 days of fetal development.



Figure 3.7: Development of the brain structures from 25 days to 100 days, at the top : brain formation, on the bottom : final brain organisation from immature structures to mature brain source : https://fmedecine.univ-setif.dz/ProgrammeCours/anatomie.DIENCEPHALE-converti.pdf

**Diencephalon** The diencephalon, also called "interbrain", has a key role in the integration of the sensory and motor information with its two main structures : the thalamus and the hypothalamus.

The thalamus, more voluminous than the hypothalamus, plays a role of relay and is in charge of filtering the sensorial information at destination of the cerebral cortex.

The hypothalamus is under the thalamus, and is present in both hemispheres. Its role is essential as it controls the production of the hormones thanks to the hypophyse. The hypothalamus has a great role in behavioral control, particularly in what concerns sleep, alimentary feeding behavior, thermoregulation or movement.

Involvement of the diencephalon in the limbic system - A particular system for which the components of the diencephalon are particularly crucial is called the limbic system. Indeed, described for the first time by Thomas Willis in 1664 [Willis 1973], this system is one of the most important circuits of our brain and participates to the determination and the characterisation of our emotions and our interactions with the environment. It determines our pleasures and our fears. Whatever the behavior, the memory is always involved. This system is composed of : the mammilary bodies, the hippocampus, the olfactory bulb, the amygdala, the septum, the fornix, the cingular cortex and the thalamus. The utility of this system has been established first by comparative physiology. All structures of the limbic system are in the heart of the brain and are phylogenetically conserved. The central structures are ancestral. The amygdala is responsible for the evaluation and the emotional importance of events. It is situated in the temporal lobes, at the end of the hippocampus. The septum is responsible for positive emotions. Globally, the functioning of the limbic system is as follows : the neocortex (prefrontal cortex mainly, center of consciousness, will and decision making), sends information to the cingular cortex that will transmit the information to the hippocampus. The hippocampus will then adjust the answer and send signals to the amygdala to create an emotional expression and trigger the appropriate answer. The behavioral response is due to a modulate of the vegetative system by the hypothalamus. The hypothalamus sends information to the thalamus that distributes the information to the cerebral hemispheres. The amygdala has a double role, because it also receives information from the cortex and is able to act on the hypothalamus to modify the vegetative nervous system. This will modulate it according to the importance given to the different emotions.



Figure 3.8: The limbic system. Adapted from Catani, Dell'Acqua, and De Schotten 2013, At the top : diagrammatic representation of the limbic system and tractography reconstruction of its main pathways, at the bottom : proposed functional-anatomical division of the limbic system into three distinct but partially overlapping networks and corresponding clinical syndromes.

**Basal ganglia** The basal ganglia are a set of nuclei situated in the anterior brain. The three main structures of the basal ganglia are the caudate nuclei, the putamen, and the globus pallidus (see figure 3.9).

Globally, two systems exist to make sure that our motor system is adapted to our environment. They are the basal ganglia and the cerebellum.

The basal ganglia are helping prevent and anticipate the movement to be realised in the frame of the condition. Parkinson's disease or Tourette syndrome are good examples of what can be caused by a disorder of the nuclei composing this structure. The nuclei of the basal ganglia that serve as entry neurons of the system are the caudate nuclei and the putamen. Then, the information is processed in the globus pallidus. The globus pallidus are a set of neurons in medial position. The principal function of the globus pallidus is to control conscious and proprioceptive movements. It is composed of the internal (GPi) and external (GPe) segments. The exit is made by the thalamus.

Two structures are tightly associated to the motor functions of the basal ganglia : the substancia nigra (SN) and the subthalamic nuclei (STN). The substancia nigra is a dopaminergic nucleus that is an entry point for the caudate nuclei and the putamen.



Figure 3.9: Main connections of the subthalamic nucleus comprising basal ganglia inputs and outputs. A) Connections of the subthalamic nucleus, B) Functional subdivisions of the subthalamic nucleus, involving the basal ganglia connections. Adapted from [Benarroch 2008].

**Brainstem** Deeper into the brain, below the two hemispheres, and ventrally, appears the brainstem. This structure makes the link between the spinal chord and the diencephalon. This gateway transmits the sensorial afferences from the organs and the efferent voices from the cortex to the motor muscles. In term of evolution, this structure is sometimes considered, with the cerebellum, as the "posterior brain" : the most ancient part of the brain from an evolutionary point of view.

The brainstem is anatomically composed of : the bulb, the pons, and the mesencephalon (tegmentum and tectum). The pons and the bulb embed vital functions such as the cardiac rhythm and body temperature controls.

**Cerebellum** The cerebellum is often called the "second brain" because it depicts similar anatomical structures to the brain following the same three-dimensional organization. Indeed, the outer part of the brain is involved to involved in high analysis functions. Similarly, the inner part embeds ancestral functions. Anatomically, the brainstem has two hemispheres (left and right); the vermis which is a central cortex, is specific of the cerebellum ; the primary fissure, on the superior dorsal part, delineates the anterior lobe from the posterior lobe, and the floculonodular lobe, on the central part, is involved functionally in the posture. The cerebellum main function, roughly speaking, is to ensure that the decided motor actions is accurately performed. Its role is to assure the proper feedback of our own movement in relation with our environment, for precise gestures. It controls all of the motor functions and sensory functions. This explains its localisation, parallel to the afferences and efferences.

# 3.2.3 White matter

Located below the cortex, the white matter embeds the multitude of connections allowing the transport of information from or to the other organs of the body and between the various brain structures. The long connections correspond to the deep structural connectivity whereas the shortest correspond to the superficial sub-cortical connectivity.

### 3.2.3.1 Deep white matter connectivity

The deep white matter connectivity corresponds to white matter bundles populating the brain. They are connecting one region or structure to another and can be associative (i.e. connecting a cortical region with another), projecting (i.e. from a grey matter nuclei to a cortical region) or inter-hemispheric (i.e. connecting the two hemispheres). It is challenging to obtain a complete overview of all the deep white matter bundles that exist.

**Projection fibers** - The projection fibers are composed of efferent and afferent fibers that connect parts of the cortex with the spinal cord or basal ganglia. The different fascicles identified are the cortico-spinal tracts (descending motor and ascending somato-sensory tracts), the thalamic radiations (comprising the optic radiations), the cortico-ponto-cerebellar tracts.

• The **descending motor tracts** transmit the motor signal sent from the brain to the spinal cord to execute the movement.

Two different circuits are at stake : the pyramidal tracts and the extra-pyramidal tracts. The pyramidal tract, involved for voluntary control of muscular movements, is itself subdivided in the cortico-spinal tract and the cortico-nuclear (or also called the cortico-bulbar) tract. The cortico-spinal tracts transmit the motor signals from the primary motor cortex, in the pre-central gyrus, to the muscles of the trunk and limbs, passing through the spinal cord while the cortico-nuclear tracts transmit the motor signals originating from the primary motor cortex to the muscles of the face, head and neck, passing through synapses with neurons from the brainstem. The extra-pyramidal tracts mostly originate within the basal ganglia and carry motor fibers to the spinal cord. These tracts have an active role in the involuntary and automatic control of all musculature (muscle tone, balance, posture and locomotion). There are four extra-pyramidal tracts: the vestibulo-spinal (arising from the vestibular nuclei), the reticulo-spinal (from the reticular formation), the rubro-spinal (from the red nuclei) and the tecto-spinal (from the superior colliculus of the midbrain also called tectum).

• The ascending somato-sensory tracts are sensory circuits that originate from the peripheral nerves, passing through the spinal cord and stretching all the way up to the cerebral cortex, in the somato-sensory cortex, in the post-central gyrus.



Figure 3.10: Tracts trajectories from the descending motor tracts and the ascending somatosensory tracts, regions of the cortex involved, representation of the tracts on an MRI using tratography, freely adapted from source : https://radiopaedia.org/cases/ascending-spinal-tractsgrays-illustration

• The **cortico-ponto-cerebellar tract** connects different regions of the cortex to the cerebellum, passing through the pons and the contra-lateral middle cerebellar peduncle. This fascicle has been described recently and seems to be involved in movement coordination as an injury of this tract can cause ataxia [Jang and Do Lee 2021].



• The thalamic radiations connect the thalamic regions to the layers of the cortex via

dedicated neurons called relay cells. They extend from the internal capsule to connect mostly the visual cortex (optic tract), the somatosensory and prefrontal motor cortex, and the auditory cortex in the brain. The visual signals from the optic tract are processed by the lateral geniculate nucleus of the thalamus, auditory signals in the medial geniculate nucleus, and somatosensory signals in the ventral posterior nucleus of the thalamus. The majority of thalamo-cortical fibers project to layer IV of the cortex.

The thalamo-cortical function is excitatory as it causes the activation of the targeted cortical regions, however it is mostly regulated by inhibitory mechanisms.

#### Global scheme of the thalamic nuclei and 3d rendering from the thalamic associated projections radiations on a brain mesh Anterior limb Head of Frontopontine and caudate other corticofugal nucleus fibres Anterior thalamic radiation Genu Posterior limb Putamen Corticocobulbar Corticopontine and tract other corticofugal Globus Pallidus fibres Superior thalamic F radiation (includes somatosensory radiation) Corticospinal tract Thalamus Auditory radiation (inferior thalamic peduncle) Medial geniculate nucleus Optic radiation Anterior thalamic radiation (posterior Superior thalamic radiation Lateral thalamic Posterior thalamic radiation geniculate nucleus peduncle)

Figure 3.12: The thalamic radiations. Global scheme of the thalamic nuclei and associated projections (left) and 3d rendering from the anterior, superior and posterior thalamic radiations on a brain mesh (right), freely adapted from source : https://neupsykey.com/the-thalamus-andhypothalamus/ and Cox et al. 2016

Association fibers - For this part, the focus is made on the deep/long association fibers, the superficial association fibers are described in the next section. These fibers connect one cortical area to another and comprises : the inferior fronto-occipital fasciculi (IFOF), the inferior longitudinal fasciculi (ILF), the middle longitudinal fasciculi (MLF), the superior longitudinal fasciculi (SLF), the ventral visual streams (VVS), the arcuate fasciculi (AF), the frontal aslant tracts (FAT), the uncinate fasciculi (Unc), the cingulum (CG) (including ventral CGv and dorsal CGd) and the fornix (FX).

• The inferior fronto-occipital fasciculi are thick bundles commonly described to originate in the inferior frontal lobe and terminate in the occipital and parietal lobe, passing



through the extreme and external capsules. These fascicles seem to be involved in semantic language processing, and more recently found to be associated to executive control and goal-oriented behavior [Waller et al. 2017].

- The **inferior longitudinal fasciculi** connect the ventro-lateral part of the temporal poles and the inferior temporal gyri to the ventral part of the occipital lobes. These bundles run ventrally to the IFOFs, parallel to their paths in the occipito-temporal lobes. The ILFs seem to be functionally involved in semantic processing though the exploration of this fascicle's cognitive functions seems to be a recent field of interest [Shin et al. 2019].
- The **middle longitudinal fasciculi** connect the dorsal part of the temporal poles and the superior temporal gyri with the parietal lobes and, to a lesser extent, with the dorsal parts of the occipital lobes. They are located dorsally to the ILFs and laterally to the IFOFs. It is fair to say that its morphology and function are still poorly understood nowadays.



Figure 3.13: The inferior fronto-occipital fasciculi, inferior longitudinal fasciculi adapted from [Thiebaut de Schotten et al. 2015], and middle longitudinal fasciculi (red :anterior / yellow : posterior), source :https://www.frontiersin.org/articles/10.3389/fnana.2020.610324/full

• The superior longitudinal fasciculi are generally divided into 3 sub-parts : SLFI, SLFII and SLFIII, they connect the parietal, occipital and temporal lobes with the ipsilateral frontal cortices. Their role is still poorly known but they could be involved in attention, memory, emotions and language [Petrides and Pandya 2002] [Mesulam 1998]. The SLF II and III are still a subject of debate among the scientific community because of whether it should be considered as sub-parts of the arcuate fasciculus or separated fascicles.



Figure 3.14: The superior longitudinal fasciculi and cortical connections in regards of the other circuits freely adapted from source : Thiebaut de Schotten et al. 2015

- The **ventral and dorsal visual streams** originate from the occipital lobe. The ventral streams then run towards the temporal lobes ventrally to the MLFs and laterally to the ILFs and terminate in the middle temporal gyri. The dorsal streams run dorsally to the MLFs to reach the parietal lobe and then the frontal lobe. The visual ventral and dorsal streams are part of a model in which the two streams play different roles including object visual identification and spatial recognition.
- The **arcuate fasciculi** are curved white matter bundles that originate from the inferior frontal gyrus and extend caudally to the temporo-parietal junction to reach the inferior temporal cortex. They are sometimes described as having a dorsal component and a ventral (or posterior) component. This bundle is usually described as connecting two major important regions involving language : Broca's area in the inferior frontal gyrus and Wernicke's area in the posterior superior temporal gyrus. This is one of the major bundles that rises a great interest among the scientific community from neural composition to structure and functions.



Figure 3.15: The arcuate fascicle and cortical connections freely adapted from Thiebaut de Schotten et al. 2015 and https://library.neura.edu.au/schizophrenia

• The **frontal aslants** are tracts that could also be classified as superficial due to their short length. They are recently identified white matter tracts and are located inside the frontal lobes, connecting the superior frontal gyri to the ventro-lateral part of the inferior frontal gyri. Recent studies suggest that these tracts are involved in speech and language functions as well as executive functions, visual-motor activities, oro-facial movements, inhibitory control, working memory, social community tasks, attention, and music processing [La Corte et al. 2021].



Figure 3.16: The Frontal aslants and cortical connections freely adapted from source : Thiebaut de Schotten et al. 2015 and https://www.researchgate.net/figure/Connections-of-the-frontal-aslant-tract

• The **fornix** consist in C-shaped bundles that originate from the hippocampal head and extend caudally alongside the hippocampus. At the most caudal part of the hippocampal tail, the FXs bend medially and dorsally. Both FXs converge together at the medial surface of both hemispheres to form the posterior pillars of the fornices, which extend vertically, rostrally to the genu of the corpus callosum. They finally curve rostrally and run ventrally to the corpus callosum. It is thought to be connected to the limbic system and seems involved in cognition and episodic memory [Benear, Ngo, and Olson 2020].



Figure 3.17: The fornix freely adapted from : Thiebaut de Schotten et al. 2015 and https://www.earthslab.com/anatomy/limbic-system/

- The **cingulum** can be decomposed into two subparts : the ventral cingulum and the dorsal cingulum. The ventral cingulums stem from the caudal parts of the cingulate gyri, passing through the parahippocampal gyri and reaching the hippocampus head. The dorsal cingulums are located underneath the cingulate cortices, coursing dorsally along the corpus callosum to reach the medial prefrontal cortices. These fascicles are important actors of the limbic system functional network.
- The **uncinate fasciculi** are curved white matter bundles which originate in the rostral part of the temporal lobes, bend upwards rostrally from the anterior insula, and extend
to the inferior frontal gyri and the orbito-frontal cortex. These bundles are traditionally considered to be part of the limbic system and also seem to be involved in mnemonic representations stored in the temporal lobe to interact with and guide decision making in the frontal lobe [Von Der Heide et al. 2013].



Figure 3.18: The Uncinate fasciculus and role in the limbic system. Freely adapted from : Thiebaut de Schotten et al. 2015 and https://www.researchgate.net/figure/Limbic-pathways-completing-a-thalamic-hippocampal-prefrontal-circuit

**Inter-hemispheric fibers or commissural fibers -** These fibers are connecting one hemisphere to the other. The main bundles of this category comprise : the anterior commissure (AC), the posterior commissure (PC) and the corpus callosum (CC).

- The **anterior commissure** crosses through the ventral part of the anterior wall of the third ventricle, rostrally to the columns of the fornix, and connects the two temporal lobes of the left and right hemispheres on their rostral and medial parts.
- The **posterior commissure** is not well described in the literature. The posterior commissure embeds fibers gathering the left and right superior colliculus, and is located at the frontier between the mesencephalon and the diencephalon.
- The **corpus callosum** interconnects all lobes of both hemispheres and is composed, rostrally to caudally, of the genu, midbody, rostrum, isthmus and splenium. The different subdivisions are usually referring to the approach described in Aboitiz and Witelson's studies.



Figure 3.19: Inter-hemispheric fibers : The anterior and posterior commisures and the corpus callosum with 3d rendering of the segmented regions of the CC, adapted from : https://www.researchgate.net/figure/Segmenting-the-corpus-callosum-based-on-corticalprojection-zones-using-DTI-tractography

#### 3.2.3.2 Superficial white matter connectivity

Several white matter bundle atlases and methods for automatically identifying white matter fiber bundles from a dataset have been proposed in recent years [Catani and De Schotten 2008, P. Guevara, Duclap, et al. 2012, Oishi, Zilles, et al. 2008, Y. Zhang et al. 2010]. They have mainly focused on the long white matter bundles while the short distance connections, also called sub-cortical fibers or U-fibers, have been poorly considered.

These bundles are particular association fibers called "Superficial white matter bundles" (SWM) because of their shorter length, around 90 millimeters in the human brain, and thus less extended cortical connections. Contrary to popular belief, the investigation of the SWM bundles is a relatively old field of investigation among neurosciences.

Many of these short association fibers lie immediately below the gray matter of the hemispheric cortex, and connect adjacent gyri. These fiber pathways have been documented for more than a century, without really understanding their function. The first mentions about these fibers in the literature were made in 1810 by Franz Joseph Gall and Johann Kaspar Spurzheim. Then, Meynert in 1885 [Meynert 1885] attempted a description of short fibers, calling them "U-fibers", in finer details and proposed that their role was mostly linked to cognition.

Sachs in 1892 [Sachs 1892], described the superficial fibers, mostly on the occipital lobe, and tried to categorize them according to their route, destination, their proximity to the cortex and their belonging to "bundles" when running parallel to other close fibers.

Cristfield Jakob described in 1906 a system of longitudinal U-shaped fibers connecting adjacent frontal gyri [Theodoridou and Triarhou 2012, Jakob 1906].

These fibers, also seen using post mortem dissections [Vergani et al. 2014], seem to be involved in neuropathological studies [T. Zhang et al. 2014].

Although several authors have speculated on the link between the process gyrification and cortico-cortical connectivity, the location of short bundles has not been precisely mapped in the past and their function in the brain is still poorly understood.

Recently, thanks to advances in dMRI acquisitions, new digital studies have been made possible, and led to new advances in the comprehension of their organisation and possible role in humans using diffusion MRI [Lawes et al. 2008, Oishi, Zilles, et al. 2008]. This also allowed to propose new modern versions of the superficial fibers brain network [Gong et al. 2009, Y. Zhang et al. 2010], and novel superficial white matter bundles atlases [M. Guevara, Román, et al. 2017, Labra Avila 2020, M. Guevara, P. Guevara, et al. 2020].



Figure 3.20: Advances in the building of superficial white matter atlases. At the top left corner : work from Sachs, from Forkel, Mahmood, et al. 2015, on the top right corner, drawing from Cristfield Jakob in 1906, adapted from Theodoridou and Triarhou 2012, on the bottom left corner : The HARDI multi-subject atlas of short association bundles from Pamela Guevara in 2011, from P. Guevara, Cyril Poupon, et al. 2011, on the bottom right corner : Atlas of the superficial white matter fibers from Claudio Román, in 2017, from Román et al. 2017.

# 3.3 Histology

The brain is a complex organ that can be observed at various scales. After depicting its macroscopic organization, we will describe in this section its organization at cellular scales. Brain tissues are of an extraordinary complexity and are composed of billions of cells whose microstructure establishes the anatomical substrate of brain functions. The main brain cells are neurons and glial cells.

# 3.3.1 Neurons

Neurons are electrically excitable cells responsible for the nerve signal transmission. Their principal components are : the dendrites, the soma, the axon, and the synapses. Their size depends on their localisation and role but their soma usually measures between 4 to 100 micrometers in diameter.



Figure 3.21: Anatomy of a neuron, adapted from "https://www.healthline.com/health/neurons/anatomy"

#### 3.3.1.1 The dendrites

The dendrites are impressive tree-like branches ramifications stemming from the cell body. These structures are the main target of the synaptic afferences from other neurons. Their size and quantity of ramification vary depending of the neuron localisation and role.

#### 3.3.1.2 The soma

The soma is the site of major metabolic activity in the neuron and is composed of : a nucleus, surrounded by a fluid called cytoplasm, himself containing floating structures called organelles. The nucleus is where protein synthesis occurs and is the container of the DNA. In the cytoplasm, we can encounter Nissl bodies ( ribosomes ), mitochondria , endoplasmic reticulum, lysosomes, and Golgi complex. The somas are responsible for the grayish appearance to the gray matter of the brain, especially within the cortical ribbon.

#### 3.3.1.3 The axons

The axon is the neural cell extension responsible for the neural signal conduction. It extends from the soma and can display a huge variability in diameter and length depending on its localisation. The small neurons composed of small axons responsible for local signal transmission are called interneurons. Neurons with a longer axon are called projection neurons. Axons transmit an electric signal called an action potential. This phenomenon can be related to a change in membrane electric potential. This signal is transmitted to the next cell via the synaptic cleft of the synaptic terminations in the form of neurotransmitters.

#### 3.3.1.4 The different types of neurons

If all neurons of the brain share a basic neuron components, they can vary in structures and can be classified by their shapes or functions (see some examples on figure 3.22). These are the main neurons found in the brain :

- pyramidal neurons, they have only one axon but multiple dendrites and form a pyramidal type shape. These neurons, mostly found in the cortex compose the principal and largest neuron shape;
- bipolar neurons, they have two ramifications extending from the cell body with the axon on one side and the dendrite on the other side. They are mostly found on the eye's retina;
- Purkinje neurons, these inhibitory neurons have multiple dendrites that fan out from the cell body.



Figure 3.22: The different types of neurons, some have no dendrites, some have a widely developed arborization of dendrites, some don't have axons, freely adapted from book Neuroscience (Purves)

In terms of function, neuroanatomists classify neurons into three main types: motor, sensory, and interneurons :

• motor neurons, as their name suggests, are involved in voluntary and involuntary movements, allowing the brain and spinal cord to communicate with muscles, organs, and glands. The two types of motor neurons found are called the lower and the upper motor neurons. While lower motor neurons would carry the neuronal signal from the spinal cord to the smooth and skeletal muscles, the upper motor neurons would carry the signal between the spinal cord and the brain;

- sensory neurons are involved in the reception of the sensory inputs from the environment, such as touch, sound, heat and also smell and taste;
- the interneurons act as intermediates and are the most common type of neuron. They can be found in the brain and the spinal cord, and transmit the neural signal from sensory neurons/interneurons to motor neurons/interneurons.

The neural signal is called an "action potential" and consists in a depolarization of the neuronal membrane. The signal is transmitted along the axon of the neuron (pre-synaptic neuron), and reaches the synaptic cleft at the axon terminal were there is a particular space called a "synapse" where the signal is sent to another neuronal cell (post-synaptic neuron). Two modes of synapses are possible:

- the chemical synapse mode. The neuron would release neurotransmitters, which are chemical molecules that bind to receptors of the post-synaptic dendritic endings. They can cause two actions : trigger a new action potential in the post-synaptic neuron or prevent the activity of the post-synaptic neuron,
- the electrical synapse mode, only excitatory. In this case, the two neurons are connected by a "gap junction" made up of ion channels that transmit the excitatory signal.



#### 3.3.2 Glial cells

Figure 3.23: The different types of glial cells, freely adapted from the book "Neuroscience" (Purves)

The neuroglial cells, commonly called "glial" cells have a supporting role for the neurons. They are relatively shorter than neurons and don't directly act in the synaptic transmission. Like them, they can present branching, with lower and shorter extensions. There are three types of glial cells : astrocytes, from the central nervous system, oligodendrocytes also in the CNS that deposit around certain axons a particular membrane called "myelin". Myelin has an important role in the speed conduction of the action potential. The third type is the microglial cells, that have a scavenger role in the brain. They also secret signaling cells called cytokines, actors of the immune system, brain inflammation monitoring and cell apoptosis.

This thesis work is not centered on the study of the cellular components of the brain tissue which is why the presentation of the cellular organisation remained limited in this chapter.

# 3.4 Conclusion

This chapter presented the anatomy of the human brain from the macroscopic to the cellular level. This presentation was essential for the comprehension of the scope of this thesis since it aims to compare anatomical components between human and chimpanzee brains, particularly regarding the white matter bundles anatomy. If long white matter fiber bundles are, for most of them, already well-known in the human brain, the superficial or short white matter connections are still poorly understood, which is a real challenge for comparative neuro-anatomy. If this chapter encompasses the main human brain structures and functions, the next chapter will focus on what is mostly known about the neuroanatomy of the chimpanzee brain and which methods are relevant for its study.

# Chapter 4

# Exploring the chimpanzee brain

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Figure 4.1: 3D representation of the chimpanzee brain and human brain structures, Courtesy of Aida Gómez-Robles and José Manuel De La Cuétara

# 4.1 Introduction

This chapter discusses the exploration of the chimpanzee brain and the relevant and ethical methods used to carry out this study.

A first part in this chapter addresses the study of non-human primates in research, whether in their investigation on the field or in laboratories. The second part of this chapter focuses on what is known about the chimpanzee brain using magnetic resonance imaging (MRI) with different modalities : anatomical MRI, diffusion MRI and functional MRI.

### 4.2 Non-human primates in research

There is a paradox when it comes to the study of non-human primates, and especially chimpanzee research. Indeed, there is this remarkable willingness to understand them, to try to see what separates the great apes from humans and what unites them. This amazing species, endangered by our presence on their territory, their population being reduced due to poaching and farming of their soils, are the only witnesses of our own evolution. Chimpanzees are one of the 7 races of great apes, and are part of the species called "Pan". The chimpanzees are threatened to disappear in the foreseeable future (in the rest list of conservation). Approximately 300 000 individuals still live nowadays. With the development of ethical considerations for these beings, the scientific community has been trying for decades to find the right approach to answer fundamental as well as clinical questions. In its search for the best way to proceed, lots of mistakes were made concerning recognition of pain in monkeys, self-consciousness and fear. As the scientific community has tried to adapt the best way to conjugate research necessities and respect of our living primate cousins, different operating procedures have been implemented starting from the fact that research on chimpanzees and research about chimpanzees are two different things.

#### 4.2.1 Field investigations

A direct, possible way of investigation of the behavior of chimpanzees is by observation in their natural environment. This method has advantages but also disadvantages. Indeed, despite it being the least invasive investigational method, there is still a perturbation of the chimpanzee's environment by being present on its territory and so questioning its control of the place. The chimpanzees are aware that they are observed, this also means that even if the contact isn't direct, there is still a question of disturbance of the living of the species. Winning their trust and being as efficient and unobtrusive as possible is the mission for the researchers that choose this method.

The field investigation is particularly relevant in the study of chimpanzee behavior, whether alone, or in group. It is a good way to study the chimpanzee rhythm of life, self medication, mother/child rearing or tool-use and manufacturing.

Chimpanzees share their territories with gorillas, but not with bonobos. Part of their nests are on the soil and part are on trees. Chimpanzees live with a model of fusion-fission. Part of the research on wild chimpanzees in Uganda is about the living of the chimps. For example, the team of Dr. Krief studies the interaction of the chimps on their natural environment, notably the use of plants for self-medication, by ingestion or external use [Krief, Martin, et al. 2004]. Chimpanzees have cultural behaviors, they are able of cooperation, sharing, and transmission of knowledge. It has been observed for example that cooperation is traduced by a handshake over the head or delousing, which leads to a reduction of social stress, and has a certain action on immunity and susceptibility. The handshake over the head is a behavior that is operated by certain groups, and is an example of the fact that all behavioral features are not universally shared among chimpanzees.

While some behaviors seem clear, others, such as the "dance of the rain", have an unknown signification.

Chimpanzees are able of sharing. For example, they are capable of interacting for a hunting trip or to exchange meat.

By field investigations, the fact that chimpanzees associate certain plants while being sick is an important observation. It has been discovered that the Neanderthal man also did selfmedication [Hardy, Buckley, and Huffman 2013], [Krief, Daujeard, et al. 2015]. This observation was notably made possible thanks to field observation and samples of droppings from chimpanzees in the wild. This suggests that the observation of the chimpanzee behavior directly on the field could inform about their proper way of living and cognitive abilities but also on what could have been our ancient Homo parents behavior, and the first uses of pharmacology.

The emotional substrate of chimpanzees are hard to analyse, however, certain behavior suggest an inclination for empathy, with a reaction to the loss of a close individual. For example, when a baby chimpanzee dies, its mother continues to carry him [Biro et al. 2010].



Hand-shake over the head

Rain dance



Figure 4.2: Illustration of some of the different behaviors observed concerning chimpanzees in the wild. (top left corner): hand-shake over the head (source: MNHN primatology course 'tools and cultures'), (top right) : rain dance (source : https : //www.youtube.com/watch?v =<sub>A</sub> rewxI7tbU), (bottom left): delousing (source : https : //sylvaincordier.com ), (bottom right): self-medication, chimpanzees are eating plant leaves to get rid of parasites (source : https : //theconversation.com).

One of the growing subjects of investigation concerning the behavior of the primate is the use of tools that has been linked for a long time with the human race. In the 1960s, while the anthropologist Louis Leakey in Tanzania discovered fossils and stone tools from Homo Habilis, the primatologist Jane Goodall observed that chimpanzees from Gombe used chopsticks to collect termites. This observation was confirmed in 1980 by C. and H. Boesch who noticed that chimpanzees were also using tools made of stones. These observations led to the conclusion that the use of tools is not only a human feature. Chimpanzees use them to collect food, hunt or for social interactions. A debate is to know what is to be considered a tool instead of a simple object. This is implicitly linked to the level of elaboration of the tool that is used [Sanz and Morgan 2010], with a fine comprehension of the task that has to be made, a context of use for a same species and the complexity of sequence of tool fabrication. For chimpanzees, the tools can be smartly manufactured. For example, in the honey hunt from the soil bees, which corresponds to a particularly difficult task for a chimpanzee, there is a sequential fabrication of chopsticks that perfectly matches the definition of a tool [C. Boesch and H. Boesch 1990].



Termites hunting J. Goodall



Ant-fishing T. Nishida



Termites consumption C. Boesch

Ant-dipping T.Humle

Figure 4.3: Examples of uses of the different tools that can be developed by chimpanzees, images from MNHN courses from Dr. Sabrina Krief, "tools and cultures". On the top left corner : chimpanzee using a chopstick during termite hunting, work from Goodall 2013 ; on the top right corner : a chimpanzee is using a chopstick for ant-fishing, work from Nishida 1973 ; on the bottom left corner : a chimpanzee during termites consumption , to be able to access to the termites, Taï chimpanzees would use a long process for tool-making, work from C. Boesch and H. Boesch 1990 ; on the bottom right corner : ant dipping of a chimpanzee using a chopstick, work from Humle and Matsuzawa 2002.

Different observations made on the field allowed to gather all the observations required to

understand the variability of behaviors, related to different cultures between chimpanzee groups [Whiten et al. 1999], yielding the creation of a directory of activities for each community. Such a directory allowed to understand that the behavior doesn't answer to a genetic or environmental determinism, but is transmitted by social learning through imitation, teaching and social facilitation.

Another precious information provided by field studies concerns the social organisation of chimpanzees. Indeed, they shade the light on the way their society is established in the wild, how they divide the work to hunt in the forest, how are treated the young generations and the reproduction, how is occupied the territory and what kind of hierarchy is established. Such valuable information that cannot be obtained from alternative methods.

#### 4.2.2 Laboratory investigations

Ethical considerations - The need for animals in biomedical research has long been and still is a subject of debate among the scientific community. Their evolutionary relationship with humans make them a particular model in research in terms of ethical consideration, however sometimes difficult to replace. The use of primates in nowadays bio-medical research is of 0.17 percent of total research made on animals. In France, the use of great apes is forbidden and the use of monkeys for research must be strictly justified and supervised. The non-human primate species commonly used in the context of biomedical research is the macaque *cynomolgus*. This species is principally raised in Mauritius, China and Vietnam. The rhesus macaque, also used in biomedical research, is only raised in China. In Europe, three principal research areas use primates : testing for drug safety, infectious diseases, and neuroscience. It is important to note that primates are never used as a first-line treatment, and are recommended if no other species is suitable. They have a model status very different compared to other species [Carlsson et al. 2004]. Indeed, whereas mice or rats are widely spread models in biomedical research and have a short lifespan, with no more than one or two babies.

**Cognitive tasks** - Most of the tasks that have been driven out of the context of pharmacological tests on non-human primates are cognitive tasks. A great variety of cognitive capacities have been studied in this frame : memory, learning, numerical capacities, spatial capacities, problem solving, and social cognition (self-awareness, theory of mind). There is a possibility to perform some of these tasks in their natural habitat, however, in the case of research, the gain of captivity is the presence of a controlled environment.

Numerical tasks have revealed, that this species is able to count objects, and also to see if an object has been added or removed [Hauser and Carey 2003].

Memory tests have also been performed with chimpanzees [Matsuzawa 2009] submitted to touchscreen tasks consisting in putting disorganized numbers on screen in the right order as fast as possible. In order to reach this goal, chimpanzees used visual and spatial memories.

The objective of these various tasks is to investigate the strategy that these species have in their natural environment. For example, using the experiment of Menzel in 1973, it has been shown that chimpanzees use mental maps to identify the place where they can find some food [Carlsson et al. 2004]. The experimenter was having a walk with a chimpanzee while dropping some food on the floor. At the end of the walk, the chimpanzee chose the fastest way to collect all the food back.

# 4.3 MRI to study the chimpanzee brain

### 4.3.1 Chimpanzee gray matter

#### 4.3.1.1 Brain size comparison and evolution

Studies performed on the chimpanzee brain generally aim to make comparisons with the Human brain to better understand the Humankind evolution. The link between humans and chimpanzees and more generally with great Apes are a merely old field of investigations and led to Homo evolution theories. Probably the most famous one is Charles Darwin's theory of evolution in its publication "Origins of species" in 1859.

First cytoarchitectural maps were produced by [Mettler 1952] in the 1950s allowing a better comprehension of the chimpanzee brain and a better appreciation of its anatomy. The first studies made on endocasts and taking benefit from the imprints left by sulci on the surface of the skull provided a global overview of the anatomy of the chimpanzee brain, although they could not provide information about deep brain structures. Such studies arose interest in the scientific community and pushed forward neuroscientific studies on primates.

The most obvious differences observed between the chimpanzee brain and the human brain concern its size (the human one is 3 to 4 times bigger) and its shape, related to genetic changes and the switch from quadrupedal posture to biped posture, which induced the brain tilting and rearrangement.



Figure 4.4: Co-registered MRI/CT datasets of a human (left) chimpanzee (right) brains, (adapted from Alatorre Warren et al. 2019).

Rilling and Insel [Rilling and Insel 1999] studied the primate brain evolution using MRI in 1999, and added information to previous studies made on endocasts. They compared the human brain with living anthropoid primates and showed that the human neocortex seems to be significantly larger in Homo, with a more convoluted prefrontal cortex. This study highlighted the fact that Hominid brain evolution follows a singular scheme. This framework of hominin evolution of the human brain compared to the chimpanzee brain has also been investigated by [Gómez-Robles, W. D. Hopkins, and Sherwood 2014]. They investigated the evolutionary trajectories of the chimpanzee and human brain structures (evolutionary patterns of brain organization) and showed that human and chimpanzee brains evolved both using a mosaic pattern, with low

correlated variations between spatially separated regions.

These studies highlighted that similar mosaic patterns of evolution could be the result of fundamental structures already present in our common hominid ancestor's brain. The fact that the resulting brains in Pan and Homo show differences could result from an evolutionary framework flexibility, leading to specifically human singular regions. Evolution in hominin seems to be also accompanied by an increased degree of encephalization and a characteristic reorganization of the frontal region as demonstrated by the study from [Alatorre Warren et al. 2019].

The observed changes such as: the reorganization of the occipital areas, the changes of the position of the lunate sulcus observed in fossil endocast [Falk, Zollikofer, et al. 2018], the reduction of the primary visual cortex [De Sousa et al. 2010] and a reorganization of the frontal region [Alatorre Warren et al. 2019] could be linked with the acquisition of bipedalism during hominin evolution, other factors such as genetics also playing an important role [Gómez-Robles, W. D. Hopkins, Schapiro, et al. 2015].

#### 4.3.1.2 Gray / white matter proportions and cortical thickness

The ratio of grey to white matter volume as well as the differences in cortical thickness in chimpanzees have also been investigated. It has been reported that the human brain seems to have a larger white compared to grey matter volume than chimpanzees and non-human primates [Rogers et al. 2010]. Since humans show regional cortical thickness differences [Fukutomi et al. 2018], some studies have investigated whether it was also the case in chimpanzees.



Figure 4.5: Vertex-wise thickness comparison significance map. The hot colour regions (yellow) show where the cortex is relatively thicker in humans than chimpanzees. The cool colors (cyan) show where the cortex is relatively thicker in chimpanzees than humans. Adapted from [W. D. Hopkins, Xiang Li, et al. 2017].

In 2013, Hopkins and Avants reported evidence of regional variation and lateralization in cortical thickness in chimpanzees [W. D. Hopkins and Avants 2013]. Chimpanzees seem to exhibit a thinner cortex in primary motor and sensory cortices, and thicker gray matter in association cortices (including prefrontal cortex) and portions of the temporal and parietal lobes. They also observed a correlation between white matter volume and cortical thickness as well as sex differences. Indeed, males seem to display higher cortical thickness measures than females in regions of precentral and postcentral gyri, superior parietal lobe and dorsal prefrontal cortex. A lateralization was also observed with population-level rightward asymmetries in gray matter thickness and a concomitant leftward asymmetry in white but not gray matter volume [Seldon 2005].

Using a cortical surface-based approach, [Donahue et al. 2018] found that the proportion of sub-cortical white matter volume underlying the PFC is 1.7-fold greater than in chimpanzees, meaning an increased white matter in humans compare to chimpanzees in the prefrontal cor-

tex. This relative increase in white matter volume and gyrification in the PFC (and temporal lobes), are thought to underlie certain human cognitive specializations [Roth and Dicke 2005, Schoenemann, Sheehan, and Glotzer 2005].

In a nutshell, the regional differences in cortical grey matter in chimpanzees is something that is also found in humans, meaning that a common ancestor probably already demonstrated this particular pattern of cortical organization. However, possibly due to the different region-specialized cognitive acquisition, these regional differences in cortical thickness, as present in both species' brains, differ in their organization. This is accompanied by a variation in white matter volume, which has been shown to be negatively correlated with cortical thickness, and by an effect of gender. However, this last effect is different in chimpanzees compared to humans. Another hypothesis of the cortical grey matter organization in the chimpanzee brain could be linked to personality. Indeed, there seems to be observed variations in gray matter volumes in chimpanzees correlated with different levels of openness, extraversion, or reactivity [Bianchi et al. 2016]. However, it is important to note that the data collected comes from sanctuaries and that the notion of attention-getting observed in the chimpanzee population could be driven by the captivity environment. This could insert a bias in the different measures combining grey matter volume and chimpanzee behavior.

#### 4.3.1.3 Brain gyrification and surface area

One major characteristic of the human brain is its folding and sulcal pattern, allowing the delineation of specific areas of the cortex cytoarchitecture dedicated to related cognitive functions. Studies have investigated whether human folding patterns, identified by sulci, have their equivalents in the chimpanzee brain, and to what extent the related cortical areas have comparable surfaces.



Figure 4.6: Cortical brain sulci of the macaque brain (a), the Chimpanzee brain (b), and the human brain (c), Adapted from S. L. Bogart, Jean-François Mangin, et al. 2012 using Morphologist toolbox of the Brainvisa software Geffroy et al. 2011. Only the macaque and chimpanzee seem to share the lunate sulcus.



Figure 4.7: Differences in sulcal patterns between chimpanzee (Pan Troglodyte) and human (Homo) in the Broca area and visual regions. Chimpanzees have two crescent shaped sulci lacking in humans : fronto-orbital sulcus and lunate sulcus. Broca area : 44,45 Brodmann areas. Adapted from Falk, Zollikofer, et al. 2018

From Conolly in 1950 [Gardner 1950], the chimpanzee brain sulcal pattern differs from the one of humans especially in two areas where sulci present in chimpanzees are lacking in humans : the fronto-orbital sulcus (called 'fo') in the inferior frontal convolution (in Brodmann areas 44, 45 and 47) and the lunate sulcus (called 'L') in the rostral border of the lateral surface of the occipital lobes. This has been confirmed by the recent study using MRI from Falk and colleagues in 2018 [Falk, Zollikofer, et al. 2018] based on sulci analyzes on living chimpanzee subjects. One of the hypotheses concerning the absence of these two sulci in the human brain could be linked to the acquisition of a developed form of language and speech. Indeed, the BA 44 and 45 regions seem conserved, while L could have disappeared with the emergence of the angular gyrus (BA 39), all of those areas being involved in language. However, even if the chimpanzee brain may display two additional sulcus compared to the human brain, a global MRI analysis of its gyrification led to the conclusion that the chimpanzee brain is on average less folded than the human brain [W. D. Hopkins, Xiang Li, et al. 2017], [Zilles, Palomero-Gallagher, and Amunts 2013].

Studies have been specifically focused on the frontal cortex of the chimpanzee brain and studied its change during primate evolution. Study of the sulcal morphological variability of the medial frontal cortex (MFC) showed that the paracingulate sulcus (PCGS) which was thought to be proper to human frontal cortex (and higher cognitive functions such as the undertaking of initiative and future action planning) is also present in the chimpanzee brain [Amiez et al. 2019]. Its presence is however contrasted with the fact that its probability of occurrence is lower in the chimpanzee brain compared to the human brain and seems equally present in both hemispheres whereas in humans, a leftward asymmetry is observed.

Another area of the medial frontal cortex that has been considered as being the siege of higher order cognitive functions is the medial frontopolar cortex (known as area 10). It has also been investigated in chimpanzees [Semendeferi et al. 2001] using histological samples of chimpanzee brains, revealing that this area is twice larger in humans compared to any other hominid.

Some particular gyral regions where three different gyral crests meet are named "three-hinge" gyral folds. Globally, the human brain displays more 3-hinges than chimpanzees (or macaques) and more individual variability. Even if six 3-hinges were consistent between human and chimpanzee (and macaque), species-specific 3-hinges were identified: 6 for the chimpanzee and 2 in the macaque brain. Most of them were found on the frontal lobe and the parietal lobe. It is interesting to note that concerning the frontal lobe, two 3-hinge gyral folds were identified both in chimpanzees and humans in the superior frontal gyrus, meanwhile the human brain has four more anatomically consistent 3-hinges than chimpanzees [Xiao Li et al. 2017].

#### 4.3.1.4 Brain asymmetries, related to: - language / - handedness / tool-use /visual system

Asymmetry is among the most popular fields of research when investigating the brain. It is of particular interest when studying language, speech and motor areas.

There are distinct patterns of population-level asymmetries: directional asymmetry when the two hemispheres of the brain are systematically different across a population, anti-symmetry with a consistent difference between hemispheres but no variation in the same direction, and fluctuating asymmetry with non-directional departure from the expected bilateral symmetry. The three of them can be found both in human and chimpanzee [Gómez-Robles, W. D. Hopkins, and Sherwood 2013], with different patterns of organization (see figure [4.8]). The level of asymmetries seems increased in rostral areas for humans (there is a particular lack of variation in the frontal lobe), while in chimpanzees (at least for the symmetric variations and the fluctuating asymmetries) variations in rostral and anterior parts of the brain are observed.



Figure 4.8: The different patterns of asymmetries in the chimpanzee and human brains. Adapted from Gómez-Robles, W. D. Hopkins, and Sherwood 2013

In humans, there exists a particularly well-known asymmetry, described as a twist of the brain about the ventral-dorsal axis, especially present in posterior regions. This is called a "Torque", and is thought to form during early human brain development. This Torque seems to be composed of two components: (1) a posterior shift of the left to the right hemisphere, which produces corresponding right frontal and left occipital "petalia"; (2) differing distributions of cerebral tissue along the anterior-posterior dimension in each cerebral hemisphere. The Torque is also associated with an "occipital bending". The study from [Xiang Li et al. 2018] using vertex-based morphometry investigated the brain asymmetry and Torque in chimpanzees and put in evidence some features present in the human brain but absent in the chimpanzee brain. Globally, the human brain seems to display more asymmetry than the chimpanzee brain, with a

Torque pattern and a leftward asymmetry of the STS; in the human brain, a posterior expansion of the lateral surface of the left temporo-occipital region (including Heschl's gyrus and planum temporale) with clockwise rotation of the left Sylvian Fissure relative to the right around the left-right axis was observed. There also seems to be a sex difference in humans on the area of the orbito-frontal surface (dorsal in females).

Language Language is processed asymmetrically by the Human brain, with a dominance in the left hemisphere compared to the right hemisphere. It is significant and modality independent (also the case in sign language) [Galaburda, Sanides, and N. Geschwind 1978]. In humans, language is usually associated with two cortical areas : Broca and Wernicke areas. Wernicke area, also being Brodmann's area 22, is specifically involved in comprehension of written and spoken language. It is located on the superior temporal gyrus. Broca area is composed of Brodmann's areas 44 and 45 found in the frontal lobe and is involved in speech production.

Identification of the regions associated with language in chimpanzees been attempted. They seem composed of: the inferior frontal gyrus (IFG), which is the equivalent of Broca's area in humans, and the Planum Temporale (PT).

Comparing the topographic localization and the quantitative cytoarchitecture of Brodmann areas 44 and 45 in the chimpanzee brain, a leftward predominance in the asymmetry concerning the regions of language in the chimpanzee brain was found [Cantalupo and W. D. Hopkins 2001]. This implies that the neural substrate for a left dominance in language areas in the brain is not unique to humans and should be considered in evolutionary process assuming that a common ancestor might probably have displayed this pattern.

The asymmetry found in the region of language seems correlated with hand-use, in terms of gestural communication. Indeed, chimpanzees having a preferred hand (most of the time the right hand) for manual gesture display a larger IFG in the left hemisphere [Taglialatela, Cantalupo, and W. D. Hopkins 2006]. Concerning the analogue Wernicke brain area in chimpanzees, [Spocter et al. 2010] showed (in *post mortem* brains) that chimpanzees display a population level asymmetry in favor to the left hemisphere in the Tpt area (a component of Wernicke area equivalent in chimpanzee, corresponding to the posterior part of Brodmann's area 22). This leftward asymmetry was explored in terms of neuron density and volume asymmetry. This study also suggests that the asymmetry in Tpt neuron density is correlated with asymmetry of neuron density in Brodmann's area 45 (component of Broca area).

The PT is also a critical region for the language functional network in the human brain, showing a striking asymmetry dominance in the left hemisphere. It has been shown that this leftward asymmetry in PT is also present within the chimpanzee brain using *post mortem* [W. D. Hopkins and Nir 2010] and *in vivo* data [W. D. Hopkins, Pilger, et al. 2012]. It can be noted that a gender effect can be observed in the PT volume asymmetry [W. D. Hopkins, A. M. Hopkins, et al. 2016], with male chimpanzees demonstrating a larger PT asymmetry (no difference is noticed in females).

Motion/Handedness Studies have investigated the link between language in communication gesture and handedness. They examined whether individual differences in the motor hand area of the precentral gyrus (region involved in motor activity) and in the inferior frontal regions (regions involved in language, equivalent to Broca) were associated with asymmetries in hand preference or motor performance for tool-use. Variability in motor performance on a tool-use task seems associated with asymmetries in the motor hand area of the precentral gyrus and IFG in chimpanzees suggesting that hand preference for tool-use is associated with anatomical asymmetries. The relation between asymmetry in brain and tool-use is also evidenced by the study from [Cantalupo, Freeman, et al. 2008], showing a torque in the cerebellum of the chimpanzee brain at the individual level. In previous studies, the term 'hand preference' is used, because it is hard to discriminate against such a preference in primate, since their gesture could have

different intentions than the ones found in humans [Papademetriou, Sheu, and Michel 2005]. More precise studies about specific sulcal patterns were led, and put in evidence the presence of hand-knobs in chimpanzees, with a larger cortical surface of the central sulcus [W. D. Hopkins, Meguerditchian, et al. 2014]. Asymmetry in the superior pre-frontal sulci (responsible for motion) was also found [S. L. Bogart, Jean-François Mangin, et al. 2012].

**Visual system** A study from De Sousa et al. in 2010 [De Sousa et al. 2010] analyzed the primary visual cortex and the lateral geniculate nucleus by comparing the position of the visual cortex with the position of the lunate sulcus of different primates with the one of Human. Showing a bigger V1 in chimpanzee in volume, and a different organization taking the lunate sulcus as reference.

#### 4.3.1.5 Brain development and aging

**Development of the brain** Brain development in chimpanzees is influenced by rearing (as it is for humans). A recent study from [Bard and W. D. Hopkins 2018] shows that structural co-variations in grey matter of chimpanzee brains rely on the different modes of mother rearing. A good rearing by the mother in infancy has a significant positive effect on long-term changes in structural gray matter in adulthood. These studies underlie a possible effect that can have captivity on the brain development of chimpanzee newborns. Indeed, the study of [S. L. Bogart, Bennett, et al. 2014] analyzed the effect of nursery rearing in captivity compared to mother rearing, and the effect on the development of the chimpanzee brain. They looked at the grey and white matter volumes and there seems that mother-reared chimpanzees have greater global white to grey matter volumes, more cortical folding, thinner grey matter within the cortical folds than nursery-reared chimpanzees.

Aging of the brain Compared to other primates, Humans display an increased longevity. With increased brain longevity comes neural deterioration and cognitive impairments. In addition to these changes, it has been shown that humans (using *in vivo* MRI studies) display a whole-brain volumetric decline with age. Possible brain diseases linked with advanced age such as amyloid- $\beta$  protein deposit disease and Tauopathies can also appear. Among Non-Human primates, chimpanzees have the longest lifespan (they can reach sixty years old in captivity conditions), but there is a lack of studies in the field of brain aging concerning chimpanzees. Even if humans are more vulnerable to age-related diseases such as Alzheimer's disease Hof et al. 2002 among primates, deposits of amyloid- $\beta$  protein in the form of diffuse plaques have been found in chimpanzees [Gearing et al. 1994] and Tauopathies have also been observed on a 41yo female chimpanzee [Rosen et al. 2008]. Chimpanzees seem less vulnerable to brain aging effects, MRI measures of the whole brain volume and grey matter structures showed that the aging of the chimpanzee brain differs from the one of the human brain. Indeed, compared to human brain aging (decrease of brain structure over life), chimpanzee brains did not display significant age-related changes [Sherwood et al. 2011]. One hypothesis for this phenomenon could be that changes in human brain come at an older human age than the maximum longevity of chimpanzees.

#### 4.3.2 Chimpanzee brain structural connectivity

The use of diffusion MRI to analyze the white matter connectivity of the chimpanzee brain is a rather recent field of research. Recent analyzes have allowed us to acquire knowledge about white matter bundles and networks [Mars et al. 2014] and the first deep white matter atlas of the chimpanzee brain [Bryant, L. Li, et al. 2020], almost systematically in comparison with the human brain connectome. Some particular focuses concern fiber connectome, such as the different gyral hubs, the Corpus Callosum, the temporal associative fibers, the corticospinal tract.

#### 4.3.2.1 Mapping of the different parts of the structural connectome

**General hubs investigations** Using tractography algorithms, similarities between the chimpanzee brain and the human brain can be found. Indeed, [L. Li, Xiaoping Hu, et al. 2013] showed evidence of a preserved structural architecture in medial, parietal, insular, retro-spinal cingulate and ventrolateral prefrontal cortices. Moreover, the chimpanzee brain displays the 3-hinge gyral folding patterns ( conjunction of 3 gyral crests), also found in humans, that seem to play a role of connecting hubs with stronger fiber connections than other gyral regions. This relation is well preserved in the neocortices of chimpanzees and humans, suggesting a common axonal fiber and gyral pattern mechanisms .This can be linked to the fact that derived connection patterns from humans and chimpanzees can be found, supporting the hypothesis of evolutionary preserved brain architectures between the hominid species, but also, logically, species-specific connecting patterns.

Studies have also been made on the mirror system connectivity in chimpanzees (system consisting in frontal-temporal connections via the external capsule) including temporal connections in human and chimpanzee. Specific connections in humans are lacking in chimpanzees. First, there are major differences in the relative weight of the dorsal *versus* ventral connections within each species "core" imitation circuit. Second, the connections of the parietal mirror region with IFC (recognition of object) is strongest in humans compared to chimpanzees. Third, connections between frontal and parietal mirror regions are lacking in the chimpanzee brain [Hecht, Gutman, Preuss, et al. 2013].

**Corpus callosum tract** It appears that the corpus callosum (CC) follows the same structural development as the one of humans [Sakai et al. 2017], with a quick development during infancy and a gradual increase during juvenile stage. At an adult stage, the corpus callosum structure is similar to the one of humans [K. A. Phillips and W. D. Hopkins 2012]. Another similarity with humans is the investigation of CC connectivity with cortical regions, showing that the distribution of fiber diameters within the CC of chimpanzees follows a similar pattern to that reported in humans. Also, chimpanzees with higher PT asymmetries demonstrate fewer large diameter fibers in the posterior portion of the CC [W. D. Hopkins and Nir 2010]. This is associated with sex differences, this trait being particularly present among females.

Studies have been made about the connecting fibers of the corpus callosum, such as the one from [K. A. Phillips, Schaeffer, and W. D. Hopkins 2013] about the organization of the CC related to intermanual transfer performance (hand preference) in chimpanzees. Indeed, the dominant hand showed greater performance benefits : performance was associated with structural integrity of the motor and sensory regions of the CC, showing a direct bound between structure and function.

**Temporal associative connectivity** Few studies have been conducted on associative bundles of the temporal part of the brain in chimpanzees. However, a recent study from [Bryant, Glasser, et al. 2019] investigated these connections with the extrastriate cortex, and compared chimpanzees with humans and macaques. Using probabilistic fiber tractography, they showed differences in organisation between fibers connecting the extrastriate cortex with the temporal cortex. In the three species, streamlines seemed to connect area V with the retinotopically matched part of the extrastriate cortex. However, in humans and chimpanzees only, streamlines were observed to connect area V1 with ventral and anterior regions of the temporal lobe, including the multimodal anterior temporal lobe (ATL) of humans and the similarly located cortex in chimpanzees.



Figure 4.9: Individual tractogram volumes for a subsample of macaques (A), chimpanzees (B), and humans (C).red : tractography between V1c and the occipital temporal cortex ; blue : between the auditory core and the occipito-temporal cortex.

**Cortico-spinal tract** As for the temporal associative fiber connections to the extrastriate cortex, there are but only few studies about the cortico-spinal tract in the chimpanzee brain. The study made on 48 captive chimpanzees from Hopkins *et al.* in 2010 using voxel based morphometry [W. D. Hopkins, Taglialatela, et al. 2010] informs us that an asymmetry of fibers exists in both pre (motor) and postcentral gyrus (somatosensory), consisting in a leftward asymmetry (as it is also the case for the superior longitudinal fasciculus, the inferior fronto-occipital fasciculus, and the uncinate fasciculus) present in the cortico-spinal tract. These findings are consistent with the study from [L. Li, Preuss, et al. 2010] reporting a significant leftward asymmetry in the cortico-spinal tract from 36 female chimpanzees, using probabilistic fiber tracking of the corticospinal tracts, and correlating the results with handedness preference, the left CST being centered more posteriorly than the right CST.

#### 4.3.2.2 Language pathways in chimpanzee

Arcuate fasciculus The arcuate fasciculus is known to be involved in human language pathways. It is also found in chimpanzees and macaques. Indeed, diffusion MRI tractography demonstrated that chimpanzees do show an arcuate fasciculus, but less expanded than humans (see figure 4.10), suggesting that the emergence of this pathway and its expansion may have played an important role in the emergence of language in humans [Rilling, Glasser, Preuss, et al. 2008]. In humans, the AF projections into the temporal cortex are mainly concentrated in STS and

MTG (ventral to Wernicke area), while in chimpanzees the projections are more numerous in the MTG.



Figure 4.10: Different patterns of arcuate fasciculus connections in macaque, chimpanzee and human from source : [Rilling, Glasser, Preuss, et al. 2008]

It is reasonable to think that the emergence of specialisation of the arcuate terminaisons in humans, based on already present fasciculus in chimpanzees, is a species-specialisation, linked to the divergence Humans had with Pan species around 6 to 8 million years ago. A particular emphasis can be made on the posterior part of the arcuate fasciculus [Rilling, Glasser, Jbabdi, et al. 2012], that seems to display a special language-related pathway specific to Humans. In comparison with the strength of these posterior connections in a sample of 26 humans versus 26 chimpanzees, the posterior part of the AF is shown to be stronger in humans compared to the ventral pathway (present in chimpanzees), with a leftward pronunciation. In both species, a leftward asymmetry is observed, suggesting an already present lateralization in the common ancestor of Homo and Pan.

#### 4.3.2.3 Aging of white matter fibers in the chimpanzee brain

While structural MRI studies did not display cerebral changes related with age in the chimpanzee brain, the study from [X. Chen et al. 2013] evaluated the effect of age in chimpanzee, macaque and human brain on grey and white matter using diffusion MRI. They observed a global marginal decrease of the chimpanzee and rhesus macaque brain volumes with age, in contrast with [Sherwood et al. 2011], depicting that no decline in WM and GM volumes was found.

The fact that chimpanzee experience a GM and a WM loss at a later stage in their lives leads to the hypothesis that humans accumulate more deterioration before dying, leading to a higher chance to develop neuro-degenerative diseases, compared to chimpanzees where such diseases are present but rare.

#### 4.3.3 Functional MRI investigations of the chimpanzee brain

Contrary to macaques, functional MRI studies were less used than PET imaging on chimpanzees. Most of them focus on 'resting state' [Rilling, Barks, et al. 2007].

The resting state is a particular mode of the brain corresponding to regional blood oxygen fraction consumption by different brain regions, thought to be activated/deactivated during a cognitive task, underlying a 'default mode' of the brain while the subject is resting. This default mode is thought to be closely linked to our own introspection, such as memory retrieval, conscious awareness, semantic and/or conceptual processing, emotional processing, reflection.

The investigation of this particular state in chimpanzees revealed, first, the existence of a resting state 'default mode' comparable to the one existing in humans [Rilling, Barks, et al. 2007]. Since this mode is linked to self consciousness in humans, and that chimpanzees seem to show this capability of self-consciousness compared to other non-human primates (Gallup 1970,

science – mirror recognition), the presence of this default mode could be a clue for researchers in the understanding of the chimpanzee self-conception, since research about this topic is only made using behavioral data, hard to interpret.

While human scans are recorded with awakened subjects, chimpanzees are sedated during scans. Results showed a high brain activity in the MPFC and in the medial parietal cortex at rest (regions particularly activated in attention-demanding tasks, self mental states and episodic memory retrieval), reinforcing an interpretation of capability of self introspection in chimpanzees, long considered as a proper human trait. However, language areas activation, present in humans, were absent in chimpanzee PET studies. If the capability of mentalizing seems to be shared by both chimpanzees and humans, it is also present in rhesus macaques. This capability would then be inherited from a more anterior ancestor.

# 4.4 Conclusion

This chapter emphasized the different goals of the research made on non-human primates and especially chimpanzees. Different techniques can be used, depending of the aims of the study. It is therefore possible to study non-human primates behavior in their living environment or in sanctuaries where the environment is more controlled. The use of chimpanzees for research is strictly supervised due to their proximity with humans and the resulting ethical considerations. However, thanks to recent advances in non-invasive imaging techniques, such as MRI, the neuroscientific community has access to valuable brain imaging data allowing a better comprehension of the chimpanzee brain and revisions of previous theories and hypotheses on human intelligence. Recent advances have been made in the comprehension of the differences between humans and chimpanzees in terms of brain sizes, brain gyrification or brain aging. However, one topic of research is still poorly investigated : the white matter bundles. The next chapter will discuss a particular modality of MRI, called diffusion MRI, and roughly explains how this principle could help improve the exploration of the primates' brain white matter fiber bundles.

# Chapter 5

# Principles of diffusion MRI

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 $\label{eq:Figure 5.1: White matter fibers of the human brain, adapted from "http://brainsuite.org/processing/diffusion/"$ 

## 5.1 Introduction

This chapter discusses the principles of diffusion MRI, or how to go from the physical principles of water molecules diffusion in a space to the reconstruction of white matter fibers' trajectories in the brain. A first part addresses the basic principles of the diffusion phenomenon, then how the diffusion process is captured in the MRI signal. This chapter then presents the local modeling of the diffusion process and finally the methods allowing to infer the brain white matter bundles.

# 5.2 The diffusion phenomenon

Diffusion is a three-dimensional process in which matter moves from its original position without mass movement. An example is shown in figure 5.2 where a drop of colored fluorescent dye is placed in a container of water. The dye initially appeared to be concentrated at the release site, but was distributed radially, spherically, symmetrically over time. In brain tissue, water molecules diffuse freely due to their thermal energy. This process is called Brownian motion.

In an unrestricted environment, Brownian motion of water molecules is observed due to : 1) a phenomenon of thermal shocks where water molecules are in constant animation and enter regularly in collision, 2) the existence of a non-zero temperature, 3) the existence of a concentration gradient of water molecules.

In the absence of restriction, an isotropic diffusion process is observed. Indeed, the molecules have the same probability of moving in any direction in space.



Figure 5.2: example of the diffusion of a colored drop in water, the diffusion is free and homogeneous.

This diffusion phenomenon can be modeled by some fundamental equations :

• Fick's first law : within a fluid, the flux of the diffusing element is proportional to its concentration gradient :

$$J = -D\nabla C \tag{5.1}$$

With J the flux of the water molecules in  $g.m^2.s^{-1}$ , C the concentration of the water molecules in  $g.m^{-3}$  and D the diffusion coefficient in  $m^2.s^{-1}$ .

• from Fick's first law follows the diffusion equation (Fick's second law), describing the temporal evolution of the concentration of the element and showing that this temporal evolution is related to the second spatial derivative of the concentration pattern:

$$\frac{\partial C}{\partial t} = D \cdot \nabla^2 C \tag{5.2}$$

• in the case of self-diffusion, the description of the motion of molecules is facilitated with the introduction of the propagator function  $P(\mathbf{r}, \mathbf{r'}, t)$ . The latter quantifies the probability for a water molecule to go from a position  $\mathbf{r}$  to a position  $\mathbf{r'}$  under a time t. The propagator function also satisfies Fick's laws and thus :

$$\frac{\partial}{\partial t}P(\boldsymbol{r},\boldsymbol{r'},t) = D \cdot \nabla^2 P(\boldsymbol{r},\boldsymbol{r'},t)$$
(5.3)

• however, a general characterization of the motion remains difficult, as there is no bulk movement of the molecules, and the average of individual trajectories is null. The introduction of the mean squared displacement by Einstein allowed to link the distance traveled by a diffusive molecule to the duration of the diffusion and the diffusion coefficient :

$$\langle R^t R \rangle = \sqrt{D \cdot 6\Delta t} \tag{5.4}$$

Where  $\langle R^t R \rangle$  is the squared mean displacement of the molecule during the diffusion time  $\Delta t$ .

The Einstein equation is central to the development of the dMRI framework because it quantifies the displacement of the molecules depending on the diffusion time, and thus helps to define distinct diffusive behaviors inside the brain.

In a free environment, a free movement of the molecules is observed, this phenomenon is called "isotropic" movement. In a restricted environment, an "anisotropic" movement of the water molecules is observed due to the presence of obstacles. This implies that the molecules do not have the same probability to move in any direction of space, which is the case in the brain. Within the white matter in the brain, which consists of myelinated axons organized in parallel fiber bundles, the myelin sheath surrounding the axon creates an almost impenetrable barrier. The water molecules trapped inside the axons can only "follow" the main direction of the axons while the water molecules located outside the axons must bypass the axons. The average free path of water molecules is then higher in the direction of the fibers than in any other direction.

Assuming Einstein's relation,  $R^t R$  during the time  $\Delta t$  can be used to find an apparent diffusion coefficient (ADC) that is smaller than the diffusion coefficient D because of molecule movements restrictions. Understanding the influence of the restrictions on the ADC gives information about the geometry of the boundaries of the surrounding medium; i.e. in our case, the white matter fiber bundles. This is the phenomenon that diffusion MRI attempts to capture. Roughly speaking, ADC is the index of how freely water can move.

#### 5.3 Sensitizing the MRI signal to the diffusion process

The human body is composed of more than 70 percent of water. Water molecules are composed of an oxygen atom and two hydrogen atoms. The hydrogen nuclei presents a magnetic dipole, often referred as "spin", that can be exploited to perform magnetic resonance imaging, a totally non-invasive modality to explore brain tissues.

It is out of the scope of this thesis to explain in detail the principles of nuclear magnetic resonance used to create magnetic resonance images, so only its basic principle will be briefly described in this section. The spin of water molecules, abundant in living tissues, that are put in a static magnetic field "B0" induce a net magnetization which is aligned with the direction of this static field. The use of a second dynamic magnetic field "B1" often referred as "radio-frequency" pulse can induce a resonance phenomenon when its frequency matches the Larmor frequency 5.3. This frequency corresponds to the precessional speed of spins around the static field axis and it is proportionnal to the static field magnitude,  $\gamma_H$  being the gyromagnetic ratio of the hydrogen nucleus :

$$\omega_0 = \gamma_H . B_0 \tag{5.5}$$

This resonance mechanism is at the heart of magnetic resonance imaging, allowing the design of basic MRI pulse sequences such as spin echo sequences. The MRI signal resulting from the resonance phenomenon induced using a radiofrequency pulse corresponds to two concomitant relaxation processes characterizing the return of the excited magnetization to its equilibrium position along the static field axis : a transverse relaxation process corresponding to an exponential decay of the transverse magnetization component driven by a T2<sup>\*</sup> or T2 relaxation time, and a longitudinal relaxation process corresponding to an exponential regrowth of the longitudinal magnetization component driven by a T1 relaxation time.

Each brain tissue displays specific T1, T2 and T2<sup>\*</sup> relaxation times, and will as such emit a different MRI signal than another brain tissue, thus yielding a contrasted image of the brain.

The basic pulse sequence used for diffusion MRI is the spin echo sequence represented on figure 5.3.



Figure 5.3: Pulse diagram of the spin echo sequence. Adapted from Beaujoin 2018.

It uses a first excitation pulse inducing a rotation of  $90^{\circ}$  of the longitudinal magnetization in the transverse plane, followed by a second  $180^{\circ}$  refocusing radiofrequency pulse at TE/2 which allows to cancel any magnetic fields heterogeneity and thus allows to acquire at the echo time TE a signal :

$$S = \rho \cdot e^{-TE/T^2} \cdot (1 - e^{-TR/T^1})$$
(5.6)

With  $\rho$  the proton density, TE the echo time (ms) and TR the repetition time (ms). If the sequence is repeated with a repetition time much larger than the T1 relaxation time, then :

$$S \approx \rho. e^{-TE/T2} \tag{5.7}$$

where  $\rho$  represents the proton density of water and T2 the transverse relaxation time specific to the imaged tissue.

The magnetic resonance signal can be made sensitive to diffusion by using specific MRI sequences. To obtain MR measurements of the ADC, a specific MRI sequence is used. This sequence was first introduced by Stejskal and Tanner in 1965 [Stejskal and Tanner 1965] and is called Pulsed Gradient Spin Echo (PGSE).

**PGSE sequence -** The PGSE sequence results from a modification of a spin echo sequence by adding two strong diffusion gradients on the left and right sides of the 180° refocusing pulse that "encodes" the position of water molecules with a specific phase.

The first gradient is applied before the 180° RF pulse inducing a phase shift that depends on the position of the water molecule in the direction of the applied diffusion gradient pulse. The second diffusion gradient, similar in magnitude (G), width and direction with the first diffusion gradient is applied after the 180° RF pulse. Both diffusion gradients starting times are separated by a time  $\Delta$ .

Due to the reversal effect of the 180 degrees refocusing RF pulse, in principle, the previous phase shift of the targeted spins will be cancelled by the reversal phase changing from the second diffusion gradient pulse. In fact, this only happens on static spins which experience the same phase shift because of their position is preserved. But for spins that have diffused in one or multiple directions during the  $\delta$  time interval between the diffusion gradients, their net phase accumulation will not be null. Therefore, the sum of magnetic moments in such a voxel with those diffused spins will be lower than the voxel with static spins and yields a further exponential attenuation related to the diffusion coefficient of these spins :

$$S = \rho.e^{-TE/T2}.e^{-b.D}$$
(5.8)

with D being the diffusion coefficient and b being the diffusion sensitization  $b = (G\gamma\delta)^2(\Delta - \delta/3)$ .

The introduced signal attenuation A can be computed by comparison with signal intensity without diffusion weight to derivate ADC map :

$$A = S/S_0 = e^{-b.D} (5.9)$$

The b-value reflects the strength and timing of the gradients used to generate the images. The higher the b-value is, the stronger the diffusion sensitization of the MRI is.

# 5.4 Local modeling of the diffusion process

In diffusion MRI, the diffusion coefficient is inferred from observations of the displacements of the water molecules over a given time period. If the diffusing water molecules encounter any obstacle along their random walk, such as cell membranes and macro-molecules, the mean squared displacement per unit of time will be lower than when observed in "free" water. Thus, when applying Einstein's equation to compute the diffusion coefficient, it will appear that the diffusion coefficient is lower. For this reason, we refer to the apparent diffusion coefficient (ADC).

In the brain, membranes of axonal fibers will restrict or hinder the displacement of water molecules in directions not aligned with that of fibers. Practically, the displacement of water molecules is greatly reduced in any direction that do not correspond to the main direction of fibers. This phenomenon is used to investigate the local orientation of the white matter fiber bundles.

The ADC therefore depends on the local organization of tissues at cellular scales and on the orientation of the diffusion direction in the 3D space. In practice, to understand this dependency, one should collect a large amount of diffusion-weighted MRI signals corresponding to a wide sampling of the diffusion directions and a wide sampling of the diffusion sensitization b. To summarize the local information about the diffusion process of water molecules, the diffusion MRI community has developed a plethora of diffusion reconstruction techniques relying on various mathematical frameworks, starting from second order tensors in the mid 1990's to more advanced multi-compartmental microstructural models nowadays. In the following, we propose to focus on the historical diffusion tensor models and describe more advanced high angular resolution diffusion imaging models (HARDI) particularly suitable to infer the structural connectivity of the brain. More described presentation of these models can be found in [Tournier, Mori, and Leemans 2011].

**Diffusion Tensor Model (DTI)-** To account for the orientation of water molecules in a restricted environment, the diffusion tensor model was developed by Basser et al. in 1994 [Basser, Mattiello, and LeBihan 1994] relying on the use of a second order tensor. The diffusion tensor is an extension of the scalar diffusion coefficient (ADC).

The scalar diffusion coefficient is described as a 3x3 symmetric positive matrix :

$$\mathbf{D} = \begin{pmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{pmatrix} = \begin{pmatrix} e_{1x} & e_{2x} & e_{3x} \\ e_{1x} & e_{2y} & e_{3z} \\ e_{1x} & e_{2y} & e_{3z} \end{pmatrix}^T \begin{pmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{pmatrix} \begin{pmatrix} e_{1x} & e_{2x} & e_{3x} \\ e_{1x} & e_{2y} & e_{3z} \\ e_{1x} & e_{2y} & e_{3z} \end{pmatrix}$$
(5.10)

In the anisotropic environment of the brain, the eigenvalues of the tensor matrix  $\lambda_1 \ \lambda_2 \ \lambda_3$ inform on the diffusivity along the eigenvector directions (e1, e2, e3). The largest value is associated with the diffusivity in the principal direction and therefore corresponds to the fiber orientation. In the case of white matter, this value is three to six times greater than that of the diffusivity in the orthogonal plane.



Figure 5.4: Modelisation of the diffusion tensor model by an ellipsoid. The eigenvalues are  $\lambda_1$ ,  $\lambda_2$ and  $\lambda_3$ , where  $\lambda_1 \geq \lambda_2 \geq \lambda_3$ , and the corresponding eigenvectors are **e1**, **e2**, **e3**. The principal diffusion direction is given by e1, with the  $\sqrt{2\lambda_1\tau}$  mean displacement of water molecules during a given diffusion time  $\tau$ , according to Einstein's equation [Einstein, 1905]

The isosurface of a second order tensor corresponding to a Gaussian propagator can be represented with an ellipsoid. DTI needs at least six diffusion-weighted images and one nul b-value image S0 to determine the six unknown coefficients of  $\mathbf{D}$ . Once  $\mathbf{D}$  is diagonalized, various rotationally invariant diffusion indices can be retrieved :

• The mean diffusivity (MD), that depicts the mean displacement of water molecules inside the voxel :

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \tag{5.11}$$

• The fractional anisotropy (FA) that depicts the degree of anisotropy in the voxel:

$$FA = \sqrt{\frac{3}{2}} \sqrt{\frac{(\lambda_1 - \langle \lambda \rangle)^2 + (\lambda_2 - \langle \lambda \rangle)^2 + (\lambda_3 - \langle \lambda \rangle)^2}{\lambda_1 + \lambda_2 + \lambda_3}}$$
(5.12)

• The transverse (also called radial) diffusivity,  $\lambda_{\perp}$ , depicts the diffusivity along the perpendicular plane of the major direction of the ellipsoid :

$$\lambda_{\perp} = \frac{\lambda_2 + \lambda_3}{2} \tag{5.13}$$

• The parallel (also called axial) diffusivity,  $\lambda_{\parallel}$ , depicts the diffusivity along the principal direction of the ellipsoid :

$$\lambda_{\parallel} = \lambda_1 \tag{5.14}$$

DTI is a simple and efficient model still widely used in classical applications and has for advantages to request a few number of input data and input parameters. However, it became evident that despite its many benefits, DTI suffers from important limitations. Indeed, while it allows to map structural connections between different regions of the brain, the reconstruction of the fibers' pathway when it comes to complex architectures where fibers cross is poorly rendered by this model.

Because DTI has limited capabilities of resolving multiple fiber orientations in a same voxel, which is an essential feature of the normal brain, new complex models had to be developed to try to overcome these limitations.

**From q-space encoding to HARDI techniques -** Compared to DTI, the q-space sampling developed models have the potential to render more accurately the complex structures within a voxel with a better modeling of the orientation within this voxel, by the application of stronger diffusion-encoding gradients and encoding steps. With the evolution of the different models developed, we can cite the diffusion spectrum imaging or DSI [Wedeen et al. 2005] and q-ball imaging [David S Tuch 2004]. However, these techniques also have their limitations, such as long MRI acquisition times.



Figure 5.5: Evolution of the q-space models, Courtesy of Dr C. Poupon

From these improvements, High Angular Resolution Diffusion Imaging (HARDI) techniques were developed to detect multiple populations of fibers within a voxel from a simple sampling shell in the q-space to prevent too long scan duration. The HARDI techniques, in practice, increase the angular resolution of the diffusion-weighted data using a stronger sensitization than DTI, and a diffusion sensitization gradient in a larger number of directions at a constant b-value.

The two main representations produced by these techniques are called "diffusion Orientation Distribution Function" (dODF) and "fiber Orientation Distribution Function" (fODF or FOD). fODFs offer a direct information on the fiber configuration within the voxel and are obtained from a spherical deconvolution technique, usually giving a better angular information than the dODF. Like DTI with its diffusion indices (FA, MD...), ODF scalar features can also be derived, like the generalized fractional anisotropy (GFA).



Figure 5.6: The diffusion orientation distribution function (dODF) and the fiber orientation distribution function (FOD) from Descoteaux and Deriche 2015

	Model-based app	roach	Model-free approach		
Model name	Publications	Guiding principle	Model name	Publications	Guiding principle
Ball and Stick	Behrens, Woolrich, et al. 2003	Multi tensor based	aQBI	Descoteaux, An- gelino, et al. 2007	SH decomposition, FHT
CHAR- MED	Assaf and Basser 2005	Hindered compart- ment separation	DSI	Wedeen et al. 2000	Cartesian sam- pling, FFT 3D
CSD	Tournier, Cala- mante, et al. 2007	Spherical deconvo- lution with	QBI	Tuch 2002	Spherical sam- pling, FRT
SDT	Descoteaux, De- riche, et al. 2008	a Gaussian fiber response	DOT	Özarslan, Shep- herd, et al. 2006	Pointwise conver- gent expansion of the plane wave
Wisharts mixtures Jian et al. 2007		Functions of sphere	gdti / Hot	Liu, Bammer, et al. 2003; Ghosh et al. 2008	Generalization of Fick's Law, high- order diffusion tensors
			KDT	Jensen et al. 2005	Kurtosis analysis
			PAS-MRI	Jansons et al. 2003	Dirac radial propa- gator shape
			SHORE	Özarslan, Koay, et al. 2013	MAP per voxel from dMRI data

Figure 5.7: Local models of the diffusion process, adapted from Yebga Hot 2021

Among all the models that have been developed, two types of models can be distinguished : the model-dependant reconstructions and the model-free reconstructions for which a summary is provided on figure 5.7.

The pioneer work was made by Daniel Alexander in 2001 [Alexander et al. 2001], who realized that the phenomenon of crossing fibers in a voxel was not well reconstructed using a single tensor model. He implemented the idea of using two tensor models for a same voxel, however, the fitting of two tensors at the same time is particularly unstable. Then, models such as PAS-MRI were implemented as the first HARDI model to be developed, and quickly after that arrived the models from David Tuch in 2002 [David Solomon Tuch et al. 2002], proposing the numerical q-ball model (QBI). It is few years later that this numerical q-ball model, that was tacking to much time, was mathematically re-implemented, with versions in spherical harmonic decompositions, with the works from [Maxime Descoteaux et al. 2007].

Nowadays, q-ball and CSD models are the most commonly used, and allow the production of accurate ODF maps over the entire brain.

# 5.5 Inference of white matter bundles

#### 5.5.1 Fiber tracking methods

In the 2000's, a field of fiber reconstruction called "tractography", attempting to reconstruct the white matter pathways in the brain, experienced a great expansion thanks to the diffusion local models.

There are different types of methods to try to reconstruct the connectivity of the brain :

- the Bayesian method, which is a probability map of connections of one point in relation to all others, with the FSL software [Jenkinson et al. 2012];
- the streamlining methods, which consist in plotting the curves that follow the profiles given by the ODF map;

- the "global" methods; [Cyril Poupon 1999, Jbabdi and Johansen-Berg 2011, Reisert et al. 2011, Neher et al. 2012, Mangin et al. 2013 ], computing simultaneously all the trajectories in a competitive manner to avoid the creation of fiber configurations that would not correspond to plausible anatomical connections. In these methods, are found the particle filtering and the spin glass approaches,
- the deep-learning based models.



Figure 5.8: Scheme of the fiber tracking, from one seed in a voxel. On the left : brain dMRI imaging, middle : ODF map, on the right : tractogram

Different types of streamlining methods are possible :

- the streamline deterministic approach, [Pierpaoli et al. 1996, Poupon et al. 1998, Mori et al. 1999] where the algorithm follows the most likely direction of the underlying dODF or FOD [Conturo et al. 1999];
- the streamline probabilistic approach [T. E. Behrens et al. 2003, Parker and Alexander 2003, Perrin et al. 2005, Chao et al. 2009], that allows to moderate deviations from the most likely direction, which enables to increase the robustness of the tractography algorithm to the noise corrupting the dMRI dataset and thereby the ODF field.

#### 5.5.2 Assessing the structural connectivity

When using reconstructed tractograms, there are two major possible applications :

- using regions of interest (also called "ROI"). This method relies on the computation of individual connectivity matrices between regions of interest (cortical areas provided by cortex labelling and deep gray structures). This is a connectomics approach introduced by Sporns in 2005 [Sporns, Tononi, and Kötter 2005] and the gold standard approach of the Human Connectome Project which aims to obtain the most complete structural connectome of the human brain. This approach also comprises a semi-manual operation where one must select the bundles at the intersection of 2 regions. This process can sometimes be challenging due to the bias in the fiber continuities from the fiber tractogram. This method is moslty used by clinicians and cognitivists,
- with the inference of high-resolution white matter atlas of the structural connectivity. This approach, relying on neuro-anatomical studies, allows the building of white matter bundles atlases, using fiber clustering approaches. Clustering algorithms use a criterion of geometric distance between 2 fibers to regroup them together. This approach already led to new atlases of the long and superficial white matter bundles [Guevara Alvez 2011, Labra

Avila 2020, M. Guevara, P. Guevara, et al. 2020]. Such atlases are a unique opportunity to investigate the inter-subject variability of structural networks and to establish novel imaging markers in brain pathologies possibly related to abnormal structural connectivity patterns.

# 5.6 Conclusion

This last background chapter reviewed the diffusion MRI modality, from its basic physic principle to its application in the identification of white matter bundles in the brain. This thesis work relies on the principles of diffusion MRI, using fiber clustering approaches, with the goal to build new atlases of the brain connectivity of the chimpanzee and human brains. This will be the subject of the next part and chapters.
# Part II

# Singularity of the structural connectivity of the human brain compared to the chimpanzee brain

# Chapter 6

# Singularity of the structural connectivity of the chimpanzee brain and comparison to the human brain

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Figure 6.1: Deep white matter atlases of the chimpanzee and human brains. Figures generated thanks to the ginkgo toolbox using subjects from YNPRC and HCP.

### 6.1 Introduction

From the discoveries humans have made with time in terms of fossils and genetic investigations, we know that our species is the fruit of a long and complex evolution. Identifying the human brain specificities generally involves two complementary approaches: tracking and understanding the pathways of its evolution over ages looking at its ancestral and non-ancestral characteristics and proceeding with comparisons to other species.

Among hominids, our closest phylogenetic living relative is the chimpanzee (Pan troglodytes), from the Pan order, with whom we shared a common ancestor around 6 million years ago [Goldman, Giri, and STEPHEN J O'Brien 1987]. Despite different ancestors have existed between chimpanzees and modern Humans, this comparison is the only way to appropriately evaluate brain features heritability, shared or evolved brain characters, allowing us to evaluate the Human brain evolution. Chimpanzees share about 96 percent of their gene proteins with humans and they often seem to suffer from the same cerebral pathologies as humans [Edler et al. 2017]. However, the chimpanzee brain is approximately one third of the human brain in size and is less folded, with a lower neuron density [Alatorre Warren et al. 2019].

The close phylogenetic proximity between chimpanzees and humans prohibits their use in clinical research for obvious ethical reasons, but the existence of non-invasive neuroimaging tools, such as magnetic resonance imaging (MRI), has made it possible to set up studies aimed at understanding the differences and commonalities of the chimpanzee and human brains, in order to better understand their compared singularity.

Examples of such studies are the exploration of the cortical folding pattern of the chimpanzee brain using anatomical MRI [W. D. Hopkins, Coulon, and Mangin 2010] or more recently the exploration of its deep structural connectivity using diffusion MRI (dMRI) [Bryant, L. Li, et al. 2020]. Diffusion MRI is now a well-established MRI tool to explore the brain microstructure through the observation of the anisotropy of the Brownian motion of water molecules present in tissues. To date, it remains the only method to explore *in vivo* the brain anatomical connectivity. Sulco-gyral anatomy and structural connectivity are intimately linked, with brain functions resulting from the connection of cortical regions and/or deep grey matter regions via axonal fiber bundles populating the cerebral white matter, thus establishing functional networks. One of the great challenges of neuroscience from an evolutionary point of view, is to build and compare models of the brain connectome [Sporns, Tononi, and Kötter 2005] between species, in order to be able to compare species between them.

The community has been working actively for almost twenty years to establish the human brain structural connectome. Several atlases of deep fascicle anatomical connectivity have been proposed following different methodological approaches [Sporns, Tononi, and Kötter 2005,P. Guevara, Duclap, et al. 2012, Yendiki et al. 2011]. More recently, new atlases of the superficial anatomical connectivity with more challenging inference have been proposed for humans that allow for a finer exploration of the link between sulco-gyral anatomy and sub-cortical connectivity [Sporns, Tononi, and Kötter 2005, Labra Avila 2020]. These methodological advances in humans have opened the way to study the connectome of other animal species including the chimpanzees.

A first atlas of deep fascicle connectivity was recently released by [Bryant, L. Li, et al. 2020], using diffusion MRI acquired on a cohort of 29 female individuals. This atlas was built from predefined regions of interest corresponding to long fascicle crossing points in each individual and allowed the identification of 23 fascicles. To our knowledge, this atlas does not include any information about the superficial structural connectivity. Furthermore, the chosen cohort was exclusively composed of females which can be a source of bias with respect to gender variability.

In this chapter, we propose an extended deep and superficial white matter atlas of the chimpanzee brain. Having access to both deep and superficial white matter connectivity will more thoroughly contribute to the exploration of the commonalities and differences of the Human brain with respect to our closest chimpanzee cousin at finer scales. In this frame, another part of this chapter is dedicated to a new developed atlas of the human brain following the same methodological approach in order to be able to compare human and chimpanzee atlases obtained with rigorously identical methodological processes. The development of these new atlases for both the chimpanzee and the human brains relies on the development of a sophisticated fiber clustering pipeline which does require very few anatomical priors, and thus, allows to automatically infer the superficial connectivity of the chimpanzee brain whose anatomy is largely unknown today.

# 6.2 Cohorts

#### 6.2.1 Chimpanzee cohort

We considered data coming from 39 healthy in vivo chimpanzees including 23 females and 16 males, imaged between 9 and 35 years old (mean = 19 years old) and housed at the National Yerkes Primate Research Center (YNPRC, Atlanta).

Each individual was scanned using a 3 Tesla Trio MRI system (Siemens, Erlangen) using a birdcage coil with a dedicated imaging protocol including : a high resolution 3D T1-weighted inversion recovery fast gradient echo anatomical scan (MPRAGE sequence) of 0.625mm isotropic resolution (echo time TE/repetition time TR=4.38ms/2600ms, inversion time TI=900ms, flip angle FA=8°, matrix size 256 x 256, read bandwidth RBW=130Hz/pixel). Five diffusion-weighted MRI scans were acquired using a 2D single-shot twice refocused Pulsed gradient spin echo (PGSE) echo-planar (EPI) sequence of 1.9mm isotropic resolution (TE/TR = 86ms/6s, flip angle FA=90°, read bandwidth RBW=1563Hz/pixel, matrix size 128x128, FOV=243.2x243.2 mm) at b=1000s/mm<sup>2</sup> along 60 diffusion directions and 5 b=0 s/mm T2-weighted references images.

All procedures were carried out in accordance with protocols approved by YNPRC and the Emory University Institutional Animal Care and Use Committee.

#### 6.2.2 Human cohort

We used anatomical and diffusion MRI scans from a cohort of 39 healthy human subjects stemming from the Human Connectome Project (HCP, release : http: //www. humanconnectome-project .org /) including 23 females and 16 males, imaged between 22 and 35 years old. It includes for each subject a series of diffusion-weighted MRI (dMRI) sequences performed on a Connectome Skyra 3T MRI system using a 2D spin-echo single-shot multiband EPI sequence (multi-band factor of 3, monopolar diffusion gradient pulses, 1.25 mm isotropic spatial resolution, TR/TE=5500/89.50ms) over 3 shells at b=1000/2000/3000s/mm2 along 90 diffusion directions for each shell, and 6 non-diffusion-weighted (b=0s/mm2) reference images. The data were preprocessed with eddy current and susceptibility artifacts correction steps.

## 6.3 Post-processing of anatomical and diffusion MRI data

#### 6.3.1 Fiber tracking

#### 6.3.1.1 Chimpanzees

Anatomical and diffusion MRI data were processed using a Python pipeline dedicated to the chimpanzee species using the CEA/NeuroSpin in-house C++ Ginkgo toolbox available at https: //framagit.org/cpoupon/gkg.

All T1-weighted images of the 39 chimpanzees' brains were matched to the Juna.chimp chimpanzee template (template release : https://www.chimpanzeebrain.org/) [Vickery et al. 2020]. To this aim, direct and inverse non-linear 3D registration transformations from each individual brain T1-weighted scan to the Juna.chimp template were computed using the ANTs (Advanced Normalization Tools) software, allowing a diffeomorphic registration based on Symmetric Normalization (SyN) [Avants, Tustison, Song, et al. 2009] with a mutual information similarity measure. The Juna.Chimp template is released with a high spatial resolution suitable for our project and corresponds to the size of a standard chimpanzee brain (from anterior to posterior =106mm; from up to bottom = 72mm; from left to right = 87mm). It also includes a cortical parcellation further needed to create the superficial white matter bundle atlas. In total, 76 regions corresponding to cortical areas from the DAVI 130 atlas were selected (38 per hemisphere).



Region	Abbreviation	Region	Abbreviation
anterior superior frontal gyrus	aSFG	posterior middle temporal gyrus	рМТG
middle superior frontal gyrus	mSFG	anterior inferior temporal gyrus	alTG
posterior superior frontal gyrus	pSFG	posterior inferior temporal gyrus	pITG
anterior middle frontal gyrus	aMFG	anterior fusiform gyrus	aFFG
posterior middle frontal gyrus	pMFG	posterior fusiform gyrus	pFFG
anterior inferior frontal gyrus	alFG	superior postcentral gyrus	sPoCG
middle inferior frontal gyrus	mIFG	middle postcentral gyrus	mPoCG
posterior inferior frontal gyrus	pIFG	inferior postcentral gyrus	iPoCG
medial orbitofrontal cortex	mOFC	superior parietal lobule	SPL
lateral orbitofrontal cortex	IOFC	supramarginal gyrus	SMG
superior precentral gyrus	sPrCG	angular gyrus	AnG
middle precentral gyrus	mPrCG	precuneus	PCun
inferior precentral gyrus	iPrCG	cuneus	Cun
paracentral lobule	PCL	lingual gyrus	LG
anterior insula	alns	superior occipital gyrus	sOG
posterior insula	plns	middle occipital gyrus	mOG
anterior superior temporal gyrus	aSTG	inferior occipital gyrus	iOG
posterior superior temporal gyrus	pSTG	entorhinal Cortex	EnC
superior middle temporal gyrus	aMTG	parahippocampal gyrus PHC	

Figure 6.2: The Juna.chimp template and selected cortical regions. Top : on the left : axial, coronal and sagital renderings of the template, on the right : the 38 cortical regions selected on each hemisphere. Bottom : table of the cortical regions selected and corresponding abbreviations.

At the individual scale, diffusion-weighted MRI data were first corrected for susceptibility artifacts with a method similar to that described in [J. L. Andersson, Skare, and Ashburner 2003], as implemented in FSL [Smith et al. 2004]. The corrected reference volume acquired at

b=0s/mm2 was then matched to the anatomical T1-weighted MRI using a rigid transformation computed with the Ginkgo registration tool relying on a mutual information criterion.

Individual maps of local orientation distribution functions (ODF) were reconstructed from the corrected diffusion MRI scans using the analytical Q-ball model [Maxime Descoteaux et al. 2007] at spherical harmonics order SH=6 with a Laplace-Beltrami regularization factor  $\lambda =$ 0.006. A whole-brain streamline regularized deterministic tractography algorithm (1 seed/voxel, forward step 0.4mm, aperture angle 30°, lower GFA threshold = 0.15) [Perrin et al. 2005] was then applied to each ODF map to generate streamlines within a mask corresponding to the brain established from the anatomical MRI, yielding the 39 chimpanzees' individual tractograms composed of several million fibers.

Streamlines whose length did not belong to the 5mm-300mm range were filtered out.

#### 6.3.1.2 Humans

Similarly to chimpanzees, we designed an analysis pipeline for diffusion-weighted MRI data processing based on the Ginkgo toolbox. Three consecutive steps were performed for each subject: registration of the subject's brain MRI to a common atlas space (the MNI ICBM 2009c non-linear asymmetric template) with the ANTS toolbox ; computation of the diffusion Orientation Distribution Functions (ODF) with the analytical Q-ball model ; computation of a whole-brain tractography with a regularized deterministic algorithm (parameters: 8 seeds/voxel, aperture angle: 30°, fiber length range: 1.25 - 300 mm, step: 0.3 mm, SH : 6,  $\lambda$  : 0.006).

#### 6.3.2 Fiber clustering

A 2-step clustering strategy similar to that proposed in [P. Guevara, Cyril Poupon, et al. 2011] was used to build up fascicle clusters relevant at the population level. This strategy is based on a first clustering step establishing fascicles (e.g. individual small fiber clusters) at the subject level, followed by a second step providing fascicle clusters at the population level.

#### 6.3.2.1 Intra-subject fiber clustering

Because fiber tracking methods can produce millions of streamlines per subject, establishing white matter bundle atlases from a group of subjects is a difficult task from a computational point of view due to the large size of the connectivity matrices involved at the group level, even if the group size remains small. The approach that was originally proposed in [P. Guevara, Cyril Poupon, et al. 2011] and that we also used is to decompose the problem into several steps in order to take benefit from different strategies to subsequently reduce the dimension of the problem. A first stage consists in clustering the streamlines of a single subject, relying on 8 consecutive steps (see figure 6.3):

- step 1: the streamlines are separated into 4 subgroups corresponding to the brain area they mostly belong to, e.g. right or left hemispheres or the brain-stem/cerebellum region. If a streamline is considered to equally belong to both hemispheres using a specified threshold (50 percent), it is classified into a further 4th subgroup, the inter-hemispheric subgroup;
- step 2: each streamline subgroup is then subdivided into 9 new subgroups corresponding to 9 equally spaced fiber length ranges between 7mm and 133mm;
- step 3: for each of the 9 subgroups and each brain area, a fiber density mask is computed and thresholded to provide a binary mask corresponding to the brain region populated by the streamline of the chosen length range;
- step 4: a k-means algorithm is used to compute a parcellation of each binary mask with parcels of similar size;

- step 5: an affinity matrix is computed between parcels that simply quantifies the level of connectivity of each pair of parcels;
- step 6: a hierarchical clustering algorithm is applied to this affinity matrix providing a dendrogram allowing to define clusters of strongly connected parcels;
- step 7: parcel clusters are finally intersected with the input streamline subgroup of interest, yielding the set of fiber clusters (or fascicles) corresponding to the fiber length range and brain area of interest. A streamline is considered to belong to a given parcel cluster if it has at least 40 percent of its length inside the cluster ;
- step 8: each fiber cluster is then further subdivided into smaller fascicle clusters based on their extremities using a watershed algorithm. The centroid of each fascicle corresponding to the streamline of the fascicle being the closest to all the other streamlines (using a symmetric mean of mean closest point distance) is computed to provide a synthetic representation of the fascicle that will be used during the next stage operated at the population level.



Figure 6.3: Intra-subject fiber clustering pipeline. Pipeline depicting the different steps of the fiber clustering, from the individual tractogram to the individual clusters centroid map.

#### 6.3.2.2 Inter-subject fiber clustering

A second stage aims to regroup the previous resulting individual fascicle sets in order to create white matter bundles representative of the population's structural connectivity. It relies on 5 consecutive steps (see figure 6.4):

- step 1: the centroids of all subjects collected during the first stage and providing a synthetic representation of all the individual fascicles are registered to the Juna.Chimp template space (MNI ICBM for humans) and resampled to further reduce their representation to 21 equally spaced points, thus allowing to drastically speed-up the computation of the distance between two centroids;
- step 2: all 21-point resampled centroids representing the individual fascicles are aggregated into 4 centroid maps corresponding to the left hemisphere, the right hemisphere, the interhemispheric fibers and the brainstem/cerebellum region;
- step 3: an affinity matrix is computed for each of these 4 centroid maps using a corrected pairwise maximum Euclidean distance between centroids. The objective of the correction is to take into account the actual morphometric difference between "long" and "short" white matter bundles: long bundles can have different extremity decussing while short bundles show less dispersed connections at their extremities. The implemented distance correction is further detailed. Using this modified distance, an affinity measure can be easily computed for all pairs of centroids using a Gaussian kernel  $e^{-d^2/\sigma^2}$  (with affinity variance equal to  $\sigma^2 = 140625mm^2$ ). The affinity of a centroid pair is stored in a sparse matrix when its value is greater than a specific threshold equal to  $e^{-d_{max}^2/\sigma^2}$ ,  $d_{max}$  representing the maximum distance allowed to aggregate centroids, and considered as null otherwise.
- step 4: a density-based spatial clustering (DBSCAN) [Ester et al. 1996] of each of the 4 centroid affinity matrices is subsequently performed providing 4 set of fascicle clusters for each brain region including the left hemisphere, the right hemisphere, the inter-hemispheric region and the brainstem/cerebellum region;
- step 5: Resulting fascicle clusters are discarded if they do not represent at least 40 percent of the subjects (percentage chosen considering the intra-subject variability). Discarded centroids are reintegrated to the kept fascicle clusters if their distance to the closest cluster remained below a maximum distance of  $d_{max_{exclusion}=4mm}$ .



Figure 6.4: Inter-subject fiber clustering pipeline. Pipeline depicting the different steps of the inter-subject fiber clustering, from the individual centroid maps to the final inter-subject bundle clusters.

Formula of the corrected distance chosen to compute fascicle clusters - The objective of this formula is to correct the evaluation of the symmetric pairwise distance between 2 centroids representing 2 individual fascicles in order to relax the constraints over the centroid distance when addressing long fascicles while keeping the distance unchanged for superficial (short) fascicles.

Let  $C_1$  and  $C_2$  be two centroids stemming from the intra-subject fiber clustering step. The centroids are represented by  $N_p$  control points  $\{P_{c_1}(i)\}\$  and  $\{P_{c_2}(i)\}\$  (21 control points in our case). Let  $d_{pairwise}(c_1, c_2)$  be the symmetric pairwise distance between centroids  $c_1$  and  $c_2$ . It yields:

$$d_{pairwise}(c_1, c_2) = min(\sqrt{\sum_{i=0}^{N_p - 1} (P_{c_1}(i) - P_{c_2}(i))^2}, \sqrt{\sum_{i=0}^{N_p - 1} (P_{c_1}(i) - P_{c_2}(N_p - i))^2})$$
(6.1)

A corrected distance was implemented to relax constraints over the distance function when the minimum centroid length  $L_{min} = min(length(C_1); length(C_2))$  increases in order to take into account the behavior of centroids showing more fanning configurations at their extremities in long fascicles in comparison to superficial ones:

$$d_{corrected}(c_1, c_2) = d_{pairwise}(c_1, c_2) - N_f(t_1T_1 + 1.3t_2T_2 + 1.6t_3T_3)$$
(6.2)

where:  $t_1 = 1$  if  $L_{min} \ge l_{min}$  or 0 otherwise  $t_2 = 1$  if  $L_{min} \ge l_{min} + (l_{max} - l_{min})/3$  or 0 otherwise  $t_3 = 1$  if  $L_{min}l_{min} + 2(l_{max} - l_{min})/3$  or 0 otherwise  $T_1 = \frac{\min(L_{min}, l_{min} + (l_{max} - l_{min})/3) - l_{min}}{l_{max} - l_{min}}$   $T_2 = \frac{\min(L_{min}, l_{min} + 2(l_{max} - l_{min})/3) - (l_{min} + (l_{max} - l_{min})/3)}{l_{max} - l_{min}}$  $T_3 = \frac{\min(L_{min}, l_{max}) - (l_{min} + 2(l_{max} - l_{min})/3)}{l_{max} - l_{min}}$ 

The normalizing factor  $N_f$  controls the degree of relaxation of the distance, being typically chosen to 26 mm in our case for chimpanzees and 6 mm for humans.  $l_{min}$  and  $l_{max}$  define the lower and upper fiber lengths that were defined from the input subject tractograms (chosen to be 7mm and 133mm respectively) in order to remove the smallest and longest artifactual fibers.

Optimization of the normalization factor of the corrected distance  $N_f$  and of the affinity maximum distance dmax - In order to maximize the number of generated intersubject fascicle clusters, the distance normalization factor  $N_f$  and the maximal centroid distance threshold  $d_{max}$  are optimized using a grid search algorithm for 50 values of  $N_f$  uniformly sampled within the [2;100] range and for 17 values of  $d_{max}$  uniformly sampled within the [2mm;34mm] range. This pre-evaluation is performed on a 10-subject subset of the population, which ensures to sufficiently take into account the cross-subject variability and allows to significantly speed-up the computation time. As shown in figure 6.5, the representation of the number of fascicle clusters with respect to  $N_f$  and  $d_{max}$  depicts a convex landscape which facilitates the identification of the optimal setting  $(N_f, d_{max})_{opt} = (26, 18mm)$ .



Figure 6.5: Optimization of the normalization factor of the corrected distance  $N_f$  and of the affinity maximum distance dmax for identification of the optimal setting :  $(N_f, d_{max})_{opt} = (26, 18mm)$ 

Concerning humans, the parameters used are summarized in figure 6.6.

		Value		
	Parameter name	CHIMPANZEE	HUMAN	
	Parcellation resolution	200 µm	200 µm	
	Average cluster size	2000 voxels	2000 voxels	
Intra-subject	Minimum cluster size	300 voxels	300 voxels	
fiber	Min. percentage of fiber length intersecting a cluster	40 %	33 %	
clustering	Length range of the fibers	7.72 - 133.26 mm	1.25 – 300 mm	
	Number of length ranges	9	10	
	Minimum fiber count in a cluster	5	5	
	Type of centroid distance	Normalized pairwise	Normalized pairwise	
	Normalization factor Nf	26 mm	6 mm	
	Minimum centroid length Imin	7.72 mm	1.25 mm	
	Maximum centroid length Imax	133.26 mm	300 mm	
Inter-subject	Minimum normalized distance	0.1 mm	0.1 mm	
clustering	Maximum distance for the centroid affinity	18 mm	NA	
	Maximum distance after exclusion	4 mm	10 mm	
	Variance of the centroid affinity $\sigma$ 2	140625 mm <sup>2</sup>	NA	
	Centroid point count	21	21	
	Minimum population percentage	40 %	50 %	

Figure 6.6: Table of the parameters used in the intra and inter-subject fiber clustering for chimpanzees and humans cohorts.

### 6.3.3 Atlasing

Fascicle clusters stemming from the two-step clustering stage were separated into long or superficial fascicle clusters according to their average length with respect to an empirically chosen threshold established from the histogram of fiber lengths at the population scale. Fascicle clusters whose lengths were under this threshold were considered 'superficial' whereas those whose lengths were above this threshold were considered 'long' or 'deep'.

For chimpanzees, the threshold was of 50mm. For humans, this same threshold was of 90mm.

**Deep white matter bundle atlas.** The deep white matter fiber bundles obtained were between 50 millimeters to 133 millimeters long for chimpanzees and 300 millimeters long for humans. The DBSCAN clustering allowed an effective grouping of the centroids to facilitate the selection of the chimpanzee white matter fascicles. The deep fascicles did not require the definition of regions of interest to be selected, they were established from the grouping of cross-subject fascicle clusters using a visual inspection confirmed by two independent neuro-anatomists.

Superficial white matter bundle atlas. After manually discarding fascicle clusters showing artifactual trajectories, fascicle clusters were further merged using a distance criterion, in order to obtain final sets of superficial fascicle clusters relevant from an anatomical point of view. Superficial clusters were then selected using the Davi130 parcellation atlas for chimps and a novel cortical parcellation atlas for humans. Each superficial cluster connecting two parcels A and B was attributed a name following the syntax A\_B\_Id (Id corresponding to the cluster index in the set of all clusters connecting parcels A and B).

# 6.4 Results

#### 6.4.1 Structural connectivity atlas of the chimpanzee brain

This novel deep and superficial connectivity atlas of the chimpanzee brain was established from the analysis of a diffusion MRI data set acquired on 39 individuals (23 females, 16 males), using a novel high performance clustering pipeline adapted to the chimpanzee brain. This algorithm automates the inference of deep and superficial white matter bundles from the set of virtual axonal fibers (represented by streamlines) that were computed using a diffusion MRI-based fiber tracking method for all individuals. In summary, the implemented analysis pipeline inherits the approach proposed in [P. Guevara, Cyril Poupon, et al. 2011] and is based on the use of 4 consecutive steps:

- Computation of individual tractograms using a streamline regularized deterministic tractography approach [Perrin et al. 2005].
- Computation of fascicles at the subject level from each individual tractogram separated into 9 equally spaced length ranges between 7.7 and 133.3mm using a hierarchical clustering algorithm. Each resulting individual fascicle represents a small set of individual fibers whose distance (defined as the symmetric mean of mean closest point distance) remains below a predefined threshold. Each fascicle is then represented by its centroid being the fiber depicting the shortest distance to all the other fibers populating the fascicle. This first clustering stage resulted in 39 fascicle sets composed of 19,920±1,273 individual fascicles. 10,016±1,273 individual fascicles were found for the left hemisphere and 9,904±1,169 individual fascicles were found for the right hemisphere, showing a slight asymmetry in favor of the left hemisphere.
- Computation of fascicle clusters at the group level from the set of all fascicle centroids previously transformed to a common template space using a density-based spatial clustering

algorithm (DBSCAN). Each resulting fascicle cluster corresponds to a connection hub at the group level. This stage yielded a total of 4862 fascicle clusters present in at least 40 percent of the population, subdivided into 2420 fascicle clusters for the left hemisphere and 2438 fascicle clusters for the right hemisphere

• Creation of deep and superficial white bundle atlases from the fascicle clusters using a semi-manual step. This last stage consists of aggregating for each target white matter bundle the set of fascicle clusters that matches the definition of the bundle. The definition varies between deep and superficial white matter bundles. On the one hand, deep white matter bundles are well identified from an anatomical point of view and typically defined by regions corresponding to known crossing areas or known exclusion areas. On the other hand, superficial white matter bundles, for which no anatomical atlas currently exists, are identified and named by the pair of cortical areas they connect.



Figure 6.7: Histograms of the number of clusters relatively to the fibers length. a) Histograms of the number of clusters and fibers relatively to the fibers length, b) Cumulative histogram of fiber lengths from the tractograms allowing to select fibers from 7mm to 133mm (top) and histogram of fiber lengths from the inter-subject fiber clustering allowing partially the discrimination between deep and superficial fibers (bottom)

#### 6.4.1.1 A new deep white matter fiber bundles atlas of the chimpanzee brain

We have considered them as 'deep' bundles, those composed of a majority of fascicle clusters whose length exceeds 50 mm (see figure 6.7, b.). This threshold resulted from a trade-off between a visual inspection and a brain size-based scaling of the length threshold conventionally used in the literature for the human brain (typically 80mm) to separate long-associative white matter bundles from superficial white matter bundles. Using this criteria, forty-six long white matter bundles were identified (see figure 6.8).



Figure 6.8: A new deep white matter fiber bundles atlas of the chimpanzee brain. 3D renderings of the 46 white matter bundles composing our long white matter atlas and including : the middle longitudinal bundle, the inferior longitudinal bundle, the arcuate, the frontal aslants, the uncinate, the fornix, the cingulum (dorsal and ventral), the motor and sensory ascending and descending fibers (cortico-spinal), the anterior commissure, the optic radiations, the ventral visual stream, the thalamic radiations (anterior, superior and posterior), the inferior fronto-occipital bundle ; the cerebellar fiber components : the hypothalamic and subthalamic fibers, the parallel fibers, and the cortico-ponto-cerebellar fibers ; the corpus callosum (CC) components : (left) the four subparts of the CC following Aboitiz labeling (splenium, isthmus, midbody, genu) and (right) the seven subparts of the Witelson labeling. (inf : inferior). White matter bundles are all represented with different colors and superimposed to the cortex pial surface computed from the DAVI130 atlas and rendered with transparency.

The deep white matter bundles identified are : the inferior fronto-occipital fasciculus, the middle longitudinal fasciculus, the arcuate fasciculus, the frontal aslant, the uncinate fasciculus, the fornix, the cingulum (dorsal and ventral), the motor and somato-sensory ascending and descending fibers (cortico-spinal tract and thalamo-cortical radiations), the corpus callosum, the anterior and posterior commissures, the ventral visual stream, and the optic radiations. In order to remove any specificity related to putative lateralization effects (such as for the cortical spinal tract for instance), the established white matter bundle atlas was further symmetrized

with respect to the two hemispheres to avoid any bias related to the dominant laterality of the subjects used to create the atlas.

The **commissural fibers** are composed of the anterior commissure (AC) and the corpus callosum (CC).

The AC (see figure 6.9) crosses through the ventral part of the anterior wall of the third ventricle, rostrally to the columns of the fornix, and connects the two temporal lobes of the left and right hemispheres on their rostral and medial parts.

The **CC** (see figure 6.10) interconnects all the lobes of both hemispheres and is composed, rostrally to caudally, of the genu, midbody, isthmus and the splenium, as proposed by following [Aboitiz et al. 1992] convention and the 7 labels segmented parcellation from [Witelson 1989]). Segmentation of these regions were performed in the mid-sagittal plane using the approach described in Aboitiz and Witelson's studies.



Figure 6.9: A commissural fiber : the anterior commissure. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.10: A commissural fiber : the Corpus Callosum. Left : Aboitiz labelling of the CC displayed on the Juna. Chimp template mesh and anatomical image ; right : Witelson labelling of the CC displayed on the Juna. Chimp template mesh and anatomical image.

The projection fibers proposed in our long white matter bundle atlas are composed of efferent and afferent fibers. They correspond to pairs of contralateral white matter bundles including : the cortico-spinal tracts (CST), the thalamic radiations (anterior, superior, posterior) (TRa, TRs, TRp), the cortico-ponto-cerebellar tracts (CPCT), and the optic radiations (OR).

The **CSTs** (see figure 6.11) originate from the cortical motor areas, mainly from the precentral gyrus but also from the more rostrally located cortical areas (premotor cortex and supplementary motor area). Then, they pass through the corona radiata, the posterior limb of the internal capsule, and reach the anterior part of the brainstem (midbrain, pons and medulla oblongata). The **TRs** (see figure 6.12) arise from the thalamus and reach different cortical areas: the frontal cortex for the TRas, the parietal cortex for the TRss, and the occipital cortex for the TRps. Projection fibers connecting the cerebral cortex and the pons or the cerebellar cortex were identified as The **CPCTs** (see figure 6.13). They originate from the superior frontal and parietal cortices and connect the cerebellum through the superior and middle cerebellar peduncles. It is important to note that a larger number of fibers connect the cerebellum through the ipsilateral rather than the contralateral peduncles. The **ORs** (see figure 6.14) arise from the lateral geniculate nucleus, extend around the occipital horn of the lateral ventricle and project caudally to the primary visual cortex around the calcarine fissure in the occipital lobe.



Figure 6.11: The cortico-spinal tracts. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.12: The Thalamic radiations. Sagital left and right, and superior view of the thalamic radiations on a 3D mesh of the Juna template brain. Ant : Anterior, Sup : Superior, post : Posterior



Figure 6.13: The cortico-ponto-cerebellar tracts. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.14: The optical radiations. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.

Among the **association fibers** reconstructed in our deep white matter atlas are pairs of contralateral white matter bundles including : the inferior fronto-occipital fasciculi (IFOF), the inferior longitudinal fasciculi (ILF), the middle longitudinal fasciculi (MLF), the ventral visual

streams (VVS), the arcuate fasciculi (AF), the frontal aslant tracts (FAT), the uncinate fasciculi (Unc), the cingulum (CG) (including ventral CGv and dorsal CGd) and the fornix (FX).

The **IFOFs** (see figure 6.15) are long fasciculi connecting the inferior frontal gyrus and the medial part of the occipital lobe, passing through the external capsule where their sections narrow. The **ILFs** (see figure 6.16) connect the ventro-lateral part of the temporal poles and the inferior temporal gyri to the ventral part of the occipital lobes. These bundles run ventrally to the IFOFs, parallel to their paths in the occipito-temporal lobes. The MLFs (see figure 6.17) connect the dorsal part of the temporal poles and the superior temporal gyri with the parietal lobes and, to a lesser extent, with the dorsal parts of the occipital lobes. They are located dorsally to the ILFs and laterally to the IFOFs. The VVSs (see figure 6.18) originate from the occipital lobe, run towards the temporal lobes ventrally to the MLFs, laterally to the ILFs, and terminate in the middle temporal gyri. The AFs (see figure 6.19) are curved white matter bundles that originate in the inferior frontal gyrus and extend caudally to the temporo-parietal junction. The **FATs** (see figure 6.20) are shorter bundles located inside the frontal lobes, connecting the superior frontal gyri to the ventro-lateral part of the inferior frontal gyri. The Uncs (see figure 6.21) are curved white matter bundles which originate in the rostral part of the temporal lobes, bend upward rostrally from the anterior insula, and extend to the inferior frontal gyri and the orbito-frontal cortex. The CGs (see figure 6.22) are divided into two subparts : the dorsal CGd and the ventral CGv parts. The CGv parts stem from the caudal parts of the cingulate gyri, passing through the parahippocampal gyri and reaching the hippocampus head. The CGd parts are located underneath the cingulate cortices, coursing dorsally along the CC to reach the medial prefrontal cortices. The **FXs** (see figure 6.23) could also be partially reconstructed : they consist in C-shaped bundles that originate from the hippocampal head and extend caudally alongside the hippocampus. At the most caudal part of the hippocampal tail, the FXs bend medially and dorsally. Both FXs converge together at the medial surface of both hemispheres to form the posterior pillars of the fornices, which extend vertically, rostrally to the genu of the CC. They finally curve rostrally and run ventrally to the CC.



Figure 6.15: The inferior fronto-occipital fasciculus. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.16: The inferior longitudinal fasciculus. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.17: The middle longitudinal fasciculus. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.18: The ventral visual streams. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.19: The arcuate fasciculus. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.20: The frontal aslants. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.21: The uncinate fasciculus. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.22: The ventral and dorsal cingulums. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.23: The fornix. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.

**Ponto-cerebellar fibers** could also be identified including : the cortico-ponto-cerebellar tracts, described above, the parallel fibers (see figure 6.24) and the hypothalamic/subthalamic

fibers (see figure 6.25).



Figure 6.24: The parallel fibers. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.



Figure 6.25: The hypothalamic/subthalamic fibers. (Top) tracts superimposed on a 3D mesh of the Juna. Chimp template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the Juna. Chimp template. left sagittal, coronal, and right sagittal views.

From the last and only previously released deep white matter bundles atlas of the chimpanzee brain from [Bryant, L. Li, et al. 2020], we are now able to complete this atlas with : the corticoponto cerebellar tracts, the ventral visual streams, the hypothalamic and subthalamic fibers, the parallel fibers and the complete corpus corpus callosum following both Aboitiz's and Witelson's labeling.

Some previously described bundles using seeding regions of interest were not identified using our fiber clustering method, such as the superior longitudinal fasciculus and the acoustic radiations.

#### 6.4.1.2 A new superficial white matter fiber bundles atlas of the chimpanzee brain

In order to map the superficial white matter connectivity, two sets of neighboring cortical regions were defined for the left and right hemispheres using the Davi130 atlas. The 38 cortical regions considered for the left and right hemispheres were : the anterior/middle/posterior superior frontal gyrus (aSFG/mSFG/pSFG) ; the anterior/ posterior middle frontal gyrus (aMFG/pMFG) ; the anterior/middle/posterior inferior frontal gyrus (aIFG/mIFG/pIFG) ; the medial lateral orbitofrontal cortex (mOFC/ lOFC) ; the superior, middle, inferior precentral gyrus (sPrCG / mPrCG / iPrCG) ; the Paracentral Lobule (PCL) ; the anterior and posterior insula (alns / plns) ; the anterior/posterior superior temporal gyrus (aSTG/pSTG) ; the anterior/posterior middle temporal gyrus (aMTG/pMTG) ; the anterior/posterior inferior frontal gyrus (aSTG/pSTG) ; the superior/posterior gyrus (aITG, pITG) ; the anterior/posterior fusiform gyrus (aFFG/pFFG) ; the superior/middle/inferior postcentral gyrus (sPoCG/mPoCG/iPoCG) ; the superior parietal lobule (SPL) ; the supramarginal gyrus (SMG) ; the angular gyrus (AnG) ; the Precuneus (PCun) ; the cuneus (Cun) ; the Lingual Gyrus (LG) ; the superior/middle/inferior occipital gyrus (sOG / mOG/ iOG) ; the entorhinal Cortex (EnC) ; the parahippocampal gyrus (PHC).

111 pairs of cortical regions in the left hemisphere and 116 pairs of cortical regions in the right hemisphere present connections, corresponding to 422 white matter bundles (aggregating 76,845 fibers stemming from the individual tractograms) for the left hemisphere, and 400 white matter bundles (aggregating 74,091 fibers stemming from the individual tractograms) for the right hemisphere (see figure 6.26, and 6.27). Connections were found for all the 38 cortical regions composing the Davi130 atlas.



Figure 6.26: Graphical renderings of the 822 white matter bundles composing the superficial white matter connectivity atlas of the chimpanzee brain. a) 422 white matter bundles interconnecting 111 pairs of cortical regions from the left hemisphere as defined in the DAVI130 cortex atlas and b) 400 white matter bundles interconnecting 116 pairs of regions from the right hemisphere; c) 3D superimposition of the full set of white matter bundles composing the superficial white matter atlas and of the pial surface stemming from the DAVI130 template; a different color is attributed to each of the 822 white matter bundles; d): zoom over 3 superficial white matter bundles with the corresponding surrounded sulci highlighting the coherence of the reconstructed fiber trajectories populating each bundle

A significant variability of the number of fascicles (e.g. fiber clusters) originating from each

cortical region was observed (see figure 6.28.). Notably, cortical areas AnG, pMTG and SMG depicted the largest number of fascicles in both hemispheres : AnG (LH : 56 ; RH : 45), pMTG (LH : 54; RH : 49), SMG (LH : 38 ; RH : 39). Some other cortical areas showed significant differences in connectivity between hemispheres, such as the mPoCG with 25 clusters in the left hemisphere versus 6 clusters in the right hemisphere. Cortical areas with a very low connectivity were also observed in both hemispheres such as the EnC, aSFG and plns areas : EnC (LH : 4 ; RH : 3); aSFG (LH : 4 ; RH : 3), plns (LH : 2; RH : 2). In the left hemisphere, the PCL regions notably contained few clusters (5), and in the right hemisphere, we noticed the sPoCG region to also display few clusters (6). The pair of regions sharing the highest number of clusters on both hemisphere were : pMTG\_AnG (LH : 16 ; RH : 12), aMFG\_pIFG (LH : 14 ; RH : 11), iPoCG\_SMG (LH : 12 ; RH : 13). We also noticed that in the left hemisphere, the pair pMTG\_pITG had 12 clusters.

Left Hemisphere		Right Hemisphere		Left Hemisphere		Right Hemisphere	
Pairs of regions	Number of clusters						
aFFG_aFFG	1	aFFG_iOG	1	mPrCG mPoCG 002	3	mPrCG mPoCG	Ż
aFFG_LG	4	aFFG_LG	1	mSFG PCL	3	mPrCG mPrCG	1
aFFG_pFFG	9	aFFG_PCun	1	mSFG_pIFG	1	mPrCG_sPoCG	1
aFFG_PHC	1	aFFG_pFFG	6	mSFG_pMFG	5	mSFG_aMFG	5
alFG_alns	1	alFG_alns	1	mSFG_pSFG	3	mSFG_iPrCG	2
aIFG IOFC	7	aIFG IOFC	6	PCun Cun 002	4	mSFG mPrCG	2
alTG aFFG	7	alTG aFFG	4	PCun LG	1	mSFG PCL	4
alTG pITG	6	alTG LG	1	pFFG iOG	7	mSFG pIFG	2
ains aSTG	2	aITG PHC	2	pFFG_LG	5	mSFG_pMFG	8
alns nSTG	1	alTG plTG	7	PHC Cun	8	mSFG pSFG	1
aMEG alos	1	ains aSTG	1	PHC_iOG	1	PCun_Cun	4
aMEG mIEG	11	alos SMG	1	PHC LG	5	PCun LG	1
aMEG pIEG	15	aMEG alos	1	PHC PCun	1	pFFG iOG	7
aMEC pMEC	15	aMEG LOEC	1	pIFG alns	1	pFFG LG	4
aWIC aITC	4	aMEC mIEC	6	pIFG iPrCG	6	PHC Cun	7
awing_ang	2	alviro_niro	0	pIFG IOFC	1	PHC IOG	1
amig_pirg	3	aMFG_DIFG		pITG aFFG	2	PHCLG	7
amig_pmig	3	aMFG_pMFG	3	pITG iOG	3	PHC PCun	2
AnG_AnG	1	aMTG_alTG	3	pITG mOG	3	pIFG alns	1
AnG_Cun	9	aMTG_PHC	1	pITG PHC	1	pIFG iPoCG	1
AnG_mOG	7	aMTG_pITG	3	pins pSTG	2	pIFG iPrCG 002	3
AnG_sOG	3	aMTG_pMTG	3	pMFG iPrCG	6	pIFG SMG	1
aSFG_IOFC	1	AnG_Cun	5	pMFG mPrCG	8	pITG aFFG	1
aSFG_mSFG	2	AnG_mOG	5	pMFG pIFG	5	pITG iOG	2
aSFG_pSFG	1	AnG_PCun	1	pMFG sPrCG	7	pITG LG	1
aSTG_aMTG	1	AnG_sOG	7	pMTG aFFG	1	DITG DEFG	2
aSTG_pMTG	5	aSFG_aMFG	1	pMTG alTG	1	pins pSTG	1
aSTG_pSTG	7	aSFG_IOFC	1	pMTG AnG	16	pins SMG	1
Cun_Cun	1	aSFG_pSFG	1	pMTG Cun	1	pMFG iPrCG	5
Cun_LG	3	aSTG_aMTG	4	pMTG iOG	1	pMFG mPrCG	7
Cun sOG	2	aSTG pMTG	8	pMTG mOG	2	pMFG pIFG	5
EnC PHC 003	5	aSTG pSTG	4	pMTG pITG	12	pMFG sPrCG	7
PoCG SMG	12	Cun Cun	1	pMTG pMTG	1	pMTG aFFG	1
iPoCG SPL	1	Cun sOG	1	pMTG sOG	2	pMTG alTG	1
iPrCG iPoCG	7	EnC PHC	3	pSFG iPrCG	1	pMTG AnG	12
iPrCG iPrCG	1	iPoCG SMG	13	pSFG mPrCG	1	pMTG iOG	1
iPrCG mPoCG	2	iPrCG iPoCG	12	pSFG PCL	2	pMTG mOG	6
iPrCG SMG	2	iPrCG mPoCG	1	pSFG PCun	1	pMTG PHC	1
	1	iPrCG_sPoCG	1	pSFG pSFG	1	pMTG pITG	7
	1		3	pSFG sPrCG	3	pMTG sOG	4
LO_LO	6		1	pSTG AnG	4	pSFG mPrCG	2
IOFC aSTC	2		7	pSTG pMTG	8	pSFG PCL	6
IDFC_aSIG	2		2	pSTG pSTG	1	pSFG PCun	2
	2		2	pSTG SMG	3	pSFG pMFG	4
mIFG_IOFC	3		3	pSTG_SPL	2	pSFG_pSFG	1
mIFG_DIFG	3	MIFG_IOFC	6	SMG AnG	5	pSTG AnG	5
mOFC_ains	2	mIFG_pIFG	2	SMG SMG	3	pSTG pMTG	5
mOFC_aMIG	1	mOFC_aMIG	1	sOG mOG	3	pSTG_pSTG	4
mOFC_aSTG	1	mOFC_aSTG	3	SPL_AnG	10	pSTG_SMG	2
mOFC_EnC	2	mOFC_IOFC	7	SPL_Cun	1	SMG_AnG	4
mOFC_IOFC	7	mOG_iOG	3	SPL PCun	1	SMG SMG	2
mOG_iOG	4	mPoCG_iPoCG	8	SPL SMG	9	sog mog	6
mPoCG_iPoCG	8	mPoCG_mPoCG	1	SPL SPL	2	SPL AnG	6
mPoCG_mPoCG	4	mPoCG_SMG	1	sPoCG iPoCG	4	SPL PCun	1
mPoCG_SMG	1	mPoCG_SPL	1	sPoCG mPoCG	3	SPL SMG	11
mPrCG_iPrCG	9	mPrCG_iPrCG	8	sPrCG iPoCG	1	sPoCG iPoCG	1
				sPrCG iPrCG	2	sPoCG mPoCG 002	1
				sPrCG mPrCG	6	SPOCG SMG	1
				sPrCG sPoCG	2	sPrCG iPrCG	2
						sPrCG mPoCG	2

Figure 6.27: Table of the number of cluster per pair of regions.

sPrCG sPoCG

After proceeding with the segmentation of the superficial white matter bundles of all the subjects of our cohort using our superficial atlas, we observed differences in the number of interconnections between regions. Indeed, the most interconnected regions were the angular (AnG) and supramarginal gyri (SMG). Some areas in the frontal lobe such as the middle frontal

gyrus and superior parietal lobule also displayed a large number of connections. The motor and sensory motor areas, located along the central sulcus in each gyrus, presented a gradient of connectivity with a higher number of connections present in the inferior, pre- and postcentral gyri compared to the middle and superior pre/post central gyri. A higher number of superficial white matter bundles was observed in the motor regions (e.g. precentral gyrus) compared to the somatosensory regions (e.g. postcentral gyrus). The temporal lobe also depicted a higher density of connections in the posterior temporal gyrus (including the posterior superior, posterior middle and posterior inferior gyri) compared to the anterior temporal gyrus (containing the anterior superior, anterior middle and anterior inferior gyrus). In both hemispheres, the posterior middle temporal gyrus was the most interconnected gyrus in the temporal lobe.



Figure 6.28: Average density maps of superficial streamlines (top) and white matter fascicle clusters (bottom) for the left and the right hemispheres resulting from the automatic segmentation of the superficial white matter bundles of all chimpanzees using the established superficial white matter atlas

We could also notice a diversity in the short fibers shapes (see figure 6.26, d. and figure 6.29). Indeed, symmetrically between the left and the right hemisphere, we could observe : "U"-shaped fibers, "V"-shaped fibers and "L"-shaped fibers. The "U" fibers seem located in all lobes of the brain, the "V" fibers were mostly found in the superior frontal areas and superior temporal lobe, and the "L" fibers depicting a flatter shape could be seen running ventrally.



Figure 6.29: Diversity in the superficial fibers shapes. Representation of the distribution of the superficial white matter bundles with respect to 3 identified superficial bundle shapes: "L" bundle shape, "V" bundle shape and "U" bundle shape

## 6.4.2 Structural connectivity atlas of the human brain

#### 6.4.2.1 Comparing chimpanzees with humans

To establish a relevant comparison between humans and chimpanzees, we carefully matched the post-processing pipelines and cohorts. Since the Desikan [Desikan et al. 2006] and Davi130 atlases did not exactly present homologous cortical regions, we had to further redefine the Desikan atlas and propose an inherited cortical atlas sharing the same number of cortical areas (76) as the chimpanzee DAVI 130 atlas. To do so, we used an in-house tool (Voi) allowing the clipping and definition of 76 cortical regions.



Figure 6.30: Cortical parcellation of the chimpanzee and human brains: (left) the chimpanzee cortical parcellation where the 38 left parcels are shown, these parcels were extracted manually from the DAVI130 atlas; (right) the human cortical parcellation used for the superficial bundle atlas, drawn on the MNI template using the Desikan-Killiany atlas as a reference for corresponding regions of the DAVI130. The 38 regions were manually drawn using Voi from the Ginkgo toolbox

#### 6.4.2.2 A new deep white matter fiber bundles atlas of the human brain

We have considered them as 'long' bundles, those composed of a majority of fascicle clusters whose length exceeds 90 mm. This threshold resulted from a trade-off between a visual inspection and a brain size-based scaling of the length threshold conventionally used in the literature for the human brain (typically 80-90mm) to separate long associative white matter bundles from superficial white matter bundles. Using this criteria, 45 long white matter bundles were identified.



Figure 6.31: A new deep white matter fiber bundles atlas of the human brain. 3D renderings of the 45 white matter bundles composing our long white matter atlas and including : the middle longitudinal bundle, the inferior longitudinal bundle, the arcuate, the frontal aslants, the uncinate, the fornix, the cingulum (dorsal and ventral), the motor and sensory ascending and descending fibers (cortico-spinal), the anterior commissure, the optic radiations, the ventral visual stream, the thalamic radiations (anterior, superior and posterior), the inferior fronto-occipital bundle ; the cerebellar fiber components : the hypothalamic and subthalamic fibers, and the cortico-pontocerebellar fibers ; The corpus callosum (CC) components : (left) the four subparts of the CC following Aboitiz labeling (splenium, isthmus, midbody, genu) and (right) the seven subparts of the Witelson labeling. (inf : inferior). White matter bundles are all represented with different colors and superimposed to the cortex pial surface computed from the MNI template and rendered with transparency.

The deep white matter bundles identified for the human brain correspond to the ones found for the chimpanzee brain, in a goal of comparison : the inferior fronto-occipital fasciculus, the middle longitudinal fasciculus, the arcuate fasciculus, the frontal aslant, the uncinate fasciculus, the fornix, the cingulum (dorsal and ventral), the motor and somato-sensory ascending and descending fibers (cortico-spinal tract and thalamo-cortical radiations), the corpus callosum, the anterior and posterior commissures, the ventral visual stream, and the optic radiations. In order to remove any specificity related to putative lateralization effects (such as for the cortical spinal tract for instance), the established white matter bundle atlas was further symmetrized with respect to the two hemispheres to avoid any bias related to the dominant laterality of the subjects used to create the atlas. For the purpose of comparison, the organisation of this part is the same as the one from the chimpanzee.

**The commissural fibers** are composed of the anterior commissure (AC) and the corpus callosum (CC).

• The AC extracted for humans was thicker compared to chimps (see figure 6.32). The two species tracts followed the same trajectory, crossing through the ventral part of the anterior wall of the third ventricle, rostrally to the columns of the fornix, and connecting the two temporal lobes of the left and right hemispheres on their rostral and medial parts. The temporal connections of the fibers in humans where more numerous than for the chimpanzees.



Figure 6.32: A commissural fiber : the anterior commissure. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

 $\bullet\,$  Following the same clipping of the  ${\bf CC}$  for both humans and chimpanzee (see figure 6.33

and 6.34), using both Aboitiz and Witelson's labeling of CC regions, we can observe that the CC follow the same pattern of organisation.



Figure 6.33: A commissural fiber : the Corpus Callosum in humans. Left : Aboitiz labelling of the CC displayed on the MNI template mesh and anatomical image ; right : Witelson labelling of the CC displayed on the MNI template mesh and anatomical image



Figure 6.34: Clipping of the Corpus Callosum for the chimpanzee and human, following Witelson labelling.

The projection fibers proposed in our long white matter bundle atlas are composed of efferent and afferent fibers. They correspond to pairs of contralateral white matter bundles including the: cortico-spinal tracts (CST), the thalamic radiations (anterior, superior, posterior) (TRa, TRs, TRp), the cortico-ponto-cerebellar tracts (CPCT), and the optic radiations (OR).

• Concerning the **CSTs**, the course of the tract seems to basically stay the same, with fibers originating from the precentral gyrus and post-central gyrus passing through the corona radiata, the posterior limb of the internal capsule, and reach the anterior part of the brainstem (see figure 6.35). However, the global shape of the tract looks different, indeed, in humans while our spinal chord is somehow aligned to our foramen magnum do to our


bipedal postural station, the ones of the chimps are ventrally banded, in order to reach the spinal chord following the convolution of a quadrupedal specie.

Figure 6.35: The cortico-spinal tracts. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **TRs** from humans arise from the thalamus and reach different cortical areas: the frontal cortex for the TRas, the parietal cortex for the TRss, and the occipital cortex for the TRps (see figure 6.36). No differences could really be observed between the two species at this level of details. Further investigations about the thalamic regions connecting the cerebral cortex of both species could help rise some singularities.



Figure 6.36: The Thalamic radiations. (Top) Sagital left and right, and superior view of the thalamic radiations on a 3D mesh of the Juna template brain; (Bottom) Sagital left and right, and superior view of the thalamic radiations on a 3D mesh of the MNI template brain.

• Projection fibers connecting the cerebral cortex and the pons or the cerebellar cortex were identified as the **CPCTs** (see figure 6.37). These tracts from humans, as for chimps, originate from the superior frontal and parietal cortices and connect the cerebellum through the superior and middle cerebellar peduncles. It is to be noted that we observe much thicker tracts for the chimpanzee than for humans.



Figure 6.37: The cortico-ponto-cerebellar tracts. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• Unlike chimpanzees, the **ORs** from humans followed and entire course from the occipital lobe to the thalamic regions, depicted a bended aspect before reaching the thalamic nucleus (see figure 6.38).



Figure 6.38: The optical radiations. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

Among the **association fibers** reconstructed in our long white matter atlas are pairs of contralateral white matter bundles including : the inferior fronto-occipital fasciculi (IFOF), the inferior longitudinal fasciculi (ILF), the middle longitudinal fasciculi (MLF), the ventral visual streams (VVS), the arcuate fasciculi (AF), the frontal aslant tracts (FAT), the uncinate fasciculi (Unc), the cingulum (CG) (including ventral CGv and dorsal CGd) and the fornix (FX).

• The **IFOFs** of the human brain depicted an aspect and a tract course identical to the one of the chimpanzee, implying that this bundle seems well conserved between the two species (see figure 6.39).



Figure 6.39: The inferior fronto-occipital fasciculus. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **ILFs** appear pretty similar between the two species (see figure 6.40).



Figure 6.40: The inferior longitudinal fasciculus. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **MLFs**, for both species, connect the temporal anterior pole (see figure 6.41). However, their endings seem to differ. Indeed, in the chimpanzee, the tracts barely connect the occipital lobe meanwhile, the human tracts showed important connections with the occipital region, in addition to the ones of the parietal lobe.



Figure 6.41: The middle longitudinal fasciculus. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **VVSs** showed a similar course of tracts between humans and chimpanzees, except concerning the anterior temporal connections (see figure 6.42).



Figure 6.42: The ventral visual streams. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

By looking at both species temporal tracts connecting occipital regions, we can observe different patterns of organization (see figure 6.43). Indeed, while the different tracts courses seem roughly the same, we can observe that the inferior longitudinal fasciculus seems to be dorsal to the ventral visual stream in humans, while it is ventral to the one of the chimpanzee.



Figure 6.43: Overlapping projection fibers of the temporal lobe. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal view. inf : inferior, mid : middle.

• The **AFs** are surely among the most different tracts between humans and chimps (see figure 6.44). Indeed, as they depict a curved aspect with fibers originating in the inferior frontal gyrus and extending caudally to the temporo-parietal junction in chimpanzee, lacking a ventral component, the AFs of the humans are thicker, bigger, and displays a ventral trajectory passing in the temporal lobe to reach the inferior temporal pole.



Figure 6.44: The Arcuate fasciculus. Top: views of the tracts previously seen on the chimpanzee Juna.chimp template. For human: (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **FATs** between humans and chimpanzees are very similar (see figure 6.45). The differences that can be noted are that for chimpanzees, the tracts would reach more anterior inferior frontal regions than in humans, and appear to be thinner.



Figure 6.45: The Frontal aslants. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **Uncs** were closely similar between the two species (see figure 6.46).



Figure 6.46: The Uncinate fasciculus. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **CGs** were closely similar between the two species (see figure 6.47).



Figure 6.47: The dorsal and ventral cingulums. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **FXs** were closely similar between the two species (see figure 6.48).



Figure 6.48: The Fornix. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

• The **hypo-subthalamic fibers** were closely similar between the two species (see figure 6.49).



Figure 6.49: The Hypo-subthalamic. Top : views of the tracts previously seen on the chimpanzee Juna.chimp template. For human : (Top) tracts superimposed on a 3D mesh of the MNI template; (Bottom) tracts superimposed on the T1-weighted anatomical image of the MNI template. left sagittal, coronal, and right sagittal views.

# 6.4.2.3 A new superficial white matter fiber bundles (SWMB) atlas of the human brain

As for the chimpanzee brain, we focused on reconstructing the superficial fibers of the human brain. On figure 6.50 is depicted a global overview of the SWMB atlas of the human brain, with the circular matrix of connections between cortical regions for the left and right hemispheres. On figure 6.51 and 6.52 are presented the two tables of the corresponding superficial bundles from the SWMB atlas, with the corresponding number of clusters found.



Figure 6.50: A new superficial white matter fiber bundles atlas of the human brain. Top : left and right hemisphere connectivity matrices for bundles connecting the cortical regions, at the bottom : rendering of the superficial white matter atlas of the human brain, based on a fiber clustering from 39 subjects. Each bundle is represented with a color

Left hemisphere		aSFG_pSFG	1	mPoCG_SPL	3	pSFG_iPoCG	1
		aSTG_aSTG	2	mPrCG_iPoCG	10	pSFG_iPrCG	2
	California - California -	aSTG_EnC	1	1 mPrCG_mPoCG		pSFG_mPrCG	6
Pairs of regions	Number of	aSTG_iPoCG	1	mPrCG mPrCG	3	pSFG_PCL	2
al a ana a a a a a a a a a	clusters	aSTG_pSTG	4	mPrCG_SPI	1	pSFG_PCun	2
aFFG_pFFG	2	Cun Cun	11	mSFG aMFG	13		3
aFFG_PHC	1	Cup iOG	1	mSFG mlFG	3	pSFG_pMFG	8
alFG_alFG	2	Cup LO	6	mSFG mSFG	18	pSFG_pSFG	27
alFG_IOFC	6		2	mSFG_plFG	2	pSTG_aMTG	3
alFG_mOFC	2		3	mSFG_pMFG	2	pSTG_AnG	2
alTG alTG	13	Enc_arrg	3	mSFG_pSFG	2	pSTG_iPoCG	1
all G EnC	1	EnC_LG	1	PCL_PCL	4	pSIG_pMIG	1
alTG mOG	1	EnC_pFFG	1	PCL_PCun	3	pSTG_pSTG	6
	7		2	PCL_SPL	1	pSTG_SMG	8
	1	IUG_IUG	3	PCL_sPoCG	2	SMG_SMG	21
allo_SMG	1	iPoCG_POCG	10	PCun_LG	1	sOG_mOG	13
ains_ains aine_aSTG	2		2	PCun_PCun	7	sOG_sOG	7
alse EnC	1	iPrCG_alos	1	pFFG_AnG	2	SPL_AnG	11
alos iPoCG	1	iPrCG_AnG	1	pFFG_LG	2	SPL LG	1
ains pins	1	iPrCG_iPnCG	7	pFFG_pFFG	4	SPL_PCun	1
ains SMG	2	iPrCG_iPrCG	11	pFFG sOG	1	SPL_SMG	7
aMEG alEG	3	iPrCG_mPaCG	3	PHC Cun	1	SPL_sOG	3
aMEG aMEG	56	iProg_NPOCO	3	PHC_LG	3	SPL_SPL	16
aMEC iDrCC	1	inco spi	1	PHC_PHC	4	sPoCG_mPoCG	1
aMEG_IPEC	2		4	PHC_sOG	1	sPoCG_SPL	4
aMEG mIEG	12	10 - 00	1	pIFG iPoCG	7	sPrCG_sPoCG	2
aMEG_mPrCG	1		2		3	3	
aMEG pIEG	3	IOEC alos	3		2	-	
aMEG pIEG	1		3	pilo_arro	2		
aMEG_pMEG	12		12	pfTG_AnG	9		
ann o_phin o	12	mIEG alne	3	pITG_mOG	3		
aMTG_aITG	4		1	pITG_pFFG	1		
aMTG_aMTG	8	miFG_miFG	15	pITG_pITG	10		
aMTG_EnC	1	mOFC ains	2	pMFG_iPrCG	6	0	
aMTG_pMTG	4	mOFC aSTG	2	pMFG_mlFG	1	<u></u>	
Ang Ang	9	mOFC_EnC	2	pMFG_mPrCG	5	<u></u>	
AnG mOG	4	mOFC_IOFC	4	pMFG_pIFG	4	<u>.</u>	
Ang_nog	2	mOFC mOFC	4	pMFG_pMFG	10		
Alig_SUG	1	mOG iOG	2	pMTG_aITG	2	Į.	
aSEC aMEC	3	mOG mOG	13	pMTG_AnG	6		
aoro_amro		mPoCG AnG	2	pMTG_mOG	1		
aSFG_aSFG	10	mPoCG iPoCG	4	pMTG pMTG	10	(C)	
aSFG_mOFC	3	mPoCG_mPoCG	7	pMTG_SMG	4	1	
aSFG_mSFG	13	mPoCG_SMG	2	pSFG aMFG	6		

Figure 6.51: Table of corresponding pairs of regions with their number of clusters for the left hemisphere superficial bundles atlas

Diabtham		aSTG SMG	1	mSFG plFG	2	nSEG INSEG	10
Right nemisphere		Cup Cup	4	mSFG_pMFG	2		15
	Number of	Cun_cun	4	mSFG pSFG	8	pare_spoce	
Pairs of regions	clusters	Cup LG	6	PCL PCL	2	pSFG_sPrCG	1
aFFG_aFFG	1	EnC aFEG	3	PCL PCun	4	pSTG_aMTG	3
aFFG_mOG	3		2	PCun Cun	1	pSTG_pMTG	5
aFFG_PHC	2	iBoCG AnG	1	PCun LG	1	pSTG_pSTG	9
alFG_alFG	3	1P0C0_AllG	12	PCun PCun	6	pSTG_SMG	3
alFG_IOFC	6	IPOLG_IPOLG	15	PCun sOG	1	SMG_AnG	2
alFG_mOFC	2	POCG_SMG	/	pFFG mOG	1	SMG_SMG	13
alTG_aFFG	1	IPOCG_SPL	2	pFFG pFFG	1	sOG_iOG	4
aITG_aITG	4	iPrCG_iPrCG	3	PHC Cun	1	sOG mOG	11
alTG_EnC	1	iPrCG_mPoCG	2	PHCIG	1	s0G_s0G	13
alTG_mOG	1	iPrCG_SMG	2	PHC PCun	1	SPL AnG	7
alTG_pITG	6	iPrCG_SPL	1	PHC PHC	3	SPL PCup	2
ains_ains	2	LG_LG	2	PHC sOG	3	SPL SMG	8
ains_asig	3	LG_s0G	3	nIEG ains	1	SPL_SING	
ains_iPoCG	1	IOFC_ains	1		1	SPL_SUG	2
ains_pins	1	IOFC_aSTG	1	pIEG_iPrCG	6	SPL_SPL	13
ains_psrg	2	IOFC_IOFC	9	pIFG pIFG	6	sPoCG_SPL	1
ains_SMG	1	mIFG_mIFG	8	pIEG_SMG	1	sPrCG_SPL	1
amrG_airG	3	mlFG_plFG	6	DITG aFFG	2	sPrCG_sPoCG	1
aMFG_aMFG	00	mOFC_aSTG	1	pITG AnG	7		
aMEG_IDEC	2	mOFC_EnC	3	pITG_mOG	7		
aMEG_mEG	6	mOFC_IOFC	4		10		
aMEG_DEG	4	mOFC_mOFC	2	pins pins	1		
aMEG pMEG	8	mOG_iOG	5	pMFG iPrCG	3		
aMTG aITG	1	mOG_mOG	13	pMFG mPrCG	7		
aMTG aMTG	8	mPoCG_AnG	1	pMFG pIFG	2		
aMTG pMTG	8	mPoCG_iPoCG	5	pMFG pMFG	8		
AnG AnG	11	mPoCG_mPoCG	6	pMTG_aITG	2		
AnG_mOG	3	mPoCG_SMG	1	pMTG_AnG	2		
AnG_sOG	4	mPoCG_SPL	4	pMTG_mOG	2		
aSFG_alFG	1	mPrCG_iPoCG	2	pMTG_pITG	1		
aSFG_aMFG	3	mPrCG_iPrCG	6	pMTG_pMTG	9		
aSFG_aSFG	8	mPrCG_mPoCG	4	pSFG_aMFG	5		
aSFG_IOFC	1	mPrCG_mPrCG	6	pSFG_iPrCG	3		
aSFG_mOFC	1	mPrCG_SPL	1	pSFG_mPrCG	9		
aSFG_mSFG	3	mSFG_aMFG	15	pSFG_PCL	3		
aSTG_aMTG	3	mSFG_mIFG	3	pSFG_PCun	1		
aSTG_aSTG	1	mSFG_mPrCG	2	pSFG_pIFG	2		
aSTG pSTG	1	mSFG_mSFG	19	pSFG pMFG	12		

Figure 6.52: Table of corresponding pairs of regions with their number of clusters for the right hemisphere superficial bundles atlas

## 6.5 Discussion

In recent years, there has been renewed interest in mapping the anatomical and functional organization of the chimpanzee brain, whose proximity to human species may provide the key to understanding its commonalities and differences with the human brain. Nevertheless, although anatomical connectivity is an essential part of the information for understanding the organization of functional networks, only a handful of studies have focused on the chimpanzee brain structural connectivity [Bryant, L. Li, et al. 2020, Bryant, Ardesch, et al. 2021, Hecht, Gutman, Bradley, et al. 2015, K. A. Phillips and W. D. Hopkins 2012, Rilling, Glasser, Jbabdi, et al. 2012, Roumazeilles et al. 2020] and these have primarily focused on long white matter bundles [W. D. Hopkins, Coulon, and Mangin 2010].

To our knowledge, none of the previous dMRI studies in chimpanzees has addressed the organization of the superficial connectivity of the chimpanzee brain on a global scale although it is the anatomical substrate for most high level cognitive functions. Thus, our findings, particularly on the superficial bundles, represent a unique contribution to the field. In this study, we have designed a novel long white matter atlas, composed of 46 long white matter bundles and have proposed a completely new subdivision of the corpus callosum. This atlas was extended with a completely new superficial white matter atlas composed of 822 subcortical white matter bundles which establishes, to our knowledge, the first superficial white matter bundle atlas of the chimpanzee brain. The methodology used to build this atlas was different in essence from the one proposed in [Bryant, L. Li, et al. 2020], using a two-steps method that does not require predefining regions of interest at any time, thus making it more general and less operator dependent.

## 6.5.1 Deep white matter bundle atlas of the chimpanzee brain

The deep structural connectivity atlas presented in this work consists of 48 bundles whose segmentation relies on a significantly different segmentation approach than the approach used by Bryant, L. Li, et al. 2020 to establish their long white matter bundle (LWMB) atlas. In particular, the approach of this work did not require the definition of specific seed ROIs and target ROIS, which typically involves a preliminary segmentation process or anatomical assumptions. The clustering approach proposed in this work is fully automatic, observer independent, and only relies on the final labeling of segmented fascicles at the very end of the process. All the well-known commissural, projection and association long white matter bundles (LWMB) could be easily segmented to devise the target long white matter bundle atlas. Some previous observations made on chimpanzee fiber bundles were consistent with the results we found in our atlas. For instance, the presence of the arcuate fasciculi (AF) in non-human primates has been a subject of debate in the scientific community. Our approach was successfully able to reconstruct them, which is consistent with previous studies Bryant, L. Li, et al. 2020, Rilling, Glasser, Preuss, et al. 2008]. While the arcuate bundle projections are connecting the inferior frontal gyrus to the inferior parietal lobe and the superior temporal gyrus, they appear to be thin and less extended than what could be expected compared with humans. We observed especially weak connections with the temporal lobe, with a bundle being present only on the superior portion of the temporal lobe. This result is also consistent with the study from [Rilling, Glasser, Preuss, et al. 2008]. This particular area corresponds to the planum temporale (PT), and is identified as having a key role in language and speech in the human brain Shapleske et al. 1999. We did not recover the superior longitudinal fasciculus (SLF), whereas other studies revealed their presence in the chimpanzee brain [Bryant, L. Li, et al. 2020, Hecht, Gutman, Bradley, et al. 2015]. However, due to their proximity and its possible overlap with the arcuate fasciculus, the fiber clustering may have merged the two of them. A finer tuning of the distance threshold will be tested in the future to see if we can recover the SLF and AF separately. The frontal aslant tract (FAT), which is also known for its role in language and speech [Dick et al. 2019] was clearly identified and strikingly resembles its homologous tracts in humans. The left FAT seems to support speech and language functions, whereas the right FAT role seems to be the support of executive functions, inhibitory control and conflict monitoring. In this study, no population-level lateralization in fiber density was demonstrated, however, the FAT had a non-negligible thickness and was present in all subjects. The fact that this fasciculus resembles its human homologue is also important considering the major differences in the frontal lobe organization of chimpanzees compared to humans Alatorre Warren et al. 2019, Amiez et al. 2019. Further investigating the language pathways, we clearly identified the IFOF, which has also been the subject of interrogation regarding its presence and role in the non-human primate brain. Its existence has recently been described in the chimpanzee brain [Bryant, L. Li, et al. 2020, Roumazeilles et al. 2020]. In our cohort, it depicted relatively strong connections between superior and inferior endings in the prefrontal cortex and the occipital lobe, and is a thick and consistent bundle. The middle longitudinal fasciculus could be reconstructed laterally to the IFOF. It ran through the superior temporal lobe and displayed two endings reaching the occipital regions and the dorsal part of the temporal lobe respectively, which is an interesting new subcomponent that has not been previously described. The other white matter fiber bundles did not depict any particular morphological difference except the effect due to the mostly quadrupedal posture of the chimpanzee, enhancing the well known brain rearrangements Alatorre Warren et al. 2019. Some bundles connecting the basal ganglia with cortical areas or with the brainstem displayed an adaptation due to the posture anatomy, it is

particularly the case considering the sensory-motor connections. The corpus callosum bundle, subdivided into its genu, isthmus, midbody and splenium components, confirms the study from [K. A. Phillips and W. D. Hopkins 2012] as its organization resembles the one of humans. To our knowledge, the new cerebellar components reconstructed in this study for the chimpanzee brain are structurally similar to the human ones.

## 6.5.2 Superficial white matter bundle atlas of the chimpanzee brain

Superficial white matter bundles (SWMB) are mostly known to be short sub-cortical association fibers or U-fibers, connecting surrounding gyri [Catani, Robertsson, et al. 2017]. In comparison to long white matter bundles extensively described in the literature, SWMB were poorly described in the literature due to their small lengths and sections and to their sub-cortical positioning making their dissection difficult using Klingler's method [Klingler and Ludwig 1956]. Fiber tracking tools based on diffusion MRI data have been used to explore this superficial connectivity for little more than a decade, albeit with intrinsic limitations related to the low resolution of MRI data, the ill-posed nature of the problem of local inference of fiber directions and fiber trajectories by tractography, but also because of the large number of superficial bundles populating the subcortical region. However, diffusion-based fiber tractography and clustering methods have been successful to reconstruct some of the human superficial white matter bundles M. Guevara, Román, et al. 2017, Labra Avila 2020, T. Zhang et al. 2014]. SWMB results from brain development and continuously evolves during the maturation process [O. R. Phillips, Clark, et al. 2013, M. Wu et al. 2014]. They are known to be affected during brain aging Nazeri, Chakravarty, Rajji, et al. 2015] or in brain disorders [Nazeri, Chakravarty, Felsky, et al. 2013], [O. R. Phillips, Joshi, et al. 2016]. Few studies have already investigated the superficial connectivity of non-human primates [Oishi, Huang, et al. 2011]. The first superficial white matter bundle atlas of the chimpanzee brain established in the frame of this study is a further demonstration of their existence in the chimpanzee brain and might contribute to the identification of commonalities and differences of the superficial connectivity between chimpanzees and humans, in order to better understand the singularity of the human brain. Since the present study is the first one depicting a whole brain superficial connectivity organization in chimpanzees, its analysis is mostly exploratory. We did observe more superficial white matter bundles populating the left than to the right hemisphere. However, the right hemisphere seems to contain more interconnected regions. Looking at both hemispheres, there seems to be a symmetry in the number of fibers connecting two cortical regions within each hemisphere. The regions depicting the highest number of connections are situated in the parietal lobe and on the ventral portion of the frontal lobe. As expected, most SWMB depicted a 'U' shape, but we did observe some other shapes such as 'V', 'L' or flattered shapes. While the 'U'-shaped fibers seem to be situated homogeneously centrally in the lateral part of the brain, the 'V'-shaped fibers were mostly found on the dorsal part of the brain. The 'L' fibers seem to be part of the longest superficial white matter bundles and are mainly located on the ventral part of each hemisphere. Because we separated SWMB from DWMB using a simple threshold over their fiber length, the SWMB atlas also includes fiber clusters belonging, for instance, to the optic radiations or to subparts of the frontal aslant tracts. As no consideration strictly compels their classification into long or short bundles, we considered them in both atlases.

## 6.5.3 Limitations

The millimeter resolution of the anatomical and diffusion MRI dataset may not be sufficient to entirely capture the subtlety of the superficial connectivity for very thin bundles. The effect of using a two-step fiber clustering together with a fiber registration to a template may have introduced some inter-individual fiber shape differences that may explain why some of the bundles could not be found, such as the SLF. However, due to the separation of the two hemispheres during the first intra-subject fiber clustering, some fibers connecting one hemisphere to the other might have been missed during the reconstruction process. This was obviously the case of the cortico-ponto-cerebellar tract for which the major tracts were connecting the cortex to the ipsilateral cerebellum instead of the contralateral cerebellum.

## 6.5.4 Conclusion and perspectives

The current work has allowed us to establish a first complete mapping of the long and superficial connectivity in chimpanzees which constitutes, with the cerebral cortex, the anatomical substrate of brain functions. If the validation of the large white matter bundles is relatively easy, the validation of the superficial bundles described in the atlas resulting from this study is more subtle, due to the lack of a reference in the matter. Therefore, a validation phase is necessary, which will require the acquisition of a few anatomical brain specimen scanned ex vivo using meso or micro scale imaging methods such as ultra-high field diffusion MRI or polarized light imaging Axer et al. 2011] whose high resolution images will allow us to better assess the bundles described in our superficial white matter bundles atlas. Having the possibility to perform functional MRI (fMRI) studies with advanced stimuli would also contribute to better identifying the functional networks to which they belong to and to better understand their functional role. The observation of a limited number of shapes characterizing the geometry of short bundles compels us to further study the link between the shape of a short bundle and the sulco-gyral geometry of the cortical areas it connects, but also to look at the distribution of these connection shapes on the surface of the cortex. Lastly, the existence of atlases of superficial connectivity in both humans and chimpanzees opens the way to comparative studies to identify their key differences and to correlate these differences in connectivity with behavioral differences within and between the two species.

## Chapter 7

# Comparative white matter bundles morphology between chimpanzee and human brains

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Figure 7.1: Arcuate fasciculus in human (violet) and chimpanzee (gold) after registration using Brainvisa.

## 7.1 Introduction

After the creation of the SWMB and DWMB atlases for the chimpanzee brain, the new focus of the work was to try to establish a relevant comparison with the human's white matter, for both the superficial and deep white matter bundles. To this aim, a manifold learning method, the isomap algorithm in our case, was used to compare the morphology of the white matter bundles. This chapter presents the methodology used and the results obtained for the comparison of both DWMB and SWMB morphologies between the chimpanzee and human brains.

Tractography from diffusion MRI (dMRI) remains a unique technique to explore the white matter and the major connections of the human brain. Few studies exploring the chimpanzee's white matter bundles have been proposed until now. Most of them focus, legitimately, on already well-known deep bundles from humans. The interest of comparative neuroscience is to establish a profile of acquired features from ancestral characters, and in the case of this work, we had the chance to explore two species that are phylogenetically very close. It is not surprising that most of the already well-known deep white matter fiber bundles of the human brain were also found in the chimpanzee brain. It is remarkable to see that in our world, tiny genetic gaps can lead to huge physiological differences. In the case of a comparison between humans and chimpanzees, it is sometimes tough to finely appreciate these differences at the level of the white matter bundles. Most of the expected bundles were present, connecting expected similar cortical regions. The question that legitimately arose after the atlases creation was : how to measure the differences between these bundles ? What features could give a clue about the evolutionary pattern of these bundles and how can we extract such information?

The article from [Zhong Yi Sun et al. 2017] proposed a relevant framework to compare the morphology of white matter bundles of humans using an isomap algorithm, that we propose to investigate for the chimpanzee brain.

In this chapter, we investigate the commonalities and differences between the chimpanzee and human white matter bundles from a morphometric point of view. The isomap algorithm was successfully used to study the brain sulci morphologies [Z. Sun et al. 2016, De Vareilles 2022]. It allows shape characterisation by identifying the shape features capturing the main variability across a data set, and allows to quantify the individual specificities relative to these shape features. The added value in this work was to improve the accuracy of white matter bundles shape assessment using the PCPM (point cloud pattern mining) method described in [Pascucci et al. 2022].

## 7.2 Comparative study of superficial white matter bundles morphometry of the human brain compared to the chimpanzee brain

Very little is known about superficial white matter bundles, even in humans. Even the definition of the frontier between deep white matter bundles (DWMB) and short white matter bundles (SWMB) remains ambiguous and without consensus among the scientific community. The lack of both anatomical and functional knowledge concerning SWMB has driven a growing interest in the scientific community, in conjunction with the development of new brain exploration techniques such as high field diffusion magnetic resonance imaging, improving the spatial resolution, and fiber clustering algorithms. The brain's superficial white matter connectivity has been examined in humans using MRI and brain dissection [M. Guevara, P. Guevara, et al. 2020] [Catani, Dell'Acqua, Vergani, et al. 2012], and was assumed to correspond to sub-cortical white matter fibers connecting one gyrus to another [Meynert 1885, Oishi, Zilles, et al. 2008, F. Zhang et al. 2018, Shah et al. 2019]. While the peculiar role of these loco-regional connections remains unclear, they appear to be important in the structural organization of the connectivity between the different brain gyri [Sporns and Honey 2006], and in the efficiency of the regional cortical functions [Meynert 1885]. Their role has been investigated to adress specific questions, for instance related to age and sex [O. R. Phillips, Clark, et al. 2013, M. Wu et al. 2014], brain lateralization [Catani, Dell'Acqua, Vergani, et al. 2012, Magro et al. 2012], neurological disorders [Ji et al. 2019] such as schizophrenia [Nazeri, Chakravarty, Felsky, et al. 2013, O. R. Phillips, Nuechterlein, et al. 2011], Alzheimer disease [Fornari et al. 2012], Huntington disease [O. R. Phillips, Joshi, et al. 2016], autism [Sundaram et al. 2008, d'Albis et al. 2018] or age-correlated cognitive decline [Nazeri, Chakravarty, Rajji, et al. 2015].

Some studies have focused on particular brain areas such as the precentral and postcentral regions [Gahm and Shi 2019,Magro et al. 2012], frontal areas [Catani, Dell'Acqua, Vergani, et al. 2012, Conturo et al. 1999, Conturo et al. 1999, Oishi, Zilles, et al. 2008], the occipital lobe [Sachs 1892], and parietal lobe [Catani, Robertsson, et al. 2017]. Morphologically, from dissection and MRI tractography analysis, the SWM bundles are described as 'U-fibers' directly referring to their appearance, in the shape of the letter "U" when following the convexity of gyral convolutions [Meynert 1885]. Some short white matter fiber bundle atlases have already been released for the human brain [Guevara Alvez 2011, Román et al. 2017 Labra Avila 2020]. Because of the major inter-species differences regarding the cortical folding patterns, the comparison of the networks of short fiber bundles circumventing the folds is a real challenge. Some brain regions being more challenging than others. Concerning primates, their comparison is particularly challenging concerning the frontal lobe [Petrides, Tomaiuolo, et al. 2012]. While comparisons in SWM bundles have been attempted between humans and macaques [Oishi, Huang, et al. 2011, Catani, Robertsson, et al. 2017], very few have addressed this question for chimpanzees [T. Zhang et al. 2014].

In this section, we present a morphological comparison of the superficial white matter connectivity of the chimpanzee and human brains, first using a visual approach, and then a geometrical approach, in order to overcome any bias due to subjective preconceptions. The pipeline was originally designed to study the shape of cortical sulci, but once adapted to our problem [Pascucci et al. 2022], it allowed the analysis of the morphology of the bundles in a short amount of time.

We ran the pipeline on a large data set of 844 clusters of fibers (i.e. bundles) represented by their respective 'centroid'. This approach allowed us to explore in finer detail the superficial connectivity of the chimpanzee brain, still poorly known, and to better understand the variability of the different shapes of the bundles that we observe, in order to know if a rationalisation exists and if similarities are found in the superficial connectivity of the human brain.

#### 7.2.1 Methods

#### 7.2.1.1 Visual exploration of the superficial bundles

Previous research conducted on superficial white matter bundles in humans have highlighted the existence of alternative shapes to the well-described U-shaped fibers. This is something that have been previously spotted in the human brain, notably in Dr. Labra's thesis focused on human superficial white fiber bundles [Labra Avila 2020], as shown on figure 7.2. Since very little is known about these fibers, their shapes are also poorly understood and seem to be naturally linked with the cortical gyrification. The question is to know whether a diversity in the SWMB shapes in humans exists and whether it is shared with chimpanzees. Do we find the same kind of shapes, and do we see them at the same brain location, in the same proportion ?

In the frame of this thesis, a first empirical study was conducted to characterize the shape of the SWMB, consisting in a visual classification of the hundreds of bundles based on their shape, using the anatomist viewer [Rivière et al. 2011]. The result of this time consuming task is summarized in figure 7.3 and 7.4 for the left and right hemispheres. Specific shape characteristics such as the flatness, curvature or elongation of the bundles that made it possible to classify all bundles and to create clusters of similar shapes. It yielded similar groups to those that were identified in the PhD work of Dr. Labra, depicting U-shaped, V-shaped, C-shaped, 6-shaped, Straight, Curved and Open-U morphologies (see figure 7.2).



Figure 7.2: Shapes of the human superficial white matter fibers found in Nicole Labra's thesis. We can see that seven shapes were spotted : U-shaped, V-shaped, C-shaped, 6-shaped, straight, curved, open-U. Courtesy of Nicole Labra [Labra Avila 2020].



#### Fiber clusters shapes of the left hemisphere

Figure 7.3: Fiber bundles shapes of the left hemisphere of the chimpanzee brain.

#### Fiber clusters shapes of the right hemisphere



Figure 7.4: Fiber bundles shapes of the right hemisphere of the chimpanzee brain.

We performed the same type of evaluation looking at the 1365 bundles of the human brain (733 on the left hemisphere and 632 on the left).

Clusters	Shapes	Clusters	Shapes	Clusters	Shapes	Clusters	Shapes	Clusters	Shapes	Clusters	Shapes
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Figure 7.5: Fiber bundles shapes of the left hemisphere of the human brain

Clusters		Shapes	Clusters		Shapes	Clusters	Shapes	Clusters	Shapes	Clusters		Shapes
aFFG_aFFG_002	u		aMFG_aMFG_001 aMFG_aMFG_002 aMFG_aMFG_004	Ū	UND.	aSFG_aMFG_003 aSFG_aSFG_001	Mary Mr.	PoCG_PoCG_013 PoCG_PoCG_014 PoCG_PoCG_015	Store and	mOFC_EnC_001 mOFC_EnC_002		No d
aFFG_mOG_002			aMEG_aMEG x57 aMEG_PrCG_001			aSFG_aSFG_004 aSFG_aSFG_005		PoCG_PoCG_016 PoCG_PoCG_017 U.6 PoCG_PoCG_018		mOFC_EnC_003	0	U
aFFG_mOG_003	L,U		aMFG_PrCG_002	Open-U.C	$\bigcirc$ $\bigcirc$	aSFG_aSFG_005 aSFG_aSFG_007 aSFG_aSFG_005	V	PoCG_PoCG_019 PoCG_PoCG_020 PoCG_PoCG_021		mOFC_IOFC_001 mOFC_IOFC_003 mOFC_IOFC_004	Open-U	
aFFG_PHC_001	-		aMFG_IOFC_001	Open-U	$\mathbf{U}$	aSFG_aSFG_009	NW 104	PoCG_PoCG_022 PoCG_PoCG_023	e	mOFC_IOFC_005 mOFC_mOFC_001		
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alFG_IOFC_002			MFG_pIFG_001 MFG_pIFG_002	c	0	aSFG_mOFC_002 Curved	Russ	PbCG_SMG_007 PbCG_SPL_001 PbCG_SPL_001 Open-U	× /	m06_06_00 m06_06_00 m06_m06_006		U
MFG_KOFC_004 MFG_KOFC_005	Curved, U, L, V	N. D. M.	aMFG_ptFG_003 aMFG_ptFG_004 aMFG_pMFG_002			aSFG_mSFG_002 aSFG_mSFG_004	x 1	Prog_Prog_010 Prog_Prog_011 U	60	mOG_mOG_009 mOG_mOG_013 mOG_mOG_015		West-
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alFG_mOFC_003	Curved, U		aMEG_pMEG_006 aMEG_pMEG_007 aMEG_pMEG_009			aSTG_aMTG_004		Open-L PrCG_mPaCG_002		mOG_mOG_021 mOG_mOG_023 mOG_mOG_024		
alTG aEEG 002	Openall		aMFG_pMFG_010			10/03/10/00		IPrCG_SMG_001	s 17	mOG_mOG_025 mOG_mOG_026		
alTG_alTG_003			aMTG_AITG_000	? Ourved	$\sim$	aSTG_aSTG_002 U			<u> </u>	mPoCG_ArG_001	Open-U	1 1
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alTG_pITG_001 alTG_pITG_002 alTG_pITG_003	II Osepili	VI Bush	aMTG_0MTG_007 aMTG_009 aMTG_0100 aMTG_0100			Cun_Cun_007	da	IOFC_alns_002 U		mPoCG_mPoCG_015		1000-1
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ains_ains_002	6	0	AnG_AnG_009 AnG_AnG_010 AnG_AnG_011			Cun_LG_001 Cun_LG_002 Cun_LG_003	N 10 10	IOFC_aSTG_001 C		mPoCG_SPL_001 mPoCG_SPL_003 mPoCG_SPL_004	U	1)
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alms_aSTG_002 alms_aSTG_003	U,6	UG	AnG_AnG_015 AnG_AnG_016		V	EnC_AFFG_001 EnC_AFFG_002 U. Curved	14 L	IOFC_IOFC_000 IOFC_IOFC_009 C	14/1990	mPrCG_PoCG_002	U	U
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Figure 7.6: Fiber bundles shapes of the right hemisphere of the human brain.

## 7.2.1.2 Geometrical morphological approach

In the chimpanzee brain, each of the 884 extracted superficial fiber bundles was reduced to one fiber representative of the bundle called 'centroid' fiber. This choice drastically reduces the number of points to analyze and yet conserves the most representative shape information contained in one bundle, which would further be relevant and easier to analyze.

The centroid fiber was calculated thanks to the ginkgo toolbox.

Then, for each pair of centroids (or fibers) we did the following: align the two centroids and calculate a geometrical distance that is small if the centroids are similar, big if they are different. The alignment procedure is PCA-based: we extracted the three principal directions from the point-clouds representing each of the fibers and then aligned these axes by calculating the optimal transformation matrix [Bellekens et al. 2014]. We tried other finer alignment strategies that took into account all the points of the point-clouds (SVD-based and ICP), both alone and after the first PCA step, but we did not see substantial differences in the result that would justify the increased calculation cost.

The geometrical distance between two fibers A and B is calculated using the pairwise distance.

Let  $C_1$  and  $C_2$  be two fibers represented by  $N_p$  control points  $\{P_{c_1}(i)\}\$  and  $\{P_{c_2}(i)\}\$ . Let  $d_{pairwise}(c_1, c_2)$  be the symmetric pairwise distance between centroids  $c_1$  and  $c_2$ .

It yields:

$$d_{pairwise}(c_1, c_2) = min(\sqrt{\sum_{i=0}^{N_p-1} (P_{c_1}(i) - P_{c_2}(i))^2}, \sqrt{\sum_{i=0}^{N_p-1} (P_{c_1}(i) - P_{c_2}(N_p - i))^2})$$
(7.1)

The map of the distances between all the fiber pairs is a 822x822 matrix, that can be seen (row- or column-wise) as a set of 822 points in a 822-dimensional space, each representing a particular fiber.

Our clustering strategy consisted of : 1) a dimension reduction of the 822-dimensional space using the isomap algorithm [Tenenbaum, Silva, and Langford 2000], the number-of-neighbors parameter required by the isomap was empirically chosen and in any case kept lower than 5 ; a drastic reduction to only 2 dimensions showed to keep enough information for the successive clustering steps. 2) Identification of the clusters in the isomap-reduced space (embedding), using k-means ; the number of clusters k was chosen empirically through observation of the results: ; it was increased as far as the resulting clusters clearly showed different shapes. 3) Alignment of the point clouds of all fibers to the one corresponding to the cluster center, followed by the computation of a new averaged point-cloud which captured the general shape of the fibers in the cluster. The clustering pipeline used in this study is implemented and distributed as a python package [Pascucci et al. 2022].

The pipeline was applied to the human SWMB dataset in a similar way.

#### 7.2.2 Results and discussion

#### 7.2.2.1 Anatomical evaluation

The former visual and empirical classification already gave clues about the expected shape clusters and confirmed the existence of various SWMB shapes such as U-fibers, V-fibers, curved bundles. It as also observed a symmetry in the distribution of these shapes between the two hemispheres. The isomap-based clustering approach confirmed this observation.

Most of the chimpanzee brain SWMB could be clustered into fiver groups of specific shapes, (see figure 7.8, A.). Globally, two main types of superficial bundles shapes were observed : 1) closed edges bundles and 2) flat edges bundles (L-shaped bundles).

While the bundles with closed edges seem to be present in every lobes of the brain, the L-shaped bundles are more or less restricted to the ventral part of the brain, at the exception of some subparts of the corpus callosum that were considered as superficial bundles and display a flat appearance. The flat edges bundles aside, the closed edges can be divided into 2 main subgroups : 1) the bent-angle fibers and 2) the U-angle fibers. Indeed, these two categories, that

are not found in the same proportion, display two different types of morphology. The bent-angle fibers correspond to V-fibers, that strikingly resembles the ones found in humans superficial bundles. While looking at them with the Anatomist viewer, the most angular ones seemed to be located on the frontal lobe and temporal lobe and appeared as a minority. The extremity of the "V-shape" bundles sometimes depicts a "fan" appearance. In the group of the U-angle fibers, different types of fibers were observed and gathered into 3 subgroups depending on whether the edges of the fibers were more or less enclosed. C-shaped fibers are so called because of their closed edges, directed inside of the gravity center of the bundle, like the letter "C". They are poorly represented in the brain but are present in all lobes. They also are the bundles with the lowest fiber length. The second group is the one composed of the majority of bundles and is called "U-shape fibers" because they resemble the letter "U". Indeed they possess enclosed edges but less bent than the C-fibers. They can be considered as "middle length" bundles. The third and last group of shapes is the "Open-U" bundles. This group is composed of bundles resembling the letter "U", but unlike the previous group they display more open edges. The bundles composing this group are the longest ones. The Open-U bundles and the V bundles are sometimes very hard to discriminate.



Figure 7.7: Histogram of shape proportions in the chimpanzee and human superficial superficial white matter bundles.



Figure 7.8: SWMB shapes of the chimpanzee brain

A particular case of bundle is shown on figure 7.8, C. The frontal aslants are bundles considered as part of the deep white matter bundles, because this is the group they are generally associated to. However, it isn't false to consider them as superficial since they are also corticocortical fibers of lower length. This is the reason they were kept in the SWMB atlas. However, thanks to the fiber clustering, we could study their different subparts. These subparts are good examples of the bundles groups of shapes description.

The figure 7.9 shows that compared to the chimpanzee brain, the human frontal aslant is



thicker and is composed of 48 subparts. Interestingly, some of these subparts had the shape of a "V", as seen in figure 7.9, B).

Figure 7.9: Sub-parts of the frontal aslants in human and different shapes found in the SWMB atlas. A. Overview of the complete set of 48 subparts of the frontal aslants. B. Particular focus on one of the subparts, two V-shaped superficial bundles (" $pSFG_pMFG_001$ " and " $pSFG_pMFG_003$ ")

In the human brain, we could recognize closely similar bundles shapes compared to the ones of the chimpanzee brain (see figure 7.9, C.). With the U-shape fibers, C-shape fibers, flat edges / curved fibers (L-shape fibers) and V-shape fibers. However, some exclusive shapes emerged in humans like for the "6-shape" fibers.

## 7.2.2.2 Isomap-based classification

We applied a dimensionality reduction of the N-dimensional space using the isomap algorithm with a number-of-neighbors parameter kept lower than 5.

A dimension-based analysis of the results led us to consider only 2 dimensions keeping enough information for the subsequent clustering steps consisting in the identification of clusters within the isomap-reduced space using a k-means algorithm.

This was followed by a visual inspection of the results while increasing the number k of clusters till the observation of morphometrically relevant clusters.



Chimpanzee SWM bundles geometrical analysis

Figure 7.10: Morphological investigation of the superficial white matter atlas of the chimpanzee brain. At the top : 2 clusters of fibers with average shapes, at the bottom : 5 clusters of fibers with average shapes



Figure 7.11: Morphological investigation of the superficial white matter atlas of the human brain. At the top : 2 clusters of fibers with average shapes, at the bottom : 5 clusters of fibers with average shapes

For both species, flattered bundles were mostly found on the ventral part of the brain while curved fibers were mostly present on the dorsal part of the brain, confirming what was previously seen using Anatomist viewer.

In the chimpanzee brain, taking into account the degree of closure of the fiber bundle shapes, it appears that the more the fibers seem to close up, the more dorsally is the progression when looking at the brain cortex. This is not exactly the case concerning humans. Indeed, there seems to be the same phenomenon, only the bundles seem to close up from the ventral anterior part to the dorsal caudal part of the brain. While the bundle shapes seem relatively the same concerning the human and the chimpanzee brains, the humans' ones display more enclosed edges, and the distribution of the different shapes is not exactly the same.

In the chimpanzee brain, the algorithm revealed that for the cluster "0" (figure 7.10 B.), most of the fibers composing this cluster were present in the frontal and in the parietal lobes. Some fibers were also present in the superior temporal lobe and very few fibers were present in the anterior temporal lobe. The cluster "1" is composed of fibers present in majority in the superior frontal lobe and the parietal lobe. Almost no fibers from this cluster were present in the other lobes. Concerning the second cluster "2" that displayed the flattest fibers, the fibers belonging to this cluster were mostly present on the temporal lobe, in its lower, ventral part. The cluster "3" that is composed of a mix between open-U and V fibers seemed to be composed of fibers that are present in all lobes, with a majority in the frontal and parietal lobes. Some fibers are present on the temporal lobe, on the superior gyri. The last cluster of fibers, cluster "4" with the shape of curved fibers, is composed of fibers present almost exclusively in the inferior frontal lobe and the occipital lobe.

In the human brain, the U fibers with enclosed edges are present in all lobes, almost uniformly throughout the brain. Another cluster, composed of flat fibers, showed that the fibers having this shape are mostly found on the ventral part of the brain, which is a trait that is shared with chimpanzees (see figure 7.11, C.).

By looking at the decomposition in five clusters (figure 7.11, D.), the shapes of the clusters are a little bit different than the ones seen in the chimpanzees.

Indeed, different types of U-shaped fibers emerged : the cluster "0" and the cluster "2" were both clusters of U-shaped fibers, however, the cluster "2" showed fibers with a shape with closed and straight edges while the cluster "0" shows closed edges resembling more to the letter "C" than the letter "U". The fibers composing the cluster "0", resembling like the letter C were present all over the brain, in all lobes. The cluster "1", composed of fibers depicting an open-u shape, were also present in all lobes, at the exception of the area around the the central sulcus (the fibers connecting the pre-central and post-central gyri belonged to clusters "0" and "2"). The cluster "2" is composed of fibers looking like a straight "U", mostly present in the parietal lobe and in the occipital lobe. They were very few in the frontal lobe and almost completely absent in the temporal lobe. The fibers that compose the cluster "3", were "open-U" fibers, with the greater aperture angle than in the cluster "1". They were mostly present in the ventral part of the brain, in the inferior temporal lobe. Some fibers were also present in the frontal, parietal and occipital lobe, almost exclusively on their inferior parts. The last cluster of fibers, cluster "4", composed of fibers with a flat appearance, depicted fibers that were only present on the inferior frontal lobe and inferior temporal lobe. These fibers were present in the ventral part of the brain in greater quantity than the cluster '3'.

This algorithm provided a good tool for the analysis of the organization and localisation of the bundles shapes in the brain, and the comparison between humans and chimpanzees SWMB atlases. However, it missed some interesting shapes that could only be found by a visual inspection of all the different bundles. The V fibers, 6-fibers and C-fibers, sometimes seen in the human and the chimpanzee brains were hardly identified in the algorithm due to : their resemblance with other shapes (V and open-U are closely alike) and their poor representation among all the other bundles.

This algorithm is a relevant tool to analyze the common main patterns of shapes between the two species, complementary with a thorough visual analysis necessary to distinguish subtle differences.
## 7.3 Conclusion

To our knowledge, the study presented here is the first one depicting the morphological organization of the superficial white matter bundles of the chimpanzee brain.

We tried to analyse as finely as possible the SWMB shapes in chimpanzees and humans to try to understand if the two species were showing similarities or major differences in their superficial connections organisation and morphologies. The question is not easily answered and it is fair to say that it is not devoid of subjectivity. We tried to stay as descriptive and objective as possible and coupled the inspection with an geometrical analysis to try to categorize the bundles shape in an automatic and reproducible manner.

The algorithm provided a rough categorization of the bundles shapes. The coupling between this method and the anatomical/visual inspection is strong because more than the global organisation, we also had a sense of shapes difference within and in between the two species, bringing more information about their cortical connectivity and the possible evolution of its link to new acquired cognitive functions.

The relation between superficial fiber bundles and brain gyrification would deserve more exploration to try to understand the real possible link between their sulcation profile and the underneath connections.

## 7.4 Comparative study of deep white matter bundles morphometry of the human brain compared to the chimpanzee brain

In this section, we analyze the morphological differences in the deep white matter bundles of the human and chimpanzee brains, using the isomap algorithm.

#### 7.4.1 Methods

To analyze the commonalities and differences between human and chimpanzee brains white matter bundles morphologies, successive data processing steps were necessary :

- the registration of the two template spaces together in order to have comparable data, using DISCO and DARTEL toolboxes;
- the application of chimpanzee and human deep white matter bundles atlases on each subjects cohorts;
- the computation of each subjects' deep white matter bundle alpha shapes.

#### 7.4.1.1 DISCO-DARTEL registration of the Juna and MNI templates

The DISCO registration tool was originally introduced in [Auzias et al. 2009] to improve diffeomorphic registration of T1-weighted MRI with the addition of a further constraint to more accurately match brain sulci. It relies on a twofold process corresponding first (1) to the alignment of the predefined sulci of two T1-weighted MRIs to initialize the diffeomorphism followed by (2) a second step corresponding to a DARTEL registration. The first sulci-based initialization allows to obtain a diffeomorphism that more accurately matches the sulcal patterns of the two subjects.

Selection of landmark sulci for the DISCO registration While the human brain sulci are, for the most part, already well known and a developing field of studies for the identification of their variability, it is a relatively new field of research for the chimpanzee brain.

Taking as reference the sulci nomenclature from the human MNI template, the existing research on chimpanzee brain sulci, and the consensus reached with neuro-anatomist and experts of brain sulcation, the Juna.chimp template was specifically processed using the Brainvisa / Morphologist toolbox to segment its sulci and label them according to this consensus. This sulci matching then facilitates the co-registration of human and chimpanzee brains using the DISCO-DARTEL tool available from BrainVISA (Rivière et al. 2011).



Figure 7.12: Identification of the brain sulci used as landmarks for the human (MNI) and the chimpanzee (Juna.Chimp) brain templates co-registration. 20 sulci were identified, abbreviations : F.I.P. : Intraparietal sulcus, S.Pe.C.sup. : superior precentral sulcus, S.F.sup. : superior frontal sulcus, F.I.P.Po.C.inf. : inferior post-central intraparietal sulcus, S.Pe.C.inter. : intermediate precentral sulcus, S.F.inf. : inferior frontal sulcus, S.C. : central sulcus, S.Pe.C.inf. : inferior precentral sulcus, S.Pe.C.inter. : intermediate precentral sulcus, F.C.L.r.asc. : ascending ramus of the lateral fissure, S.C.sylvian : central sylvian sulcus, F.C.L.p. : posterior lateral fissure, S.T.s.ter.asc.pos. : posterior terminal ascending branch of the superior temporal sulcus, S.T.i.post. : posterior inferior temporal sulcus, F.C.M.ant. : calloso-marginal anterior fissure, S.Call. : subcallosal sulcus, F.P.O. : parieto-occipital fissure, F.Cal.ant.-Sc.Cal : calcarine fissure, F.Coll. : collateral fissure, S.O.t. : occipito-temporal sulcus

Some sulci presented were more challenging than others to identify and match. Indeed, the interest of using a template is to be able to average and compare individuals in a common frame. However, while averaging the sulci from a population, especially concerning chimpanzees, a lot

of sulci information gets lost due to individual variability, which is important to be noticed. In total, 39 sulci were identified in the chimpanzee brain, from which 20, common with humans, were selected for the brains co-registration, as shown in figure 7.12.



Figure 7.13: Disco and Dartel registration illustration, step 1: disco registration, based on the correspondence between the same sulci from different brains, step 2: Dartel registration based on the different brains cortical ribbons

The DISCO pipeline from the Brainvisa toolbox uses brain sulci to perfom a first diffeomorphic registration step between the two brains, followed by a second step, using the well-known DARTEL toolbox (see figure 7.13). A preliminary pre-processing step consists in the selection of the corresponding sulci from the chimpanzee and human templates. The success of this step is of upmost importance since the result of the DISCO pipeline directly depends on it. It revealed to be a real challenge : some well-identified sulci in the two species such as the superior temporal sulci (STS) or the central sulci (CS) were easy to name, but, for some others such as the lunate sulcus in chimpanzee or the frontal sulci for both species, we had to fight against strong variability and deformations of the corresponding cortical areas.

The result of the chimpanzee and human brain templates co-registration is shown on figure 7.14 and 7.15.



Figure 7.14: Average brain templates from their initial space to the DISCO-DARTEL common space.



Figure 7.15: Average brains stemming from the DISCO-DARTEL registration pipeline. At the top : the registered cortical ribbons, in pink the one of the chimpanzee brain and in white the human brain ; at the bottom : average meshes of the human (white) and chimpanzee (pink) brains. We can see on the bottom picture, indicated with arrows, that the most difficult region to register was the frontal cortex, especially the inferior frontal cortex.

The registration of the two brain templates was of quite good quality, at the exception of the most anterior part of the inferior frontal cortex. However, it remains obviously complex to

register a brain area that is barely present in the chimpanzee brain, which is why this issue was expected but considered as non impacting for the rest of the analysis to be performed.

## 7.4.1.2 Applying the atlas on subject

The human and chimpanzee DWMB atlases were respectively applied on each of the 39 subjects of the human and chimpanzee cohorts using the Ginkgo 'Advanced fiber labeling' tool. The atlases are applied to each subject individually using each subject's diffeomorphic transformation from the atlas to its own space. The bundles segmentation tool computes for each fiber its pairwise distance to each centroid of the corresponding DWMB atlas and then attributes to the fiber the label of the closest centroid, thus yielding the expected individual deep white matter bundles. However, the cross-subject variability in shape and position of the bundles has to be taken into account. The level of variability also depends on the bundle type, some being more variable in shape than others. To this aim, a threshold distance was empirically chosen for each white matter bundle tresulting from a series of labelling experiments with a subset of individuals to establish the optimal threshold distance for each white matter bundle. The set of distances was stored in a file provided as input to the "AdvancedFiberLabelling" command from the Ginkgo toolbox (see figure 7.16 ).

	Distance	vistances (mm)	
Deep white matter bundle (for left and right hemispheres)	Chimpanzee	Human	
Anterior commissure	5	10	
Anterior thalamic radiations	8	10	
Arcuate	4.5	12	
Corpus callosum (all components)	4	8	
Cortico-spinal	7	5	
Dorsal cingulum	5	7	
Fornix	5.5	8	
Frontal aslants	6.5	7	
Inferior fronto-occipital	8	7	
Inferior longitudinal	3.5	10	
Middle longitudinal	5.5	13	
Optical radiations	3.5	10	
Posterior thalamic radiations	5	10	
Superior thalamic radiations	5	10	
Uncinate	4	12	
Ventral cingulum	6.5	13	
Ventral visual stream	6	10	

Figure 7.16: Table of distances for the application of the deep white matter bundles atlas on subjects.



Figure 7.17: Deep white matter bundles of the chimpanzee called "Agatha". The application of the deep white matter chimpanzee atlas using the described algorithm with the distance file provided the result depicted in this figure for the chimpanzee subject : Agatha.



Figure 7.18: Deep white matter bundles of one human subject (subject 100408). The application of the deep white matter human atlas using the described algorithm with the distance file provided the result depicted in this figure for the human subject 100408 of the HCP database.



Figure 7.19: Graph of the number of fibers per deep white matter bundles for the left and right hemispheres after application of the atlas on the 39 subjects. Values were adjusted for multiple comparisons using false discovery rate (fdr)  $p_{cor} \leq 0.05$ ,  $p_{cor} \leq 0.01$ ,  $p_{cor} \leq 0.001$ .

Left hemisphere	Right hemisphere	T-value	P-value	Pcor-value
Anterior thalamic radiations	Anterior thalamic radiations	1.98	0.0535	0.1002
Arcuate	Arcuate	0.23	0.8164	0.8434
Cingulum dorsal	Cingulum dorsal	2.83	0.0068	0.0235
Cingulum ventral	Cingulum ventral	2.19	0.0337	0.0721
Cortico-spinal	Cortico-spinal	2.77	0.0078	0.0235
Fornix	Fornix	-0.88	0.3846	0.4438
Frontal aslants	Frontal aslants	-1.93	0.0601	0.1002
Inferior fronto-occipital	Inferior fronto-occipital	-5.06	0.00001	0.0001
Inferior longitudinal	Inferior longitudinal	1.55	0.1271	0.1906
Middle longitudinal	Middle longitudinal	3.92	0.0003	0.0021
Optical radiations	Optical radiations	1.29	0.2030	0.2567
Posterior thalamic radiations	Posterior thalamic radiations	3.34	0.0016	0.0082
Uncinate	Uncinate	-2.21	0.0319	0.0721
Superior thalamic radiations	Superior thalamic radiations	0.20	0.8434	0.8434
Ventral visual streams	Ventral visual streams	-1.28	0.2053	0.2567

Figure 7.20: Paired student T-tests between the left and the right hemispheres for the number of fibers of DWMB in chimpanzees. Values were adjusted for multiple comparisons using false discovery rate (fdr).

After applying the DWMB atlas on the chimpanzee subjects, some bundles depicted hemispheric asymmetries in their number of fibers. Indeed, concerning the dorsal cingulum, the cortico-spinal tract, the middle longitudinal fasciculus, and the posterior thalamic radiations, the mean number of fibers was more important on the left hemisphere compared to the right hemisphere. Surprisingly, the inferior fronto-occipital fasciculus showed the opposite, with more fibers on the right hemisphere compared to the left (see figures 7.19 and 7.20).

#### 7.4.1.3 Alpha-shape mesher

Once the atlas is applied and the bundles retrieved from all subjects, the amount of information is colossal, with millions of streamlines. Each streamline is defined by such a number of points that the resulting point cloud becomes too heavy to be processed using the isomap algorithm. To overcome this limitation, a command of the ginkgo toolbox was further developed to compute the alpha shape of each deep white matter bundle, which remains sufficient to describe its morphology. The alpha shape corresponds to the surface envelope of the white matter bundle, which drastically reduces the size of its representation to a few hundred points (see examples on figure 7.21).



Figure 7.21: Extraction of the alpha shapes of the white matter bundles. At the center, summary of the process from the fiber bundle to the points cloud describing the shape of the bundle. Around, some examples of results for the arcuate fasciculus, the dorsal cingulum, the uncinate fasciculus, the cortico-spinal tract, the inferior fronto-occipital tract, and the fornix, all coming from the left hemisphere of the human subject 100408 of the HCP database.

## 7.4.2 Results and discussion

Here we considered only bundles that we considered relevant for this morphological analysis between the two species: the arcuate fasciculus, the inferior fronto-occipital fasciculus, the corticospinal tract, the anterior commissure, the uncinate fasciculus, the frontal aslants, the inferior front-occipital, the inferior longitudinal and the middle longitudinal fasciculi. Most of the time, the first dimension of the isomap would show the best separation between the human and chimpanzee bundles.

For brevity concerns, are only present, in the following section, the visual representations of the dimensions relevant for the analysis. Usually, the first dimension is the most discriminant, and sometimes can directly allow the separation between two clusters, one for humans and one for chimpanzees.

#### 7.4.2.1 Arcuate fasciculus

A striking geometrical separation between the two species was expected for the arcuate fasciculus. Indeed, by looking at the atlas, the bundles' shapes already looked very different between humans and chimpanzees, so the first dimension of the isomap distinguished the two species very well (see figure 7.24).

The discriminant factor in this case is believed to be the volume and curvature of the bundle. As described in the previous chapter, the chimpanzee's arcuate fasciculus reached the inferior frontal lobe in the equivalent of Broca area, and reaches the temporal lobe at its upper segment, leading to believe that only the dorsal part of the arcuate fasciculus exists in the chimpanzee brain compared to humans. The various connected cortical regions are displayed on figure 7.22 for both species.



Figure 7.22: Cortical connections of the arcuate fasciculus in chimpanzees and humans, using Brodmann's cytoarchitectural map. For each species is depicted the alpha shape of the atlases' bundles for the arcuate fasciculus (pink). For each extremity of the bundle reaching the cortex, the corresponding Brodmann area is highlighted (light green and numbers)

As illustrated in figure 7.22, the two species arcuate bundles look very much different. The human arcuate fasciculus seems to connect multiple cortical areas : the supplementary motor areas, Broca's areas, the angular gyrus, the fusiform gyrus and the inferior temporal gyrus.

The pattern of limited (compared to human) cortical connections of the chimpanzee's arcuate fasciculus tends to indicate that the frontal extremities reach Brodmann areas 44 and 45, known in human to be called "Broca's areas" due to their functional implication in language processing [Brodmann 1907]. The posterior extremity reaches the supramarginal gyrus, known for humans to be playing a role in phonological processing [Hartwigsen et al. 2010].

It is important to notice that the aspect in the morphology of the bundles could be the result,

in some subjects, of the fusion with a possible superior longitudinal fasciculus. Even if this bundle is not described in the atlas because it was not part of the inter-subject fiber clustering results, we could see, once the arcuate bundles from the atlas was applied on the different subjects, that it would subdivide itself into dorsal and ventral parts (see figure 7.23). Hecht, Gutman, Bradley, et al. 2015 also considered similar fronto-parietal bundles corresponding to the superior longitudinal fasciculus III (SLF III).



Figure 7.23: The superior longitudinal fasciculus of the chimpanzee brain. Top row : fiber representation, middle row : mesh representation and bottom row : fiber representation superposed on a olor-coded fractional anisotropy map of Artemus' brain. Two bundles are present at the expected place of the arcuate fasciculus as it is described in the atlas. One of the subpart is really close to the description made by [Hecht, Gutman, Bradley, et al. 2015].

As illustrated in figure 7.24 representing the individual arcuate bundles along the isomap axis, the shape features splitting humans from chimpanzees seems to be due to the arcuate bundle's volume and curvature.



Figure 7.24: Geometrical analysis of the arcuate fasciculus between humans and chimpanzees. At the top, on the left : the averaged bundles coming from the atlases of each species, center : the average shapes pointed out by the isomap algorithm, on the right : the embedding dimensions histogram. At the bottom : the isomap axis along dimension 1

To go a step further, since the AF bundle is known to present an asymmetry between hemispheres in humans, a deeper investigation of the arcuate fasciculus morphology was conducted at the individual scale, keeping the chimpanzee and human bundles in their respective template space in order to study their left-right asymmetry.

**Human arcuate fasciculus -** The results obtained after the projection of all human subjects' arcuate fasciculi with the isomap algorithm are shown on figure 7.25.

### Arcuate fasciculus in human



Figure 7.25: Geometrical analysis of the arcuate fasciculus in humans. At the top, the average left and right human fascicles from the atlas, on the right : histogram of the embedding dimensions, at the bottom : the isomap axis along dimension 1 and 2, with classification of the left (green) and right (pink) fascicles along the axes with underlying moving averages.

Two dimensions were relevant. The first dimension revealed that the left arcuate fasciculus' shape seem to display a temporal extremity, mostly present on the left hemisphere compared to the right. The second dimension also tends to demonstrate a difference between the two hemispheres' bundles shapes, but difficult to interpret. It seems that the shape criteria driving the classification of shapes along the axis is the degree of curvature of the fasciculus, with potentially the left arcuate fasciculus having a more "developed" and "open" shape compared to the right fasciculus.

**Chimpanzee arcuate fasciculus -** In the case of the chimpanzee brain, the analyses is a little bit more challenging. If we put aside the idea of an hiding SLF inside our data, some asymmetry inside the group could be seen (see figure 7.26). Indeed, the left arcuate fasciculus' shape seems to mostly belong to the second half of the axis, with a more "open" shape, while the right arcuate fasciculus shape is mostly found on the first half part of the axis, depicting a more angled shape.

Arcuate fasciculus in chimpanzee



Figure 7.26: Geometrical analysis of the arcuate fasciculus in chimpanzees. At the top, the average left and right human fascicles from the atlas, on the right : histogram of the embedding dimensions, at the bottom : the isomap axis along dimension 1, with classification of the left (green) and right (pink) fascicles along the axes with underlying moving averages.

#### 7.4.2.2 The Cortico-spinal tracts

140 CST bundles were recovered from both human and chimpanzee cohorts. The main separation criteria to differentiate the two species using isomaps seems to be the curvature of the bundle. Indeed, the dimensions axes from the embedding (dimensions 1, 2 and 4) showed an interesting insight into the distinction between human and chimpanzee CSTs, as shown on figure 7.27.

The first dimension depicts the most important separation along the axis, with chimpanzees (violet color) being on the left side of the axis where the curvature of the bundle is the most pronounced, when the human bundles are mostly found on the right side of the axis with a straighter shape. This criteria clearly separates the species into two groups, even if some exceptions can be observed at both sides.

The second dimension still puts in evidence a difference in the curvature angle, but restricted to the caudal face of the bundles. Indeed, in the direction of the left side of the axis, we observe a bent shape of the bundles, while it is less the case on the right side of the axis. This dimension is worthwhile because it doesn't really separate the two species but shows an actual diversity of the CST shape for both of them. This shape diversity appears more pronounced in the chimpanzee brain (chimpanzees' bundles are spread all along the axis) than in the human brain (were the bundles seem more restricted to the right side of the axis).

The third dimension showing interesting results was the fourth dimension of the embedding. It puts in evidence more than just a separation between the two species due to curvature, but also a separation caused by the fiber decussing at the dorsal extremity of the bundle. Indeed, while one can objectively say that the two species' bundles are seen all along the axis, it is fair to say that a larger proportion of chimpanzees is found on the left side compared to the right side, and a higher percentage of humans are, on the contrary, found on the right side of the axis compared to the left one. On the left side, the shape of the bundles is twisted and the fiber

decussing is less pronounced. On the contrary, if we go to the right direction, we observe a flatter bundle, not twisted, with a larger fiber decussing.



**Corticospinal tracts** 

Figure 7.27: Geometrical analysis of the Corticospinal tracts between humans and chimpanzees. At the top, on the left : averaged bundles stemming from the atlases of each species, center : the registered average shapes pointed out by the isomap algorithm, on the right : histogram of the dimensions of the embedding. Bottom : Three dimensions axes from the embedding (dimensions 1,2 ans 4) with classified bundles from both species along the axes (violet : chimpanzee, gold : human) and underlying moving averages.

#### 7.4.2.3 Anterior commissure

The isomap algorithm was launched on the AC, depicting only one dimension of interest. The first dimension of the embedding puts in evidence the geometric difference between the two species' bundles, as shown on figure 7.28.

Regarding the first isomap axis of the dimension N°1, towards the left part of the axis, the bundles depict a "round" shape, while progressing along the axis, the bundles' shapes seem to be sharper and pyramidal. There appears to be a higher proportion of human bundles on the extreme left side of the axis compared to the right side, whereas, in chimpanzees, we observe a movement of progression in the direction of the right side of the axis. This dimension shows that the difference between the two species' ACs comes from the aperture between the two branches of the AC. For the chimpanzee, the aperture angle seems sharper than for humans, suggesting that for the chimpanzee, the trajectory of the fibers is influenced by a reduced frontal structure compared to humans.



Figure 7.28: Geometrical analysis of the anterior commissure between humans and chimpanzees. 68 bundles were analysed in total from the two species. At the top, on the left : averaged bundles stemming from the atlases of each species, center : the registered average shapes pointed out by the isomap algorithm, on the right : histogram of the dimensions of the embedding. Bottom : the dimension axis from the embedding (dimensions 1) with classified bundles from both species along the axes (violet : chimpanzee, gold : human) and underlying moving averages.

#### 7.4.2.4 The uncinate fasciculus

In the case of the Unc, 149 bundles were recovered from the group of subjects. The first 2 dimensions were the most discriminant (see figure 7.29). The Uncs were part of the bundles where a difference between the two species was very hard to spot only by looking at the subjects' bundles.

The isomap algorithm revealed two identification criteria from two different dimensions. The first dimension revealed that in the human brain, the uncinate fasciculus seems to possess a temporal ending more developed than the one of the chimpanzee. Indeed, when moving along the axis towards the left side, we can observe a disappearance of the temporal fibers of the bundle. The angle between the temporal portion of the bundle and the rest of the bundle also seems to be flatter. However, when moving to the right side of the axis, we observe that the temporal portion of the bundle is thicker and forms an angle with the rest of the shape. There is a higher proportion of bundles belonging to the human species than to the chimpanzee species on the right side of the axis of this first dimension. This implies that humans may possess a most prominent portion of temporal fibers from the uncinate fasciculus than chimpanzees.

The second dimension revealed that there is a variability in the volume and angle of the frontal part of the Uncs. Indeed, on the left side, the bundle displays a thinner appearance and also a flat body with a reduced frontal extremity decussing of the bundle. When moving to the right side, the bundle is thicker with a well-developed decussing at its frontal extremity. Along the axis, both species are present on the left and the right side, which means that there is a variability in the morphology of this bundle that is present in both species. It is nevertheless important to note that there seems to be a higher proportion of bundles belonging to chimpanzees on the left portion of the axis, while most of the bundles belonging to humans are present at the center and right side of the axis. Even if both species showed diversity in shape for these criteria (appearance in the frontal extremities and general thickness), both species seem to be driven towards a particular type of morphology.

**Uncinate fasciculus Dimensions histogram** Average bundle from chimpanzee atlas Registered species averaged bundles Average bundle from human atlas Chimpanzee bundles Human bundles **Dimension 1** Flatter, almost no Present extremity extremity with a sharp angle **Dimension 2** Reduced frontal Thicker frontal extremity extremity and superior closure

Figure 7.29: Geometrical analysis of the uncinate fasciculus between humans and chimpanzees. 68 bundles were analysed in total from the two species. At the top, on the left : averaged bundles stemming from the atlases of each species, center : the registered average shapes pointed out by the isomap algorithm, on the right : histogram of the dimensions of the embedding. Bottom : dimensions axes from the embedding (dimensions 1 and 2) with classified bundles from both species along the axes (violet : chimpanzee, gold : human) and underlying moving averages.

## 7.4.2.5 The inferior fronto-occipital fasciculus

In the case of the IFOF, by looking at the atlas, the two species bundle shapes tend to look similar. Indeed, the IFOF is an already well-known thick and long fiber bundle in humans, and its shape in the chimpanzee brain seemed very close to the already well-known morphology of the human bundle. When applied to the subjects used in the isomap algorithm, three dimensions

were relevant from a classification point of view as shown in figure 8.5.

The first dimension from the embedding shows that when progressing along the axis, the body of the bundle seems to curve. Even if both species tend to show a large variability of the IFOF curvature, a higher proportion of human IFOFs are found towards the left side of the axis while a higher proportion of chimpanzee IFOFs are found on the right side of the axis. This implies that chimpanzees have the tendency to display IFOF bundles with a more pronounced curvature than humans, probably linked to the difference in between the frontal regions in chimpanzees (easier to reach) than in humans (where the bundles needs to elongate to reach more anterior inferior frontal areas).

The second dimension depicting interesting results was dimension three of the embedding. Indeed, when progressing along the axis to the left, the caudal extremity of the bundle displays a thick, fan-shaped decussing of the fibers. Whereas, when progressing towards the right side of the axis, the decussing is more restricted. There is a global tendency of the chimpanzee bundles to be more present towards the left side of the axis when the human bundles are preferentially found on the right side of the axis. This suggests that, even if both species show different types of morphologies regarding the caudal extremity of their IFOF bundles, chimpanzee bundles tend to have a thicker decussing extremity compared to humans. An interesting study could consist in looking at the pattern of connections of these extremities between humans and chimpanzees to see whether the difference is also present at the level of their cortical connectivity: could the chimpanzee's IFOF connect more cortical regions than for humans?

The third dimension of interest was the dimension six that puts in evidence a difference along the axis, in the IFOF anterior extremity morphology. On the left side of the axis, there seems to be a thinner anterior extremity whereas on the right side of the axis there is a developed anterior extremity, showing more thickness and decussing.

The chimpanzee's IFOF seems to be more concerned by a thinner anterior (rostral) extremity morphology when humans have a more developed anterior portion. This is to be possibly linked to the developed frontal regions in humans compared to chimpanzees, the pattern of frontal connections is then more furnished and allow an extended fiber connectivity.



Figure 7.30: Geometrical analysis of the inferior fronto-occipital fasciculus between humans and chimpanzees. At the top, on the left : averaged bundles stemming from the atlases of each species, center : the registered average shapes pointed out by the isomap algorithm, on the right : histogram of the dimensions of the embedding. Bottom : dimensions axes from the embedding (dimensions 1, 3 and 6) with classified bundles from both species along the axes (violet : chimpanzee, gold : human) and underlying moving averages.

## 7.4.2.6 Frontal aslants

In the case of the FAT, 146 bundles were recovered from all subjects from both species. The two species' bundle visually look closely similar, reaching two parts of the frontal cortex. However, the first dimension was able to show an interesting profile of morphology of these bundles (see

figure 7.31).

Indeed, we can see that the subjects' FAT went from flat, with an "open" shape, to more curved when progressing along the right direction of the axis. It is interesting to note that chimpanzees showed a highly variable morphological profile, going from a bundle being very flat to completely curved. In humans, this variability is not present and the bundles are restricted (for most of them) to the left side of the axis, with a flat shape. We could linked this to a possibly highly consistent profile of connections of the different bundles in humans, where the frontal regions that are connected are recovered for all subjects. This is possibly a little different in chimpanzees, with a profile of frontal connections showing more variability between subjects.



Figure 7.31: Geometrical analysis of the frontal aslants between humans and chimpanzees. Only one dimension was necessary. At the top, on the left : averaged bundles stemming from the atlases of each species, center : the registered average shapes pointed out by the isomap algorithm, on the right : histogram of the dimensions of the embedding. Bottom : the dimension axis from the embedding (dimension 1) with classified bundles from both species along the axes (violet : chimpanzee, gold : human) and underlying moving averages.

## 7.4.2.7 The inferior longitudinal fasciculus

150 iLF were recovered. Three dimensions showed interesting insights on the bundles morphology (see figure 7.32). The first dimension from the embedding, established a classification with bun-

dles going from flat (left part of the axis), to cylindrical (right part of the axis). The chimpanzee subjects seem to have a flat shape, while the humans subjects' bundles were more restricted to the right side of the axis. However the distinction between the two species morphologies was not easy with this dimension. We saw that some of the chimpanzees display a flat and twisted bundle body, while the aspect of the human's bundles has a rounded shape, somehow like a tube.

The second dimension from the embedding emphasizes the curved aspect of the bundle. Indeed, towards the left side of the axis, we can see that the bundles display a curved shape, while when progressing to the right side of the axis, the more flat becomes the bundle. This criteria seems to be the most discriminating one between the two species : we can almost subdivide the axis in two parts. On the left side we can find the humans bundles with a curved morphology, and on the right side, we find the chimpanzees bundles with a flat morphology. This difference is harder to explain. Especially since it is not easily spotted when looking at the bundles at the first sight. This could be linked to the profile of connections due to a smaller occipital lobe in humans compared to chimpanzees.

The third dimension that depicted interesting information was the dimension number four of the embedding. Indeed, along the axis, when going from left to right, we go from a thick posterior occipital extremity to a thin one. This does not seem to divide humans and chimpanzees, but it would rather gather them around the same shape variability. It also supports the fact that chimpanzees do not seem to globally show a thicker occipital extremity compared to humans, which could have been an explanation to what was seen on the previous dimensions.



Figure 7.32: Geometrical analysis of the inferior longitudinal fasciculus between humans and chimpanzees. At the top, on the left : averaged bundles stemming from the atlases of each species, center : the registered average shapes pointed out by the isomap algorithm, on the right : histogram of the dimensions of the embedding. Bottom : dimensions axes from the embedding (dimensions 1, 2 and 4) with classified bundles from both species along the axes (violet : chimpanzee, gold : human) and underlying moving averages.

## 7.4.2.8 The middle longitudinal fasciculus

154 MFL bundles were analysed. In this case, only the first dimension is relevant. Along the axis, we go from an elongated and long bundle's body (left side of the axis) to a thick and short body (right side of the axis). There is an important variability between humans and chimpanzees. The results from the isomap that are shown in this study hardly reflect thin morphological differences but rather mostly the fact that in humans, this bundle shape was clearly identified and reproducible, but in the chimpanzee brain, the MFL shape is highly variable and hard to reconstruct. It is also sometimes merged with the inferior longitudinal fasciculus. The first dimension was the one depicting these major differences. The other ones did not show relevant information.



Figure 7.33: Geometrical analysis of the inferior longitudinal fasciculus between humans and chimpanzees. At the top, on the left : averaged bundles stemming from the atlases of each species, center : the registered average shapes pointed out by the isomap algorithm, on the right : histogram of the dimensions of the embedding. Bottom : the dimension axis from the embedding (dimension 1) with classified bundles from both species along the axes (violet : chimpanzee, gold : human) and underlying moving averages.

## 7.4.3 Conclusion and perspectives

We believe this tool to be complementary to the visual inspection on the tract trajectory inside of the brain. However, it can be challenging to capture the morphological features that make the difference between the two species. This is a preliminary work that would need more digging, with more subjects in order to have more significant differences. It however proved itself to be a valuable tool to assess the key differences and commonalities in the shape of deep white matter bundles. It is also a performing tool to visualize a large cohort of data. Indeed, there were sometimes more than 140 bundles to compare, and trying to draw conclusions from only a visual inspection would have been impossible.

This tool could be further relevant if correlated with behavioral scores to see if the position of a subject's bundle on the isomap, could be somehow related to the subjects behavioral traits. It could also be interesting to have more than 2 primates species to analyse using this tool, maybe the addition of bonobos, gorillas or even orangutans bundles and the relation they would have in the isomap axis with chimpanzees and humans could bring new surprises on their phylogenetic relations between each others.

We also need to consider current limitations to be rigorous. First, the results from the isomap algorithm highly depend on the application of the atlas on all subjects, which implies a visual inspection of all the subjects bundles before lauching the investigation on the bundles morphology. Second, the interpretation of the criteria of classification of the bundles along the isomap can be sometimes challenging to interpret.

## Chapter 8

# Investigation of the inferior fronto-occipital fasciculus in the macaque fascicularis brain using ultra-high field MRI at 11.7 Tesla

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Figure 8.1: Picture of a macaque from the species Macaca Fascicularis, picture from Charles J. Sharp.

## 8.1 Introduction

The inferior fronto occipital fasciculus, also called IFOF, is one of the main association bundles populating the human brain.

As presented in the background section, this white matter bundle is one of the longest and thickest bundle present in the brain and is involved in various higher cognitive networks.

Among these functions is language processing. More precisely, this bundle seems to be involved in speech production [Friederici and Gierhan 2013; Almairac et al. 2015], which makes it a bundle of choice, in conjunction with the arcuate fasciculus, for the study of the emergence of language in humans.

It is generally assumed that the development of the IFOF in humans played a key role in the acquisition of speech during evolution [Forkel, Schotten, et al. 2014; Schotten et al. 2012]. For a long time, the IFOF was considered as specific to humans because it could not be adequately identified in non-human primates like macaques or because its structure and position was not significantly different from that of humans [Y. Wu et al. 2016, Yeterian et al. 2012, Forkel, Schotten, et al. 2014]. Quite recently, this assumption was revised by the work of [Barrett et al. 2020, Decramer et al. 2018, Sarubbo et al. 2019].

The growing interest of the scientific community concerning evolutionary neuroscience and language acquisition led to a renew of interest about the link existing between white matter bundles and functions they support as well as their comparison between the different primate species. However, few studies have addressed the morphology and the anatomy of the inferior fronto-occipital fasculus between the human, chimpanzee and macaque brains.

This chapter aims to fill the gap and presents an investigational study of the inferior frontooccipital fasciculus in the macaque brain, and more precisely of the "*Macaca Fascicularis*" species scanned using ultra-high field MRI data at 11.7 Tesla to map it at high resolution.

## 8.2 Methods

## 8.2.1 Post-mortem brain sample

The *ex-vivo* brain used for this study was collected from a 3 years old female macaque from the *Macaca Fascicularis* species by the INSERM U1253 iBrain Unit (University of Tours, France). It was scanned at the on a preclinical MR imaging platform of the NeuroSpin department (CEA, Gif-sur-Yvette) in the frame of an imaging protocol approved by the Local Animal Welfare Committee.

## 8.2.2 MRI Protocol

The subject's brain was scanned using a Bruker Biospin 11.7 T MRI system and a 60mm volume coil with an imaging protocol including a 3D T2-weighted MSME 100µm scan, a 180µm 2D T2-weighted MSME scan and a multishell diffusion MRI (dMRI) scan using a 3D segmented EPI PGSE sequence at b=1500/4500/8000s/mm<sup>2</sup> along 25/60/90 directions (TE/TR=24/250ms, 33 segments, 250µm isotropic resolution).

## 8.2.3 Pre/Post-processing

After correcting for imaging artifacts (such as eddy currents, susceptibility artefacts), dMRI data were used to compute analytical Q-ball ODF maps (SH order 6, Laplace-Beltrami regularization factor of 0.006) from which a whole brain regularized deterministic tractography was performed (1 seed/voxel, forward step 60 $\mu$ m, aperture angle 15°, GFA threshold 0.04) to obtain the subject's tractogram.

Similar to the approach described in Chapter 6, a hierarchical fiber clustering algorithm, was applied to the tractogram to create a parsimonious representation of the tractogram composed of small white matter fascicles (each populated by a few dozen of fibers and represented by a centroid fiber) subdivided in two sets corresponding to the 2 hemispheres, and further classified according to their length ranges. Diffusion MRI data set were also co-registered to the 2 anatomical T2-weighted scans using the ANTs toolbox.

## 8.2.4 Inferior fronto-occipital fasciculus reconstruction

For each hemisphere, two ROIs were then manually delineated at the level of 2 distant coronal planes: a first ROI corresponding to the middle part of the frontal lobe and a second ROI corresponding to the anterior part of the occipital lobe. Fascicles passing through the two ROIs were then selected to identify the 2 target left and right IFOFs.



Figure 8.2: Post-processing steps of anatomical and diffusion data from the macaque brain. All steps were performed using the Ginkgo (https://framagit.org/cpoupon/gkg) toolbox.

## 8.3 Results

## 8.3.1 Quantitative DTI and Qball mapping

Figure 8.3 shows the reconstructed DTI and analytical Q-ball quantitative feature maps including ADC, FA, parallel and transverse diffusivity, color-encoded direction maps, assessing the high degree of quality of the scan reached at 11.7T.



Figure 8.3: Quantitative DTI and Qball maps of the macaque subject showing its apparent diffusion coefficient (ADC), fractional anisotropy (FA), axial diffusivity (Dparallel), radial (Dtransverse), generalized fractional anisotropy (GFA) and color-encoded diffusion direction along 3 orthogonal views.

## 8.3.2 Fiber tracking and clustering

Figure 8.4 provides various planes showing the precision of the reconstructed connectogram, composed of 995 982 fibers, yielding 14 630 clusters for the left hemisphere and 14 452 clusters for the right hemisphere, being slightly higher for the left hemisphere, after the application of the hierarchical fiber clustering method.



Figure 8.4: Macaque subject's tractogram and clustering renders. Displayed on the axial, sagittal and coronal plans, at the top : the subject's tractogram, where the directions of the different fibers are color-coded ; at the bottom : the clusters of fibers resulting from the hierarchical clustering. Each cluster of fibers is represented by a color.

## 8.3.3 IFOF reconstruction

After the selection of fibers uniquely passing through the two defined ROIs, the IFOFs were reconstructed. The two IFOFs start in the occipital cortex, pass through in the depth of the

temporal lobe and end in the superior part of the frontal lobe. The frontal connections remained thin in both hemispheres. The left IFOF was composed of 42 clusters including 454 fibers, and the right IFOF was composed of 110 clusters including 1 050 fibers, making it significantly more developed than the left IFOF (see figure 8.5).



Figure 8.5: Inferior fronto occipital fasciculus of the macaque Fascicularis. The bundles are displayed on (top) meshmap of the brain in sagital and axial plans, (bottom) fractional anisotropy image, using the right top and left view, in sagital and axial plans.

8.4 Discussion : comparison of the inferior fronto-occipital fasciculus between macaques and hominids



Figure 8.6: Anatomical comparison of the IFOF between macaque, chimpanzee and human brains. macaque's IFOF (top), chimpanzee's IFOF (middle) and human's IFOF (bottom).

The left and right IFOFs from the macaque seem both to originate in the superior frontal cortex. Then, they pass through in the depth of the temporal lobe and end in the occipital lobe. When passing through the temporal lobe, the posterior extremities seem to split into two different subparts, one connecting to the superior occipital lobe and the other reaching the inferior occipital lobe (see figures 8.6).

The macaque's IFOFs appear to be much thinner than human and chimpanzee IFOFs. The course of the bundles are similar, except in the frontal area. Indeed, the frontal extremities of the IFOFs mostly reach the superior frontal cortex while in human and chimpanzee they mostly reach the middle and inferior frontal cortex.

## 8.5 Conclusion

The high field diffusion and anatomical MRI data allowed the reconstruction of the macaque's left and right inferior fronto-occipital fasciculi at the mesoscale. This finding contradict earlier studies failing to reconstruct this bundles in macaques, and assuming their presence only in humans.

The observed IFOFs fibers pathways and crossing regions are quite similar to that of humans, particularly thin connections were observed in the frontal areas. This is consistent with previous studies suggesting that the frontal lobe could be associated with higher cognitive functions, lacking in the macaque brain [Barrett et al. 2020]. This study confirms previous studies using dissection evidencing that the IFOF seem also present in other non-hominid non-human primates [Sarubbo et al. 2019].

## Chapter 9

# General conclusion and contributions

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Figure 9.1: Picture Pr. Jane Goodall, one of the pioneers of primatology, and a chimpanzee. Picture credits: Jane Goodall Institute/Michael Neugebauer

## 9.1 Conclusion

The principal goal of this thesis was to explore the connectivity of the chimpanzee brain, and to investigate its differences compared to the human brain. To achieve this, a first contribution consisted in (1) building a novel complete connectivity atlas of the *in vivo* chimpanzee brain comprising superficial and deep white matter bundles, (2) building a novel comparable complete connectivity atlas of the human brain, (3) defining a method of comparison of the superficial white matter bundles morphology between the two species using an algorithm called 'isomap', (4) defining a method of comparison of the deep white matter bundle morphology between the two species, still using the isomap algorithm but in a different manner.

In this thesis, two main methods were used : (1) a 2-step fiber clustering algorithm allowing the elaboration of the deep and superficial white matter atlases, (2) an isomap algorithm as an attempt to compare the bundles morphologies between the human and chimpanzee species.

A last contribution the study of the *ex vivo* macaque *Fascicularis*' brain using 11.7 Tesla MRI to investigate the inferior fronto-occipital fasciculus, a former controversial bundle in the macaque brain, unexplored in this particular species.

The main point highlighted by this thesis is that finer differences in white matter connectivity probably have a relevant role to play in the enhanced huge cognitive differences. We tried to understand and geometrically quantify these finer connectivity differences at the level of the superficial and deep white matter bundles. We summarize here the major contributions of this work.

## 9.1.1 Singularity of the structural connectivity of the chimpanzee brain compared to the human brain

#### 9.1.1.1 Creation of a novel complete in vivo chimpanzee white matter atlas

A first deep and superficial structural connectivity atlas of the chimpanzee brain (Pan Troglodyte) was designed from diffusion-weighted and anatomical MRI acquisitions at 3T on a cohort of 39 subjects (23 females and 16 males) from the Yerkes National Primate Research Center (YN-PRC, Atlanta, USA). The atlas is composed of 46 deep and 822 superficial labeled white matter bundles that reflect the complete structural connectivity of the chimpanzee brain.

The deep and superficial white matter bundles atlases presented in this thesis are fully available at :

- https://zenodo.org/record/7147503 Ginkgo Chauvel's left and right superficial white matter atlas of the chimpanzee brain;
- https://zenodo.org/record/7147789 Ginkgo Chauvel's deep white matter atlas of the chimpanzee brain.

This work was submitted to the journal NeuroImage.

#### 9.1.1.2 Creation of a novel complete in vivo human white matter atlas

In the frame of a future comparison, a novel deep and superficial structural connectivity atlas of the human brain, relying on a cohort of 39 subjects (23 men and 16 women) was built from the HCP database. To be able to establish a relevant correspondence with the chimpanzee cortical labeling, a new human cortical labeling was created. It resulted in 45 labeled deep white matter bundles and 1365 labeled superficial white matter bundles.

The deep and superficial white matter bundle atlases presented in this thesis are fully available at :

- https://doi.org/10.5281/zenodo.7308510 Ginkgo Chauvel's deep white matter atlas of the human brain.
- https://doi.org/10.5281/zenodo.7308606 Ginkgo Chauvel's superficial white matter atlas of the human brain.

## 9.1.2 Comparative morphology of white matter bundles between the chimpanzee and human brains

Finding a relevant way to compare two species brains is a huge challenge, we have tried to provide a relevant methodology by : (1) attempting a finer registration between the two species brains using Brainvisa toolbox "DISCO and DARTEL complete pipeline", (2) using the isomap algorithm to analyse the morphological differences of the two species in a common space, (3) using the isomap algorithm to understand if the superficial bundles' shapes observed could be automatically classified and if the same shapes were found for the human and the chimpanzee brain.

#### 9.1.2.1 Comparative study of superficial white matter bundles morphometry

From a visual exploration of all the clusters composing both species atlases, we observed common shapes (U-fibers, Open-U fibers, C fibers, V fibers, straight fibers) and exclusive shapes for the human brain (L fibers, 6 fibers). From their native spaces, both species' superficial white matter bundles were reduced to one centroid fiber, resampled to obtain the same number of points per fiber, and entered into the isomap algorithm for a semi-automatic recognition of their shapes. In the human as in the chimpanzee brain, the amount of clusters of shapes consists in 2 main shapes (closed edges and flat edges), that can further be subdivided in to 5 clusters of shapes depending on the degree of opening and curvature of the fibers.

The results provided detailed information on the main morphologies of the hominid short bundles but also on those specific to each species. Results pave the way to a better understanding of the gap between the human brain and the chimpanzee brain, and of their underlying brain superficial connectivity singularities.

A paper concerning this work is in preparation.

#### 9.1.2.2 Registration of the two species brains

To do the registration of the two species' brain, a sulci labeling for each species brain templates was done, followed by a selection of the relevant common sulci. In the case of this work, 20 sulci were selected.

The registration between the two species gave relatively satisfying results, except in what concerned the frontal regions. It is a reflection of the main areas of brain variability between the two species. This was expected due to the lake of sulci in the chimpanzee frontal regions in parallel to the huge amount of variable sulci in the human brain frontal regions.

#### 9.1.2.3 Comparative study of the deep white matter bundles morphometry

After the application of the deep white matter bundle atlases on each subject of both human and chimpanzee cohorts, all bundles were converted into alpha shapes, and then into point clouds. This allowed to keep enough information about the finer shape of the bundles as well as a reduced amount of points to be integrated by the algorithm.

The results allowed the classification of eight major deep white matter bundles from the atlases, allowing a better understanding of the singularity of the morphology of each species bundle in relation to the variability introduced by the other.
It allowed to better appreciate the degree of similarity and differences between each species bundles morphology.

A paper concerning this work is in preparation.

# 9.1.3 Investigation of the inferior fronto-occipital fasciculus (IFOF) in the macaque fascicularis brain using ultra-high field MRI at 11.7 Tesla

The last contribution of this thesis was the study of the IFOF in one macaque species, (*Macaca Fascicularis*), in which it had never been explored before. The choice of this particular bundle was made due to its controversial presence in non-human primates' brains. Indeed, it has for long been believed to be absent and linked to the ventral pathway for language, thought to be exclusively present in humans as a marker for human language acquisition.

The work of this thesis showed that this bundles was present in the macaque brain, and that its global pathway was the same as for chimpanzee and human. However, the bundles was thinner than for the other two species and displayed different frontal connected regions.

While this work was mainly exploratory, it also showed differences in the frontal cortical regions connected by the IFOF. This is possibly to be linked to the evolution of the frontal regions in primates and underlying cognitive abilities known to be linked to these regions such as planning, reasoning, problem solving, impulse control and regulation of emotions.

### 9.2 Prospects

#### 9.2.1 On the chimpanzee white matter connectivity

If the work presented here already provides consistent atlases of SWMB and DWMB for the chimpanzee and the human brain, the quality and quantity of MRI data (both anatomical and diffusion MRI) make further improvements possible.

A first perspective could be to increase the number of subjects. Indeed, in this thesis were only used subjects that went under the exact same MRI protocol, however, other chimpanzee subjects that followed different protocols (but providing good quality anatomical and diffusion data) could be used as supplementary subjects for the establishment or application of the atlases.

An increase in the number of bundles could also be considered with a finer clustering processing or the use of some regions of interest. In particular, we could attempt to separate the arcuate fasciculus of the chimpanzee from a possible superior longitudinal fasciculus as shown in the Chapter 7. A novel definition of the thalamic radiations could be proposed thanks to the amount of fibers found in the chimpanzee brain. The selection of particular fascicles reaching different cortical regions or starting from different subparts of the thalamus nuclei could be implemented to provide a new atlas of the thalamic connections of the chimpanzee brain.

The posterior commissure was found missing from the inter-subject fiber clustering algorithm. We believe that this is due to the reduced number of seeds per voxel that were used for the tractography algorithm (1 seed/voxel). Indeed, as the posterior commissure is very thin in the chimpanzee brain, 1 seed may not have been enough to be able to reconstruct the fibers from this region. It is probable that a new launch of the tractography algorithm using more seeds would help identify these fibers and then produce a new bundle to be added to the atlas.

The cortico-ponto-cerebellar bundle could also be improved, notably by the use of regions of interest to help distinguishing between the two crossing bundles from the left and the right hemispheres.

## 9.2.2 On the comparative study of the deep white matter bundles morphometry

The results coming out of the isomap algorithm are dependent of the quality of the bundles from each subject. Indeed, the bundles need to be as "clean" as possible before entering the pipeline and it is probable that some subjects' bundles were less well reconstructed than others, thus introducing a slight bias in the isomap classification. The possible upcoming work could be improving the application of the atlas enhancing a better consideration of each subject's proper individual variability. The same type of work could be done regarding the alpha shape computation.

If this work provided insights about the singularity of the hominid brains WM morphology, it would be interesting to compare the cortical connected regions from each bundles from humans and chimpanzee. This could allow to link the different variability in bundles morphologies to the degree of cortical connections for both species. In addition, we only investigated eight major white matter bundles morphology (16 if we consider both hemispheres) as the atlases contain more bundles. Thus, a future prospect could be the analysis of the remaining bundles.

## 9.2.3 On the comparative study of the superficial white matter bundles morphometry

In this work, we only considered the centroid of the SWMB. An upcoming work could be using the alpha-shape algorithm in order to obtain 3d shapes of each superficial bundle. This would imply to readjust the parameters of the alpha shape for shorter bundles and could help distinguishing the V-shaped bundles from the U-shaped bundles for example.

It is also probable that the cortical labeling used for humans and chimpanzees to pair and name the superficial bundles could be improved by redefining cortical regions following future improvements on the chimpanzee brain cortical functional and anatomical understanding.

Another prospect could also be the creation of a new tool allowing the characterisation of the SWMB not only by the regions they connect but also using the brain gyrification. The identification of these bundles depending on (1) which sulci they overlap and (2) how many sulci are concerned could provide relevant insights on their localisation and organisation. As some major sulci are common between humans and chimpanzees, this tool would help in the analysis of both species common cortical traits and differences linked to their underneath connections.

#### 9.2.4 On the investigation of the IFOF in the macaque Fascicularis brain

The investigation of the other bundles composing the macaque brain is something that would be considered. The opportunity to have ultra high resolution anatomical and diffusion data should be exploited to have a better description of the white matter bundles of the macaque brain.

# 9.3 Contributions

#### 9.3.1 Journal papers

- In vivo mapping of the deep and superficial white matter connectivity in the chimpanzee brain. M. Chauvel, I. Uszynski, B. Herlin, A. Popov, Y. Leprince, J-f. Mangin, W. D Hopkins, C. Poupon. Under review for NeuroImage.
- A novel multi modal morphological analysis of the superficial connectivity of the chimpanzee brain compared to the human brain. M. Chauvel, M. Pascucci, I. Uszynski, B.Herlin, W. Hopkins, J.-F. Mangin, C. Poupon. *In preparation for submission to NeuroImage.*

- Comparative study of deep white matter bundles morphometry of the human brain compared to the chimpanzee brain. M. Chauvel, M. Pascucci, I. Uszynski, B.Herlin, Yann Leprince, W. Hopkins, J.-F. Mangin, C. Poupon. *In preparation for submission to NeuroImage*.
- Cross-subject variability of the optic radiation anatomy in a cohort of 1065 healthy subjects. Herlin B, Uszynski I, Chauvel M, Poupon C, Dupont S. *Submitted to Surgical and Radiologic Anatomy*.

# 9.3.2 Conference papers

## 9.3.2.1 Year 2023

- Morphological comparison of superficial white matter bundles between the human and chimpanzee brain, M.Chauvel, M. Pascucci, I. Uszynski, B. Herlin, J-F. Mangin, W. D. Hopkins, C. Poupon. *Proceedings of OHBM 2023*, abstract number 2178.
- Morphological comparison of deep white matter bundles between the human and chimpanzee brain using a geometrical approach, M. Chauvel, I. Uszynski, B. Herlin, M. Pascucci, Y. Leprince, J-F. Mangin, W. D. Hopkins, C. Poupon. *Proceedings of OHBM 2023*, abstract number 2111.
- A novel atlas of the superficial white matter connectivity and variability on the whole HCP cohort, B. Herlin, I. Uszynski, M. Chauvel, S. Dupont, C. Poupon. *Proceedings of OHBM 2023*, abstract number 1204.
- Cross-subject variability of the optic radiation anatomy: a large-scale analysis on 1065 subjects.B. Herlin, I. Uszynski, M. Chauvel, C. Poupon, S. Dupont. *Proceedings of OHBM 2023*, abstract number 1204.
- FibraVasc: towards ex vivo MRI mapping of cerebral vascular territories, application to the vascularization of deep white matter bundles. S. Legeay, M. Smirnov, M. Chauvel, B. Herlin, L. Barantin, I. Uszynski, I. Lima Maldonado, C. Destrieux, and Cyril Poupon, *Proceedings of OHBM 2023*, abstract number 1259.
- Morphological comparison of superficial white matter bundles between the human and chimpanzee brain, M.Chauvel, M. Pascucci, I. Uszynski, B. Herlin, J-F. Mangin, W. D. Hopkins, C. Poupon. *Proceedings of ISMRM 2023*, abstract number 5799, poster presentation.
- Morphological comparison of deep white matter bundles between the human and chimpanzee brain using a geometrical approach, M. Chauvel, I. Uszynski, B. Herlin, M. Pascucci, Y. Leprince, J-F. Mangin, W. D. Hopkins, C. Poupon. *Proceedings of ISMRM 2023*, abstract number 5755, oral presentation.
- A novel atlas of the superficial white matter connectivity and variability on the whole HCP cohort, B. Herlin, I. Uszynski, M. Chauvel, S. Dupont, C. Poupon. *Proceedings of ISMRM 2023*, abstract number 0351, poster presentation.
- Cross-subject variability of the optic radiation anatomy: a large-scale analysis on 1065 subjects. Herlin, I. Uszynski, M. Chauvel, C. Poupon, S. Dupont. *Proceedings of ISMRM 2023*, abstract number 3116, oral presentation.
- FibraVasc: towards ex vivo MRI mapping of cerebral vascular territories, application to the vascularization of deep white matter bundles. S. Legeay, M. Smirnov, M. Chauvel, B. Herlin, L. Barantin, I. Uszynski, I. Lima Maldonado, C. Destrieux, and Cyril Poupon, *Proceedings of ISMRM 2023*, abstract number 0341, power pitch.

#### 9.3.2.2 Year 2022

- Investigation of the singularity of the chimpanzee brain superficial white matter bundles using diffusion MRI and clustering-based approaches. M. Chauvel, I. Uszynski, M. Pascucci, A. Popov, W.D. Hopkins, J.-F. Mangin, C. Poupon. *Proceedings of OHBM 2022*, abstract N° 2338, poster presentation.
- Investigation of the inferior fronto-occipital fasciculus in the macaque fascicularis brain using ultra-high field diffusion MRI at 11.7 tesla. M. Chauvel, I. Uszynski, C. Fischer, F. Poupon, C. Destrieux, I. Maldonado, C. Poupon. *Proceedings of OHBM 2022*, abstract N° 2257, poster presentation.
- Investigation of the singularity of the chimpanzee brain superficial white matter bundles using diffusion MRI and clustering-based approaches. M. Chauvel, I. Uszynski, A. Popov, W. Hopkins, J.-F. Mangin , C. Poupon. *Proceedings of ISMRM 2022*, abstract N° 2605, poster presentation.
- Length-dependent spatial distribution of short fiber bundles revealed with the mesoscopic Chenonceau dataset. A. Popov, I. Uszynski, B. Herlin, M. Chauvel, I. Maldonado, C. Destrieux, C. Poupon. *Proceedings of ISMRM 2022*, abstract N° 2605, poster presentation.

## 9.3.2.3 Year 2021

- A fiber clustering-based atlas of the chimpanzee deep brain structural connectivity using diffusion MRI. M. Chauvel, I. Uszynski, W. Hopkins, J.-F. Mangin , C. Poupon. *Proceedings of OHBM 2021*, abstract N° 1677, poster presentation.
- A new superficial white matter connectivity atlas of the chimpanzee brain. M. Chauvel, I. Uszynski, W. Hopkins, J.-F. Mangin , C. Poupon. *Proceedings of OHBM 2021*, abstract N° 1602, poster presentation.
- A fiber clustering-based atlas of the chimpanzee deep brain structural connectivity using diffusion MRI. M. Chauvel, I. Uszynski, W. Hopkins, J.-F. Mangin , C. Poupon. *Proceedings of ISMRM 2021 Congress*, abstract N° 2569, poster presentation.
- A new superficial white matter connectivity atlas of the chimpanzee brain. M. Chauvel, I. Uszynski, W. Hopkins, J.-F. Mangin , C. Poupon. *Proceedings of ISMRM 2021*, abstract N° 1715, poster presentation
- Disentangling the differential maturation of sensorimotor cortices in newborns compared to adults. L. Devisscher, M. Chauvel, C. Rolland, N. Labra, K. Aubrain, F. Leroy, H. de Vareilles, L. Hertz-Pannier, A. Grigis, J.-F. Mangin, J. Dubois. *Proceedings of ISMRM 2021*.

## 9.3.2.4 Year 2020

- A novel superficial white matter connectivity atlas of the chimpanzee brain, M. Chauvel, I. Uszynski, W. Hopkins, J.-F. Mangin , C. Poupon. *Proceedings of ESMRMB 2020 Congress*, abstract N°A-1387, oral presentation
- Exploring the microstructural properties of the newborn sensorimotor network with diffusion MRI, M. Chauvel, F. Rheault, C. Rolland, K. Aubrain, F. Leroy, H. de Vareilles, G. Girard, D. Riviere, L. Hertz-Pannier, J-F. Mangin, M. Descoteaux, J. Dubois. *Proceedings of OHBM, 2020*, poster presentation.

- Exploring the microstructural connectivity of the newborn atlas of the newborn brain cortex : a clustering approach of diffusion parameters F. Ginzburg, M. Chauvel, C. Rolland, K. Aubrain, F. Leroy, H. de Vareilles, L. Devisscher, L. Hertz-Pannier, J.-F. Mangin, J. Lebenberg, J. Dubois, *Proceedings of ISBI, 2020*.
- Mapping the developing sensorimotor network in newborns with diffusion MRI. M. Chauvel, C. Rolland, F. Rhéault, K. Aubrain, F. Leroy, H. de Vareilles, G. Girard, D. Rivière, L. Hertz-Pannier, J.-F. Mangin, M. Descoteaux, J. Dubois. *Proceedings of ECMRN*, 2020

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ÉCOLE DOCTORALE Physique et ingénierie: Electrons, Photons, Sciences du vivant (EOBE)

**Titre:** Singularité de la connectivité structurelle de la substance blanche du cerveau de l'Homme comparée à celle du chimpanzé.

**Mots clés:** IRM de Diffusion, Atlas superficiel et profond de la substance blanche, Morphologie de la substance blanche, Cerveau du chimpanzé.

L'espèce humaine est le fruit d'une évolution longue et complexe. Les récentes avancées scientifiques ont montré que les traits à la fois physiques et comportementaux partagés par les Hommes ont pour origine un ancêtre simiesque qui aurait vécu autour de 6 millions d'années avant notre ère. Les humains font partie de l'ordre des primates et de ce fait partagent d'importants traits phénotypiques avec les autres grands singes. Parmi les hominidés, notre cousin phylogénétique le plus proche est le chimpanzé (Pan troglodytes), du genre Pan, avec qui nous partageons 96 pourcent de patrimoine génétique. Cette proximité entre le chimpanzé et l'Homme interdit leur utilisation en recherche clinique pour des raisons éthiques évidentes. Toutefois, l'existence de méthodes d'imageries non invasives telles que l'IRM ont rendu possible l'élaboration d'études visant à comprendre les différences et points communs entre le chimpanzé et l'Homme, afin de mieux comprendre la singularité qui leur est propre. L'IRM de diffusion est de nos jours une méthode bien connue d'exploration de la microstructure des tissus cérébraux. A ce jour, cette méthode reste la seule permettant d'imager la connectivité structurelle du cerveau. L'anatomie sulco-gyrale et la connectivité structurelle sont intimement liées, avec des fonctions cérébrales résultant des connections entre les différentes régions corticales et/ou avec la substance grise profonde via des faisceaux de fibres axonales peuplant la substance blanche cérébrale, et de ce fait, établissant des réseaux fonctionnels. Un des challenges majeurs des neurosciences, d'un point de vue évolutif, est de créer et comparer des modèles de connectivité du cerveau entre dif-

férentes espèces. Un atlas du cerveau du chimpanzé a été établi grâce à une cohorte de 39 chimpanzés (comprenant des données IRM anatomiques et de diffusion) provenant du centre de conservation "Yerkes National Primates Research Center (YNPRC, Atlanta, Université d'Emory)" et partagée par le Pr. William Hopkins (MD Anderson cancer center, Department of comparative medicine, Bastrop, Texas), dans le contexte de la chaire d'excellence Blaise Pascal. Un atlas de la substance blanche du cerveau de l'Homme a été établi grâce à une cohorte de 39 sujets humains (aussi avec des données IRM anatomiques et de diffusion), intentionnellement identique en genre et en nombre avec la cohorte de sujets chimpanzés. La contribution principale de cette thèse est la création de deux nouveaux atlas de la connectivité structurelle des cerveaux de l'Homme et du chimpanzé, résultant d'un pipeline d'analyse de données issues de l'IRM de diffusion utilisant des algorithmes avancés de clustering de fibres, et adapté aux deux espèces. La seconde contribution de cette thèse consiste en l'étude comparative de la morphologie des faisceaux de substance blanche profonds et superficiels, grâce à une autre approche de clustering basé sur l'algorithme dit "isomap" originellement développé pour la l'étude de la morphométrie sulco-gyrale. La dernière contribution de cette thèse est l'étude du faisceau fronto-occipital inférieur chez le macaque Fascicularis grâce à l'utilisation de l'IRM à très haut champ (11.7 Tesla), permettant l'exploration de la connectivité structurelle d'un faisceau controversé chez cette espèce.

**Title:** Singularity of the white matter structural connectivity of the human brain compared to the chimpanzee brain.

**Keywords:** Diffusion MRI, deep and superficial white matter atlas, white matter bundle morphology, chimpanzee brain.

The human species is the fruit of a long and complex evolution. Recent scientific advances have shown that the physical and behavioral traits shared by all humans originated from apelike ancestors and evolved over a period of about six million years. Humans are part of the primate order, and share important phenotypic traits with the other great apes. Among hominids, our closest phylogenetic living relative is the common chimpanzee (Pan troglodytes), from the Pan order, with whom we share about 96 percent of gene proteins. The close phylogenetic proximity between chimpanzees and humans prohibits its use in clinical research for obvious ethical reasons, but the existence of non-invasive neuroimaging tools, such as magnetic resonance imaging (MRI), has made it possible to set up studies aimed at understanding the differences and commonalities of the chimpanzee and human brains, in order to better understand their compared singularity. Diffusion MRI is now a wellestablished MRI tool to explore the brain microstructure through the observation of the anisotropy of Brownian motion of water molecules present in tissues. To date, it remains the only method for the imaging of brain anatomical connectivity. Sulco-gyral anatomy and structural connectivity are intimately linked, with brain functions resulting from the connection of cortical regions and/or deep grey matter regions via axonal fiber bundles populating the cerebral white matter, thus establishing functional networks. One of the great challenges of neuroscience from an evolutionary point of view, is to build and compare models of the brain connectome between species. This thesis is part of this approach, using anatomical and diffusion MRI, two atlases

of the human and chimpanzee brains comprising superficial and deep white matter connectivity were built with the intention of comparing them. The chimpanzee white matter bundle atlas was established thanks to a cohort of 39 chimpanzees (with anatomical and diffusion MRI data) stemming from the Yerkes National Primates Research Center (YNPRC, Atlanta, Emory University) shared by Pr. William Hopkins (MD Anderson cancer center, Department of comparative medicine, Bastrop, Texas) in the frame of the chair of excellence Blaise Pascal. The human white matter bundle atlas was built relying on a cohort of 39 subjects (with anatomical and diffusion MRI data), intentionally matching the chimpanzee cohort in terms of number of subjects and gender. The main contribution of this thesis was the creation of two novel atlas of the structural connectivity of the human and chimpanzee brains, resulting from a dedicated diffusion MRI processing pipeline using an advanced fiber clustering algorithm adapted for the two species. A second contribution of this thesis consisted of a comparative study of the morphology of deep and superficial white matter bundles between chimpanzee and human brains, using another clustering approach based on an isomap algorithm originally developed to compare the sulco-gyral morphometry. A last contribution driven in this thesis was the investigation of the inferior fronto-occipital fasciculus in the macaque fascicularis brain using ultra-high field MRI at 11.7 Tesla, allowing to explore the structural connectivity of an additional primate species with regard to a former controversial bundle concerning non-human primates.