



# Tractographie des nerfs crâniens : état de l'art, développement et application en chirurgie des tumeurs de la base du crâne.

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**Timothée JACQUESSON**

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# Tractographie des nerfs crâniens : état de l'art, développement et application en chirurgie des tumeurs de la base du crâne.

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## DÉDICACE

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## RÉSUMÉ

Apparue à la fin des années 1990, la tractographie utilise le signal diffusion de l'imagerie par résonance magnétique (IRM) pour détecter l'orientation préférentielle des molécules d'eau et reconstruire l'architecture des tissus biologiques, notamment celle des fibres blanches intra cérébrales. Cette technique a suscité l'engouement de la communauté scientifique en permettant, pour la première fois, l'étude *in vivo* non invasive des structures anatomiques, et en particulier celle du cerveau. Néanmoins, la description de la trajectoire des fibres blanches reste imprécise dans les zones de croisement de fibres et pour les structures de petite taille comme les nerfs crâniens. De multiples méthodes sont développées aux différentes étapes d'acquisition et de post-traitement mais la résolution spatiale et angulaire reste encore insuffisante. L'objectif de ce travail est l'application de la technique de tractographie aux nerfs crâniens et sa validation clinique pour la détection de leur trajectoire en cas de tumeurs de la base du crâne. Après avoir rappelé les notions fondamentales nécessaires à la compréhension de chaque étape de la tractographie, je présente l'« état de l'art » dans le cas particulier des nerfs crâniens. A partir de 21 études de la littérature scientifique, je détaille tous les paramètres d'acquisition et de *tracking*, les algorithmes de reconstruction, le *design* des régions d'intérêt et le filtrage. Puis, je développe mon propre *pipeline* de tractographie et montre son impact potentiel sur la prise en charge chirurgicale à travers une série de 62 cas de tumeurs variées de la base du crâne et 2 vignettes cliniques illustratives. Enfin, je propose une nouvelle approche, la *full-tractography*, qui reconstruit les nerfs crâniens dans leur environnement anatomique complet avec ou sans tumeur, pour une exportation en routine clinique notamment lors du planning pré-chirurgical, dans le but d'améliorer le résultat fonctionnel pour les patients.

**Mots clés :** Tractographie, nerfs crâniens, IRM, diffusion, base du crane, tumeurs





## ABSTRACT

**T**ractography is a recent imaging tool that uses the diffusion signal from the magnetic resonance imaging to detect the preferential orientation of water molecules within the tissues and particularly along white fibers of the brain. This technique has caught the attention of the scientific community describing non-invasively the *in vivo* white matter architecture. Nonetheless, its application to fiber crossing areas or small-scale structures, such as cranial nerves, remains inaccurate. New methods are being developed for both the acquisition and post-processing steps, but the angular and spatial resolution is still insufficient. The objective of this work is the application of the technique of tractography to cranial nerves and in the clinical setting for the detection of their trajectory in case of skull base tumors. After reminding the basics to understand each step involved in tractography, I present the current state-of-the-art for application to cranial nerves. From 21 selected studies, I report all parameters of acquisition and tracking, the algorithms of reconstruction, the design of the regions of interest, and filtering methods. I then develop a dedicated tractography pipeline and show its value for surgical management through a 62 case series of various skull base tumors and two clinical images. Finally, I propose a new full-tractography approach that can reconstruct cranial nerves in their whole anatomical environment with or without tumor, which could be used in the clinical routine, notably for presurgical planning, aiming to improve the functional outcome of patients.

**Key words :** Tractography, cranial nerves, MRI, diffusion imaging, skull base, tumors



## ABBREVIATIONS

2D : bidimensional  
3D : tridimensional  
CN : cranial nerves  
CSF : cerebrospinal fluid  
FN : facial nerve  
HARDI : high angular resolution diffusion imaging  
HDFT : high definition fiber tracking  
IAM : internal acoustic meatus  
LN : Lower nerves  
mm : millimeters  
MRI : magnetic resonance imaging  
NR : not reported  
ODF : orientation density function  
ROI : region of interest  
T : tesla  
T1W : T1 post-contrast weighted MRI sequence  
T2 : T2 weighted sequence  
VIP : virtual imaging platform

A noter que les mots d'origine *latine* ou *anglaise* sont en *italique*, lorsqu'ils sont intégrés dans un texte en français.

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## INTRODUCTION

**L**e travail suivant retrace la progression logique de ma réflexion scientifique sur la question de la tractographie appliquée aux nerfs crâniens. Au préalable, il paraît important de décrire le contexte clinique et scientifique qui a motivé cette recherche. Ce premier chapitre introductif revient sur le défi des tumeurs de la base du crâne lié à leur rapport étroit avec les nerfs crâniens. Il retrace l'apport de l'anatomie puis de l'imagerie, avec le développement de la technique de tractographie porté par son potentiel d'application clinique.

## 1.1 Le défi des tumeurs de la base du crâne

Les tumeurs de la base du crâne constituent encore aujourd'hui un défi chirurgical. En effet, leur localisation intra crânienne profonde les rend difficile d'accès. De plus, l'environnement anatomique est complexe et dangereux avec la proximité de structures neurologiques vitales comme le tronc cérébral, la présence de nombreux vaisseaux - artères du cercle anastomotique de la base du cerveau et veines cérébrales profondes -, et le passage des nerfs crâniens qui traversent la base du crâne pour rejoindre leurs cibles et assurer les fonctions motrices, sensibles, et sensorielles de la tête.[1, 4, 84, 89] Si la vascularisation cérébrale est déjà explorée avec précision grâce à l'imagerie IRM ou l'artériographie cérébrale, il reste difficile de visualiser les nerfs crâniens au contact, déplacés ou englobés par ces tumeurs (**Figure 1.1 et 1.2**). Aussi, apprécier les rapports entre les tumeurs de la base du crâne et les nerfs crâniens nécessite d'abord de connaître l'anatomie en condition normale.

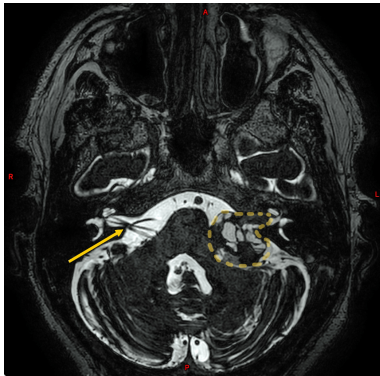


FIGURE 1.1 – **Volumineux schwannome vestibulaire G**, paquet acoustico-facial visible à Droite (flèche) mais pas à Gauche à cause de la tumeur (pointillés)  
-personal data-

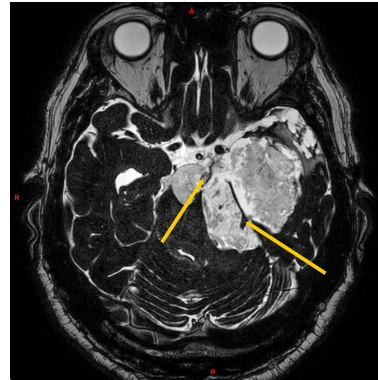


FIGURE 1.2 – **Kyste épidermoïde géant de la base du crâne à G**, la position du nerf oculomoteur ou du nerf trijumeau (flèches) est impossible à certifier à cause des modifications anatomiques liées à la tumeur -personal data-

## 1.2 Apport de l'anatomie

L'anatomie de l'encéphale qui inclut le cerveau, le tronc cérébral, le cervelet et les nerfs crâniens, a d'abord été décrite sur des dissections *post-mortem*. Il y a plus de 5 siècles, Léonard de Vinci (1452-1519) a posé les bases de l'organisation générale du cerveau en séparant substance blanche et substance grise, cortex et faisceaux. Puis, la surface du cortex a été cartographiée (Andreas Vesalius, 1514-1564) suivie de la description des premiers faisceaux, cortico-spinaux, de substance blanche (Thomas Willis 1621-1675 et Raymond Vieussens, 1641-1716). Au fil des siècles, l'anatomie des fibres blanches et la connectivité cérébrale ont été précisées (**Figure 1.3**), grâce à l'utilisation du microscope et aux corrélations anatomo-cliniques via les syndromes de dysconnexion (Carl Wernicke 1848-1904, Joseph Jules Dejerine 1849-1917, Paul Broca 1824-1880, Hugo Liepmann 1863-1925, Norman Geshwind 1926-1984). Enfin, au XX<sup>e</sup> siècle, de nouvelles techniques de préparation et de dissection ont établi l'organisation anatomique de la majorité des fibres blanches intra cérébrales dont les plus petites comme les nerfs crâniens (Josef Klingler 1934-2010, Albert Rhoton 1932-2016).[61, 77]

## 1.3 Apport de l'imagerie

Plus récemment, le développement de l'imagerie par résonance magnétique (IRM) a permis de visualiser, pour la première fois, l'anatomie humaine normale et pathologique *in vivo* (**Figure 1.4**). En effet, les séquences IRM pondérées en T2 avec une haute résolution (de type CISS, FIESTA ou THRIVE selon les constructeurs) ont été capables de montrer le trajet cisternal des nerfs crâniens mais principalement en condition saine. Les progrès de l'IRM ont ensuite apportés un nouvel outil

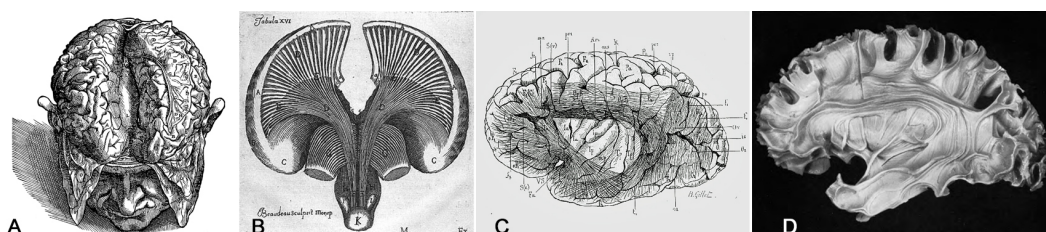


FIGURE 1.3 – **Premières descriptions anatomiques** de Vesalius (A), Vieussens (B), Dejerine (C) à Ludwig et Klingler (D)

- la tractographie - capable de reconstruire l'architecture des tissus biologiques en y détectant l'orientation dirigée des molécules d'eau, ceci à partir des images IRM de diffusion.[6] Cette technique a été naturellement utilisée pour décrire *in vivo* les fibres blanches du cerveau (**Figure 1.5**) avec les faisceaux associant les aires corticales, connectant les hémisphères et projetant les informations sensitivo-motrices.[14, 16] Les mondes de la physique, des mathématiques, de l'informatique, de l'imagerie et de l'anatomie se sont ainsi rencontrés pour permettre le *tracking* des fibres blanches du cerveau depuis le signal IRM. Toutefois, la tractographie reste encore difficile à appliquer aux fibres de petite calibre comme les nerfs crâniens.

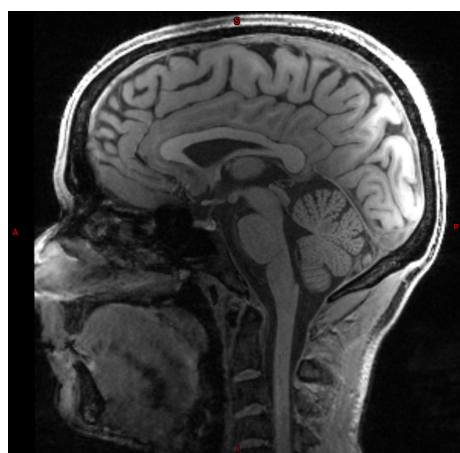


FIGURE 1.4 – **IRM T1** en coupe sagittale - *personal data* -

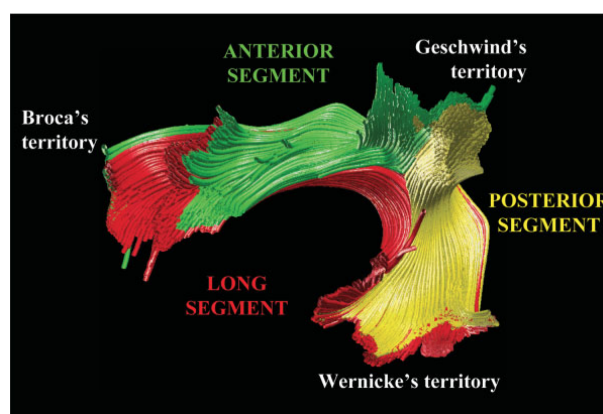


FIGURE 1.5 – **Tractographie** - *Superior Longitudinal Fasciculus*, d'après Catani et al.[15]

## 1.4 Limites de l'IRM

La trajectoire de l'ensemble des nerfs crâniens peut être difficile à « suivre » en IRM T2 classique pour plusieurs raisons (**Figure 1.6**). Leur **taille** est souvent inférieure à celle l'acquisition IRM. Par exemple, le nerf abducens mesure environ 1.3 mm de diamètre alors que la majorité des images de diffusion sont obtenues avec une résolution spatiale de de 2 à 3 mm. Aussi, il existe d'importants **artefacts et distorsions géométriques** au niveau de la base du crâne, notam-

ment du fait de l'interface rapprochée entre des tissus de susceptibilité magnétique différente (parenchyme-eau-os-air). Ceci explique également la perte du signal IRM au niveau de la base du crâne et de ses *foramen*. De plus, l'**anatomie des nerfs crâniens est modifiée** au contact des tumeurs de la base du crâne : déplacement/étirement/étalement/englobement. Enfin, le **tronc cérébral** se situe à proximité et présente de nombreux faisceaux de substance blanche ascendants/descendants/associatifs, avec des zones de **croisement de fibres** d'orientations multiples qui gênent la reconstruction de la trajectoire des nerfs crâniens.

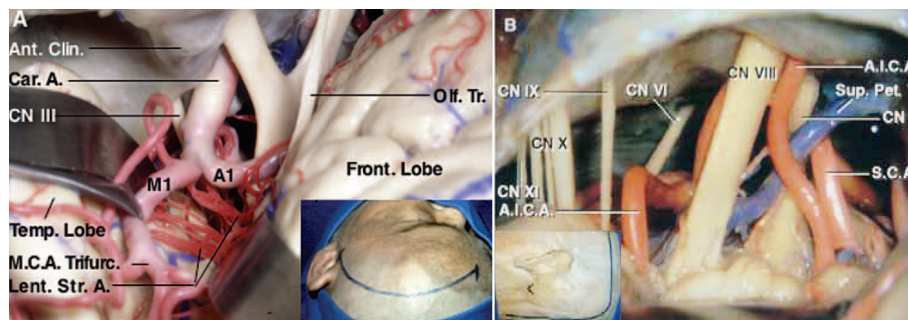


FIGURE 1.6 – **Nerfs crâniens dans leur environnement anatomique** (A : abord chirurgical ptérial, et B : abord rétro-sigmoïde) d'après Rhoton et al.[79]

## 1.5 Evolution de la tractographie

Après l'introduction de la tractographie, des études ont été menées pour optimiser la technique, décrire de nouveaux faisceaux de substance blanche du cerveau et les corrélés avec la pathologie clinique.[33] L'étude de l'architecture cérébrale s'est ensuite portée vers des structures anatomiques de plus en plus petites, et notamment vers les nerfs crâniens. Le trajet cisternal des nerfs crâniens les plus volumineux comme le nerf optique ou le nerf trijumeau a d'abord été reconstruit dans le contexte de compression vasculaire ou tumorale. [50, 52, 56, 66, 83] Plusieurs études ont alors cherché à déterminer la position du nerf facial dans le cas des schwannomes vestibulaires pour réduire le risque de paralysie séquellaire. [11, 19, 21, 36, 92, 102, 111] Puis, de nouveaux algorithmes ont ouvert la voie à une description plus précise des fibres de substance blanche en cas de croisement ou de petite taille.[94, 100, 111, 118] En 2016, seule l'étude de Yoshino de l'équipe du Dr Fernandez-Miranda de Pittsburgh, PA, USA, a réussi le *tracking* de l'ensemble des 12 nerfs crâniens en conditions saines et a illustré son application chirurgicale à partir de 3 patients présentant une tumeur de la base du crâne (**Figure 1.7**).[110]. Ainsi, l'application de la technique de tractographie à l'anatomie des nerfs crâniens a trouvé un intérêt pour détecter la position des nerfs crâniens déplacés au contact des tumeurs. Cependant, cette technique doit être développée pour permettre son application à tous les nerfs crâniens, pour tout type de tumeur, avec une validation sur un grand nombre de patients.



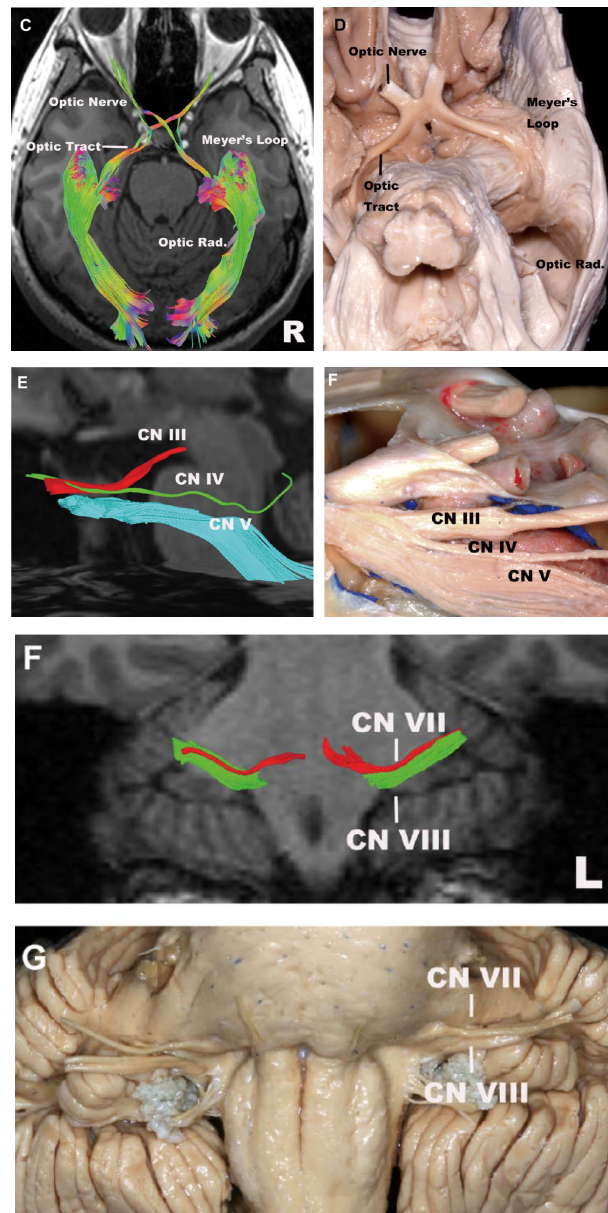


FIGURE 1.7 – Tractographie des nerfs crâniens II, III, IV, V et VII/VIII en condition normale, comparée aux dissections anatomiques, d'après Yoshino et al.[110]

## 1.6 Objectif et organisation du manuscrit

L'**objectif** de mon travail est de présenter la technique de tractographie appliquée aux nerfs crâniens, la développer et évaluer son intérêt en chirurgie des tumeurs de la base du crâne : la tractographie des nerfs crâniens est-elle capable de rendre la chirurgie plus sûre et plus efficace ?

Je présente un travail de **thèse par article** qui s'appuie sur : 1 article de revue publié, 1 série de cas publiée, 2 vignettes cliniques publiées, et 1 article de perspective technique en cours



de révision. Ce manuscrit<sup>1</sup> s'articule autour de 8 chapitres :

1. Le premier a introduit **le rationnel** de la tractographie appliquée aux nerfs crâniens dans le contexte des tumeurs de la base du crâne.
2. Le second rappelle les **notions fondamentales** nécessaires à la compréhension de la technique de tractographie appliquée aux nerfs crâniens et issues des mondes de la physique, des mathématiques, de l'imagerie et de l'anatomie. Il décrit la méthode d'acquisition IRM et le post-traitement, depuis l'extraction du signal de diffusion IRM jusqu'à la représentation des tractogrammes. Il redéfinit aussi l'anatomie normale de chaque nerf crânien.
3. Le troisième présente l'**état de l'art** en tractographie des nerfs crâniens. A partir de 21 études de la littérature scientifique, il produit une synthèse originale des paramètres d'acquisition et de post-traitement, du *design* des régions d'intérêt et des méthodes de filtrage. Il identifie les défis issus à la fois de la technique de tractographie et de l'anatomie des nerfs crâniens, ainsi que le potentiel d'application clinique.
4. Le quatrième rapporte l'expérience de notre équipe avec le développement d'un *pipeline* (= ensemble des étapes de l'acquisition IRM et du post-traitement des images) de tractographie des nerfs crâniens et son application clinique à travers une **série de 62 patients** présentant une tumeur complexe de la base du crâne. Chaque étape de la tractographie est détaillée et notre *design* original des régions d'intérêt (ROIs) est présenté. Les situations d'échec sont analysées de même que l'impact sur la stratégie thérapeutique : décision chirurgicale, choix de la voie d'abord ou amélioration de la résection tumorale.
5. Le cinquième complète l'illustration de l'application de notre *pipeline* de tractographie probabiliste grâce à **2 vignettes cliniques**.
6. Le sixième propose une nouvelle approche, la **full-tractography**, utilisant un algorithme déterministe (*generalized q-sampling imaging*) et supprimant les étapes opérateur-dépendantes comme le placement des ROIs ou l'élimination manuelle des fausses continuations. Cette approche permet une utilisation plus simple, plus rapide et plus accessible de la tractographie dans le but d'une implémentation en routine clinique, par exemple dans le planning pré-chirurgical.
7. Le septième **discute** de nos choix méthodologiques et des limitations liées à la technique de tractographie.
8. Le huitième établit les **conclusions** de notre travail et les **perspectives** qu'il apporte dans les différents domaines : radiologie, informatique, anatomie, chirurgie, économie de la santé.

---

1. Ce travail a été encodé en *Latex* puis édité dans un environnement *Overleaf* ([www.overleaf.com](http://www.overleaf.com))

## NOTIONS FONDAMENTALES

C omprendre la technique de tractographie requiert des notions fondamentales dans différents domaines : la physique classique et quantique, les mathématiques, les sciences informatiques et l'anatomie.

## 2.1 Bases physiques de l'IRM

### 2.1.1 Le spin et le proton

Le principe de l'imagerie par résonance magnétique (IRM) repose sur une propriété des particules qu'on appelle le **spin**. Il s'agit du *moment cinétique intrinsèque* lié au mouvement de rotation des particules sur elles-mêmes, comme celui d'une planète ou d'une toupie (**Figure 2.1 et 2.2**). En cas de particules avec une charge électrique, ce mouvement produit une force magnétique ou *moment magnétique* de *spin*. Le noyau de l'hydrogène est composé d'un seul proton  $^1\text{H}$  avec une charge électrique positive unique, et l'hydrogène compose les molécules d'eau ( $\text{H}_2\text{O}$ ) retrouvées en très grande majorité dans les tissus biologiques. C'est pourquoi on utilise les propriétés du proton pour induire et récupérer le signal IRM.

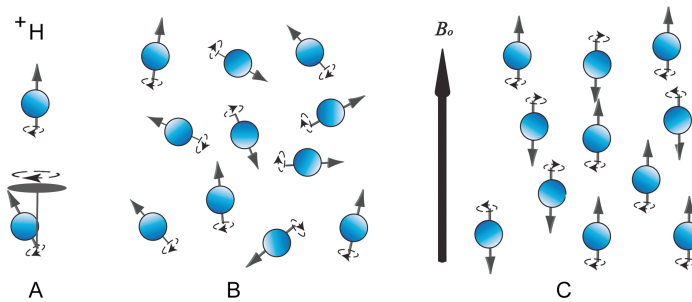


FIGURE 2.1 – **Le spin et le proton.** Les particules chargées en rotation autour du noyau d'un atome créent un *moment magnétique* ou *spin* (A). L'application d'un champ magnétique à une population de spin (B) entraîne un alignement des spin selon deux orientations opposées (C)(images adaptées de [www.voxelcube.com](http://www.voxelcube.com)).

### 2.1.2 L'imagerie par résonance magnétique

Pour obtenir un signal IRM, plusieurs étapes sont nécessaires :

1. Un champ magnétique  $B_0$  constant est appliqué pour aligner les spin des protons qui décrivent alors un mouvement de rotation autour de l'axe  $B_0$ , c'est la **précession** ;
2. Une onde de radiofréquence (RF)  $B_1$  oscillante, perpendiculaire à  $B_0$ , à la fréquence de Larmor  $\nu_0$ , entraîne un transfert d'énergie par phénomène de résonance. Il en résulte une bascule de l'aimantation dans un plan transverse à  $B_0$ , c'est l'**excitation**.
3. Après interruption de l'onde RF, le signal émis par les protons lors du retour à l'état initial est récupéré, c'est la **relaxation**.

La relaxation se déroule avec une **composante longitudinale** qui repousse et une **composante transversale** qui décroît. Ces deux phénomènes se déroulent de manière concomitante, pour une population de spins excités (on parle d'aimantation « tissulaire »), et sont caractérisés par un temps respectif  $T_1$  et  $T_2$  (**Figure 2.2**). Le signal de relaxation enregistré est défini par son intensité, sa fréquence, et sa phase qui correspond au décalage par rapport à l'origine. Il est stocké sous la forme d'une matrice bi-dimensionnelle appelée **espace  $k$**  qui représente les informations de phase et de fréquence du signal émis par les protons lors du retour à l'état initial. Une opération mathématique de type **transformée de Fourier inverse** permet la conversion de cette matrice en image (**Figure 2.3**). L'encodage spatial dans l'espace  $k$  est réalisé grâce à la modification temporaire du champ magnétique  $B_0$  : on parle de *gradients*. Ces *gradients* permettent de définir le volume anatomique exploré (gradient de sélection de coupe, GSC) et de positionner chaque point de l'image (gradient de codage par la phase, GCP, et gradient de codage par la fréquence, GCF). Le déroulé des ondes RF d'excitation, des gradients d'encodage spatial et de la mesure des signaux est résumé dans un chronogramme ou *séquence IRM*. Les caractéristiques techniques comme les délais entre chaque élément permettent de moduler l'intensité des signaux et l'on détermine ainsi une « pondération » des images en fonction des temps  $T_1$  ou  $T_2$ .

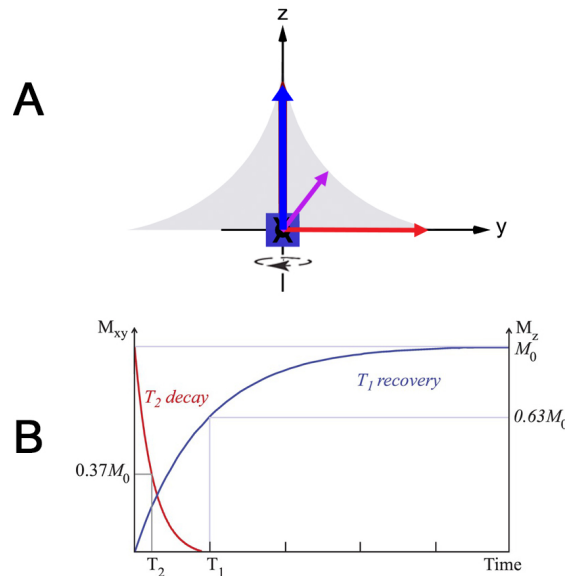
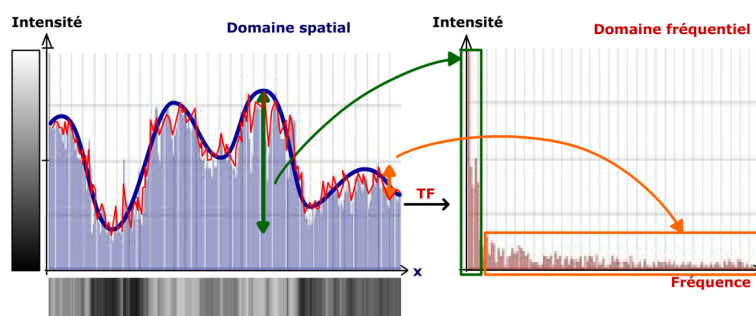


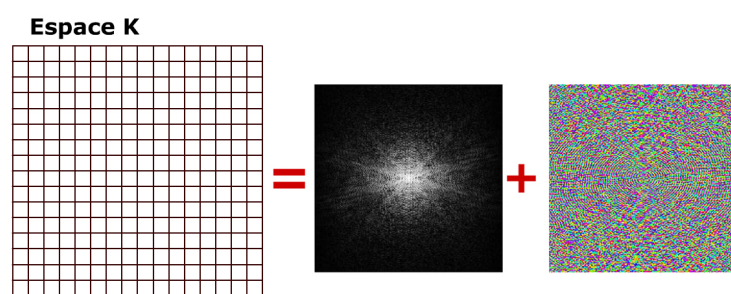
FIGURE 2.2 – **Les composantes T1 et T2.** Le retour à l'état initial du spin peut être décomposé par une composante de temps longitudinale T1 ou transversale T2, adapté d'après [www.imaios.com](http://www.imaios.com)

### 2.1.3 Du signal à l'image

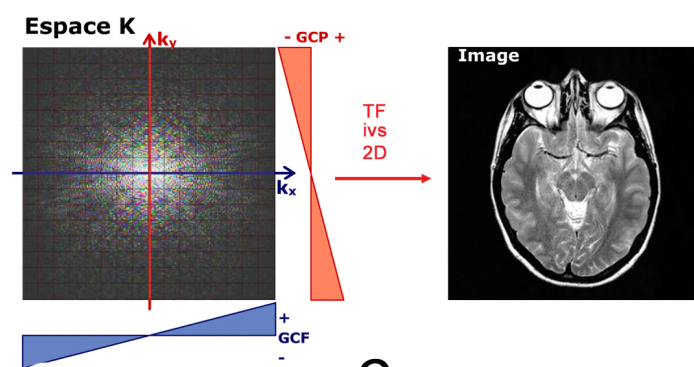
Chaque séquence d'IRM est donc une subtile combinaison d'onde RF et de *gradients* ayant pour but de : favoriser la vitesse d'acquisition, accentuer le contraste d'un tissu cible, limiter les artefacts, ne pas altérer le rapport signal sur bruit. Il s'agit donc de choisir les paramètres techniques de la séquence pour obtenir le meilleur compromis entre vitesse, contraste, qualité du signal et artefacts ([www.imaios.com](http://www.imaios.com)). Le temps entre la première impulsion RF et la récupération du signal est défini comme le temps d'écho (**TE**). Le temps entre 2 excitations des spins est défini comme le temps de répétition (**TR**). Il existe 2 grandes méthodes de récupération du signal : l'écho de spin et l'écho de gradient (**Figure 2.4**). La séquence écho de spin est caractérisée par un enchaînement impulsion RF 90°, impulsion RF 180° (dite de rephasage) à TE/2 puis lecture du signal. La séquence écho de gradient est caractérisée par une impulsion RF inférieure à 90° et l'absence de RF de rephasage. En pondération  $T_2$ , la séquence avec **état d'équilibre**, c'est-à-dire des gradients équilibrés et symétriques dans les 3 directions de l'espace, permet d'obtenir une image rapide avec un contraste tissu/liquide et un rapport signal sur bruit optimal. Il s'agit, par exemple, des séquences CISS, FIESTA ou THRIVE selon les constructeurs IRM Siemens, General Electric ou Philips.



A



B



C

FIGURE 2.3 – **Du signal IRM à l'image.** Le signal de relaxation est enregistré (A) et stocké sur une matrice bidimensionnelle (2D) représentant des informations de fréquence et de phase (B), convertie en image par opération de transformée de Fourier 2D inverse (C), adapté d'après [www.imaios.com](http://www.imaios.com).

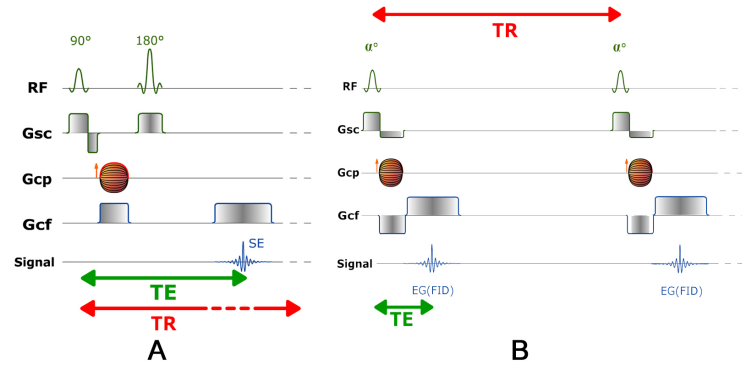


FIGURE 2.4 – **Echo de spin (A) ou écho de gradient (B)** sont les 2 méthodes de récupération du signal IRM, d'après [www.iamios.com](http://www.iamios.com)

## 2.2 La diffusion

### 2.2.1 Mouvement brownien

En fonction de la température, les molécules se déplacent dans l'espace de façon aléatoire et entrent en collision : ce sont les chocs thermiques (**Figure 2.5**). Dans les tissus biologiques, le déplacement des molécules d' $H_2O$  n'est pas libre mais dépend des obstacles rencontrés. Ces derniers peuvent être liés à l'architecture spécifique des tissus (fibres, paroi, etc.) ou à des modifications pathologiques (œdème, hyper prolifération cellulaire). A l'échelle microscopique, les molécules d' $H_2O$  se déplacent et s'entrechoquent plusieurs milliards de fois par seconde, ce qui entraîne une modification aléatoire de leur mouvement relatif. Ce mouvement décrit par Brown (Brown, 1828) peut être dirigé, soit pour rejoindre une zone moins contrainte, soit à l'intérieur d'une structure de type fibre. A l'échelle macroscopique, ce mouvement correspond au phénomène de **diffusion**. Il est décrit par la loi de Fick (Fick, 1855) et la relation d'Einstein (1905). Fick a montré que le flux  $J$  dépend de la différence de concentration  $\Delta C$  et du coefficient de diffusion  $D$  entre 2 milieux. Einstein a montré que le mouvement des particules est caractérisé par un coefficient de diffusion  $D$  qui est lié à son déplacement moyen après un temps  $t$ , avec un vecteur déplacement  $R$ .

$$\text{Loi de Fick } J = -D\Delta C$$

$$\text{Relation d'Einstein } D = \frac{1}{6\tau}(R^T R)$$

### 2.2.2 Diffusion libre ou dirigée

Dans un espace sans obstacle, les molécules d' $H_2O$  vont présenter un mouvement aléatoire libre identique dans les 3 dimensions de l'espace : on parle d'isotropie. En cas d'œdème extra

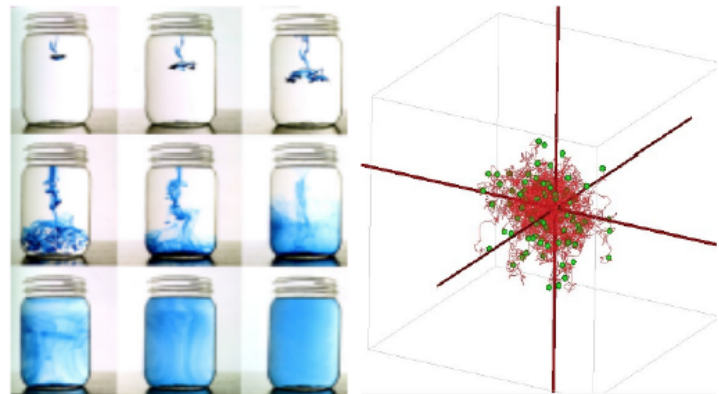


FIGURE 2.5 – **Mouvement brownien.** Dans un espace libre, les molécules d' $H_2O$  entrent en collision présentent un déplacement relatif aléatoire dans les 3 dimensions, d'après Descoteaux et Poupon, "Diffusion weighted MRI" [26]

cellulaire ou d'hyper cellularité tumorale, le mouvement sera isotrope mais restreint dans toutes les directions. Au sein d'un tissu biologique constitué de fibres, le mouvement de diffusion va préférentiellement adopter la direction des fibres, on parle d'**anisotropie** (**Figure 2.6**). Dans le cerveau humain, l'architecture est celle de faisceaux de substance blanche constitués d'axones et la mesure de l'anisotropie va révéler l'orientation de ces axones ou fibres blanches.[58]

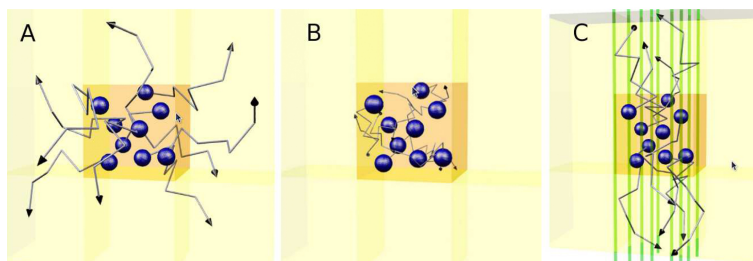


FIGURE 2.6 – **3 types de diffusion.** la diffusion des molécules d' $H_2O$  peut être soit libre, soit restreinte, soit dirigée par l'architecture des tissus biologiques, par exemple le long des fibres, adapté d'après [www.e-mri.org](http://www.e-mri.org)

### 2.2.3 Séquence IRM de diffusion

La séquence IRM de diffusion utilise les micro-mouvements browniens des molécules d' $H_2O$ . Elle produit des images dont le contraste dépend des différences de mobilité des molécules d' $H_2O$ . Cela est possible grâce à l'ajout de champs magnétiques ou *gradients* intenses et symétriques par rapport à une impulsion RF  $180^\circ$  de rephasage d'une séquence de type écho de spin pondérée en  $T_2$  appelée **séquence spin echo avec gradient de champ pulsé** ou *plused-gradient spin echo* (PGSE) (**Figure 2.7**). On décrit un degré de pondération en diffusion, exprimé en **facteur  $b$**

ou  $b$  – *value* ( $s.mm^2$ ) qui dépend des caractéristiques des gradients : amplitude, durée et délai entre les deux gradients. Le facteur  $b$  agit comme un « zoom inverse » ; plus  $b$  est grand, plus le déplacement observé des molécules d' $H_2O$  est petit. De plus, grâce à deux acquisitions de diffusion avec des facteurs  $b$  différents, on peut calculer un coefficient de diffusion apparent (apparent diffusion coefficient, ADC) dont la valeur est proportionnel à la diffusion : un hyposignal ADC correspond donc à une diffusion restreinte et inversement. Enfin, l'espace tridimensionnel où est représenté le signal de diffusion est appelé **espace  $Q$** , chaque point de cet espace correspond à une mesure de diffusion, avec une direction de *gradient* et une valeur de  $b$ .

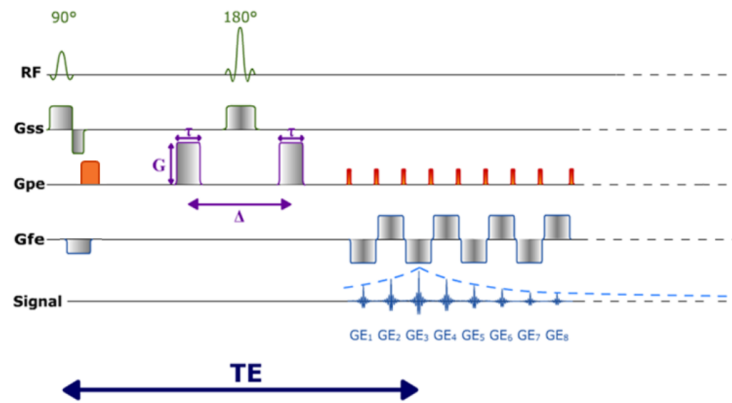


FIGURE 2.7 – Séquence de diffusion, d'après [www.imaios.com](http://www.imaios.com)

## 2.3 Les modèles de diffusion

### 2.3.1 Tenseur de diffusion

Le phénomène de diffusion des molécules d' $H_2O$  peut être modélisé sous la forme d'un tenseur défini-positif, symétrique, de second ordre ou **tenseur de diffusion** (Figure 2.8).[6, 28]

$$D = \begin{Bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{xy} & D_{yy} & D_{yz} \\ D_{xz} & D_{yz} & D_{zz} \end{Bmatrix}$$

La diffusion est isotrope si  $D_{xx} = D_{xy} = D_{xz} = D_{yy} = D_{yz} = D_{zz}$ . Le tenseur peut être décomposé en 3 vecteurs propres et 3 valeurs propres (*eigenvectors*  $e_x$  ou *eigenvalues*  $\lambda_x$ ) et la direction principale du mouvement de diffusion peut être ramenée à un vecteur et une valeur uniques propres. La construction de cette matrice 3x3 et la résolution de son système d'équation nécessite d'acquérir un signal de diffusion dans au moins 6 directions de l'espace. Toutefois, le nombre de directions peut être augmenté et les résultats seront alors moyennés sur la même matrice, ce qui améliorera la qualité de l'estimation et réduira la sensibilité au bruit.



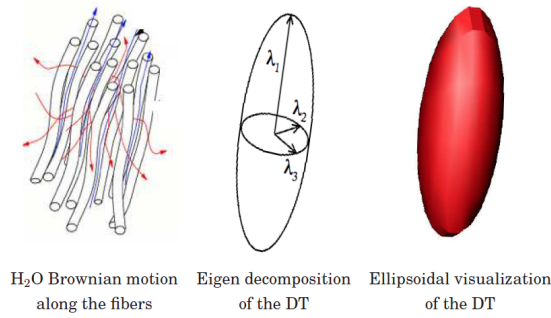


FIGURE 2.8 – **Tenseur de diffusion.** Le mouvement dirigé des molécules d' $H_2O$  le long des fibres peut être modélisé par un tenseur positif symétrique de second ordre, d'après Poupon et al.[26]

Certaines propriétés du tenseur de diffusion sont « invariantes par rotation », c'est-à-dire insensibles aux variations du champ magnétique. Ainsi, des informations quantitatives objectives peuvent être calculées pour n'importe quelle orientation du tenseur, ce sont : l'**anisotropie fractionnelle**, la **diffusivité moyenne**, et la **carte couleur d'orientation**.

### 2.3.2 Valeurs quantitatives de diffusion

#### 2.3.2.1 Anisotropie fractionnelle

Les valeurs propres du tenseur peuvent être utilisées pour décrire le degré d'anisotropie via l'indice d'anisotropie fractionnelle (*Fractional Anisotropy, FA*) qui correspond à l'écart-type des 3 valeurs propres du tenseur. Il varie entre 0 et 1, avec 0 pour une diffusion isotrope et 1 une diffusion anisotrope. Il estime la déviation de la directionnalité par rapport à une diffusion purement isotrope.

$$\mathbf{FA} = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - \hat{\lambda})^2 + (\lambda_2 - \hat{\lambda})^2 + (\lambda_3 - \hat{\lambda})^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

où  $\hat{\lambda} = (\lambda_1 + \lambda_2 + \lambda_3)/3$

#### 2.3.2.2 Diffusivité Moyenne

La diffusivité moyenne (*Mean Diffusivity, MD*) rapporte l'intensité locale de la diffusion des molécules d' $H_2O$

$$\mathbf{MD} = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} = \hat{\lambda}$$

### 2.3.2.3 Carte couleur

La carte couleur d'orientation est construite en associant une couleur à chacune des 3 directions de l'espace pour créer une carte (*color map*, *RGB map*) des fibres en indiquant leur position (coordonnées), leur direction (code couleur), et leur anisotropie (intensité). Le code couleur utilisé est le suivant : **vert** pour la direction antérieure-postérieure ou postérieure-antérieure, **rouge** pour la direction latérale-médiale ou médiale-latérale, et **bleu** pour la direction supérieure-inférieure ou inférieure-supérieure (**Figure 2.9**).

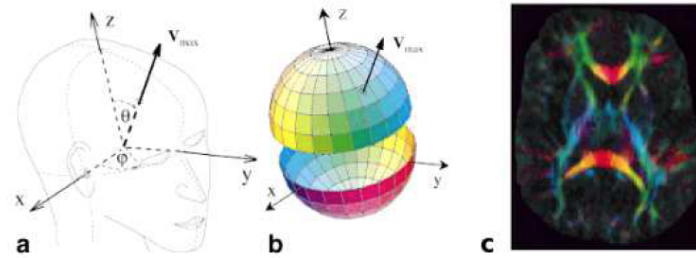


FIGURE 2.9 – **Carte couleur**. Le codage de l'orientation principale des tenseurs de diffusion permet de reconstruire une carte couleur de l'image initiale, d'après [www.e-mri.org](http://www.e-mri.org)

## 2.4 Algorithmes de reconstruction

### 2.4.1 Principe de reconstruction

Pour chaque unité volumique de l'image IRM ou **voxel**, la diffusion des molécules d' $H_2O$  peut donc être modélisée et sa direction principale estimée par algorithme mathématique, puis la trajectoire des fibres est reconstruite dans l'espace tridimensionnel (3D), voxel à voxel : c'est le principe de la tractographie. Il existe des algorithmes déterministes ou probabilistes, qui utilisent respectivement l'orientation principale ou une probabilité d'orientation de la diffusion.

### 2.4.2 Algorithmes déterministes

Les algorithmes déterministes utilisent un point de départ (*seed*) puis une propagation linéaire (*streamline*) le long de l'orientation principale de diffusion au voxel le plus proche avec un pas fixe (**Figure 2.10**). La reconstruction s'achève selon des **critères d'arrêt** préalablement définis : seuil d'anisotropie fractionnelle, angle maximal de courbure, etc. L'algorithme donne une "estimation de la vraisemblance maximale" du trajet d'une fibre en résolvant une équation différentielle ordinaire, c'est la méthode d'Euler :

$$r(s + \Delta s) \approx r(s) + \Delta s \hat{u}(r(s))$$

où  $s$  est la longueur de la trajectoire,  $r(s)$  la trajectoire,  $\Delta s$  le pas de propagation, et  $\hat{u}(r)$  la direction de la propagation estimée à la coordonnée  $r$ . [108]

Ce modèle de reconstruction déterministe, pas-à-pas, également nommée FACT (Fiber assignment continuous tracking [65]), reste simple, rapide, intuitif et applicable à tous les modèles de diffusion. Néanmoins, il est peu reproductible, sensible au bruit et pose les problèmes de « **fausses continuations** » par accumulation d’erreurs de tracking et de « **terminaisons précoces** » en cas de zone de croisement de fibres. Enfin, il dépend largement du placement des ROIs. D’autres modèles déterministes se sont développés sans parvenir à résoudre toutes ces difficultés : *tri-linear interpolation*, [24] *tensor-based interpolation*, [72] *fourth-order Runge-Kutta integration*, [6] *tensor deflection*, [57] *bi-tensor method*, [97] *high-order tensor method*. [5]

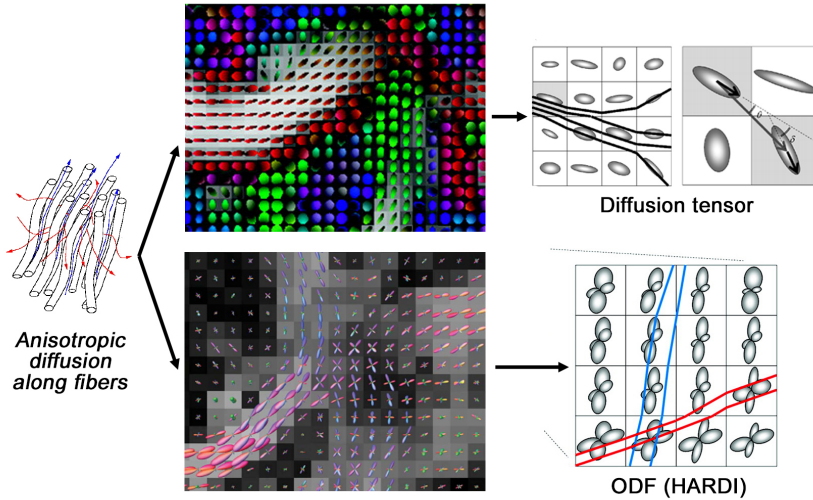


FIGURE 2.10 – **Reconstruction des fibres** à partir du tenseur de diffusion ou de la fonction de distribution d’orientation (*orientation distribution function, ODF*), modifié d’après Poupon et al., Chung et al. [23, 26]

### 2.4.3 Algorithmes probabilistes

Les algorithmes probabilistes génèrent un grand nombre de fibres probables à partir d’un point de départ (*seed*) et établissent une probabilité d’orientation vers une ou plusieurs directions. [94] Le même processus est répété à chaque voxel. Ce modèle est très reproductible et permet de réduire l’incertitude liée au bruit et à la présence de liquide cérébro-spinal ou de tumeur dans un même voxel. Il apparaît robuste au bruit et au volume partiel, et peut traverser les zones de croisement de fibres. Toutefois, il peut produire des « fausses continuations » et nécessite un temps de calcul important.

## 2.5 Nouveaux modèles de diffusion

Le modèle simple-tenseur suppose que la distribution du déplacement des molécules d' $H_2O$  soit gaussienne et ne permet de décrire qu'une seule orientation de fibre par voxel. Il est donc incapable de décrire la trajectoire de plusieurs populations de fibres dans les zones de croisement de fibres ou *fiber crossing areas*. D'autres modèles ont ainsi été proposés pour surpasser ce modèle, ce sont les modèles d'imagerie de diffusion à haute résolution angulaire (*High angular resolution diffusion imaging, HARDI*) avec, par exemple : diffusion spectrum imaging ,[101] Q-ball imaging,[96] (**Figure 2.11**). Par échantillonnage de l'espace  $q$  en autant de direction que possible, puis intégration sur une grille cartésienne 3D, ces modèles HARDI produisent une **fonction de densité d'orientation des fibres** (*orientation density function of fibers, fODF*). Celle ci est représentée par une image 3D qui montre la probabilité d'orientation d'une ou plusieurs populations de fibres dans un même voxel (**Figure 2.10 et 2.11**).

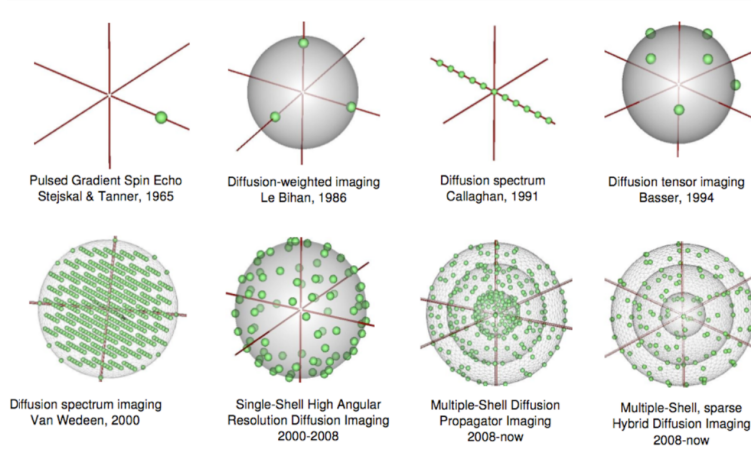


FIGURE 2.11 – **Nouveaux modèles de diffusion.** L'échantillonnage de l'espace  $q$  sur une grille ou une couche sphérique, en autant de directions que possible, permettent d'établir une probabilité ou fonction de densité d'orientation (*orientation distribution function of fibers, ODF*), d'après Descoteaux et Poupon, "Diffusion weighted MRI" [26]

## 2.6 Déconvolution sphérique contrainte

La **déconvolution sphérique contrainte** (*constrained spherical deconvolution, CSD*)[94] est également une méthode HARDI. Elle utilise une fonction réponse  $R(\theta)$  représentant l'atténuation du signal de diffusion pour une ou plusieurs population de fibres dans un même voxel. Le signal de diffusion  $S(\theta, \phi)$  peut être exprimé comme la convolution autour d'une sphère unitaire de la fonction réponse  $R(\theta)$  avec l'ODF  $F(\theta, \phi)$ .

$$S(\theta, \phi) = F(\theta, \phi) \otimes R(\theta)$$

L'opération de déconvolution permet d'extraire l'ODF dont les maxima sont alignés sur l'orientation des fibres, elle est contrainte positive (**Figure 2.12**). Les harmoniques sphériques sont les fonctions mathématiques qui permettent d'obtenir l'orientation des fibres à partir de l'ODF (**Figure 2.13**)

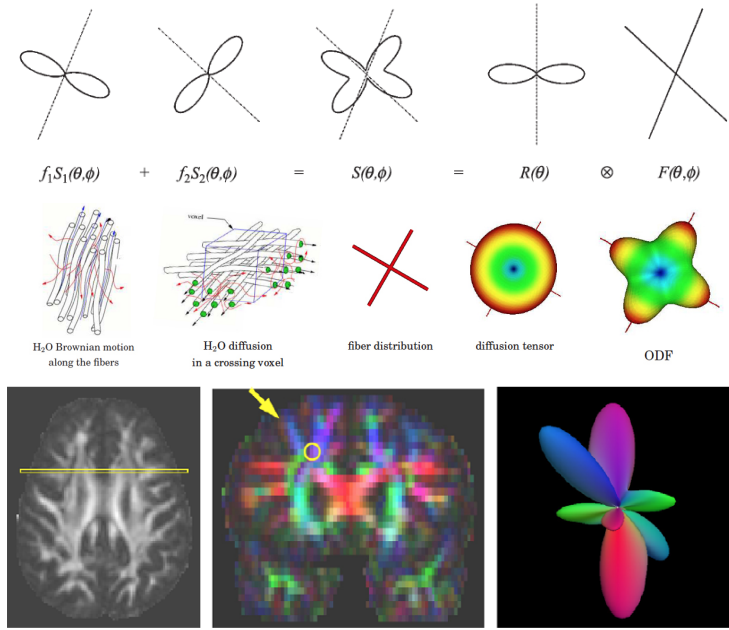


FIGURE 2.12 – **Principe de la déconvolution sphérique contrainte, CSD.** L'opération de déconvolution du signal de diffusion avec une fonction réponse, permet d'extraire l'ODF qui donne l'orientation d'une ou plusieurs populations de fibres, à chaque voxel (ce dessus, en haut et au milieu). Ici, l'ODF peut représenter 3 populations différentes de fibres : des fibres de projections cortico-spinales (bleu), des fibres commissurales du corps calleux (rouge), et des fibres d'association (vert) du faisceau longitudinal supérieur (ici en bas). Adaptation d'après Tourier et al., 2004, Descoteaux et Poupon, 2014 [26, 94].

## 2.7 Comprendre les artefacts

### 2.7.1 Différents types d'artefacts

L'acquisition de l'IRM et notamment la séquence de diffusion peut être perturbée par des artefacts : susceptibilité magnétique, courants de Foucault, non-linéarité ou instabilité des gradients, images fantômes, inhomogénéité de champ  $B_0$  ou mouvements du sujet. La susceptibilité magnétique est la capacité d'un tissu biologique à se « magnétiser », *i.e.* se modifier sous l'effet d'un champ d'excitation magnétique. Au niveau de la base du crâne, l'interface rapprochée de

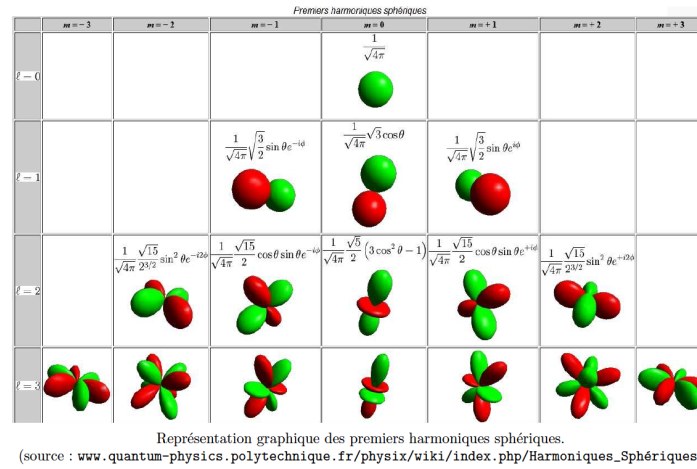


FIGURE 2.13 – **Fonctions harmoniques sphériques** d'ordre 0 à 3, permettent d'extraire une ou plusieurs orientations de fibres à partir de l'ODF, d'après [www.lptms.u-psud.fr](http://www.lptms.u-psud.fr)

plusieurs tissus biologiques avec des propriétés magnétiques différentes, comme l'air des sinus, l'eau des citernes de liquide cérébro-spinal, l'os ou le système nerveux central, perturbe le signal IRM et engendre une déformation non linéaire locale voire une perte du signal de diffusion (*induced off-resonance fields*, **Figure 2.14**). Les courants de Foucault (*eddy currents*) sont des courants électriques induits par les changements rapides des *gradients* de la séquence de diffusion, responsables d'une distorsion globale et rigide de l'image. Aussi, il existe des artefacts liés à la non-linéarité ou l'instabilité de ces *gradients*. Enfin, comme la séquence de diffusion peut durer quelques minutes, le sujet peut bouger et les minimes mouvements de la tête peuvent altérer la qualité de l'image.

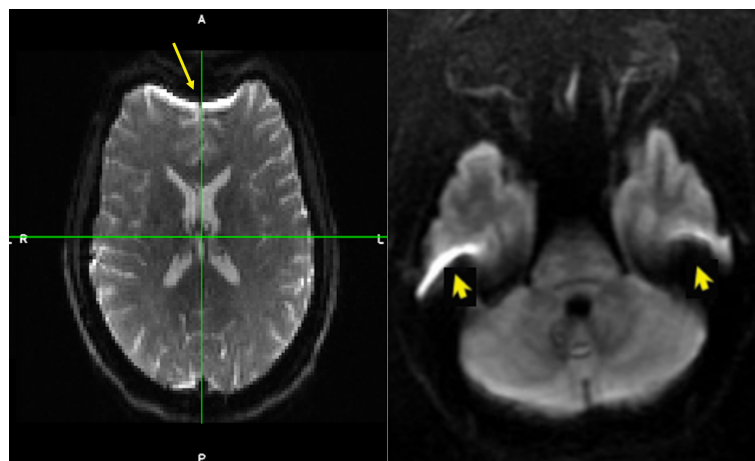


FIGURE 2.14 – **Artefacts de susceptibilité magnétique.** au cours de l'acquisition IRM, les variations rapides des gradients diffusion peuvent créer des distorsions (gauche). Au niveau de la base du crâne, l'interface entre des tissus différents favorisent l'apparition d'artefacts (droite), d'après *Oppenheim et al.*

### 2.7.2 Correction des distorsions et artefacts

Deux outils sont communément utilisés pour corriger ces artefacts et distorsions. Ils sont issus du logiciel libre FSL (*FMRIB's - Functional Magnetic Resonance Imaging of the Brain - Software Library*). Le premier - *eddy* - corrige les distorsions induites par les courants de Foucault et les mouvements du sujet. Il modélise les effets des courants de Foucault sur l'image pour les inverser, et supprime les images où le signal a été perdu du fait des mouvements du sujet. Le second - *topup* - corrige les artefacts de susceptibilité magnétique aux zones d'interface tissulaire à l'aide de deux acquisitions de sens opposé dans l'espace k. La différence de distorsions entre les images permet de récupérer le signal correct à l'aide de la méthode du calcul de la somme des carrés.[2]

## 2.8 Anatomie des nerfs crâniens

En plus des notions fondamentales de physique et de mathématique, appliquer la technique de tractographie aux nerfs crâniens requiert une connaissance précise de leur anatomie normale. Il existe douze paires de nerfs crâniens qui assurent les fonctions motrices, sensitives et sensoriels de la tête : la mimique, la motricité oculaire, la sensibilité du visage, les 5 sens, etc. Les deux premiers nerfs crâniens sont considérés comme des prolongements du télencéphale du fait d'un premier neurone périphérique court (rétine et muqueuse nasale), alors que les 10 suivants appartiennent au système nerveux périphérique. Certaines exercent une activité motrice ou sensitive exclusive, d'autres une fonction mixte. Les nerfs crâniens « moteurs » présentent 2 neurones, alors que les nerfs crâniens « sensitifs » s'organisent en 3 neurones dont le premier possède toujours un corps cellulaire dans un ganglion (trijumeau, géniculé, vestibulaire, glossopharyngiens, vague). Certains nerfs crâniens ont enfin une composante végétative toujours parasympathique. Classiquement, on décrit les nerfs crâniens avec la segmentation suivante, en adaptant l'ordre si le signal est sensitif ou moteur :

1. ORIGINE RÉELLE, correspondant à leur noyau dans le tronc cérébral (**Figure 2.15**);
2. TRAJET INTRA-ENCÉPHALIQUE, à travers le tronc cérébral;
3. ORIGINE APPARENTE, ou leur émergence visible depuis le tronc cérébral;
4. TRAJET CISTERNAL, dans les citernes de liquide cérébro-spinal de la base du crâne;
5. TRAJET FORAMINAL, en lien avec la traversée de la base du crâne à travers un *foramen*;
6. TRAJET EXTRA-CRÂNIEN, pour atteindre la cible ou leur récepteur périphérique : muscles, téguments, etc;

### 2.8.1 Nerf olfactif - I

Le nerf olfactif est sensoriel pour l'olfaction. Les cellules olfactives de la muqueuse nasale capturent les molécules odorantes et envoient des fibres à travers la lame criblée de l'éthmoïde



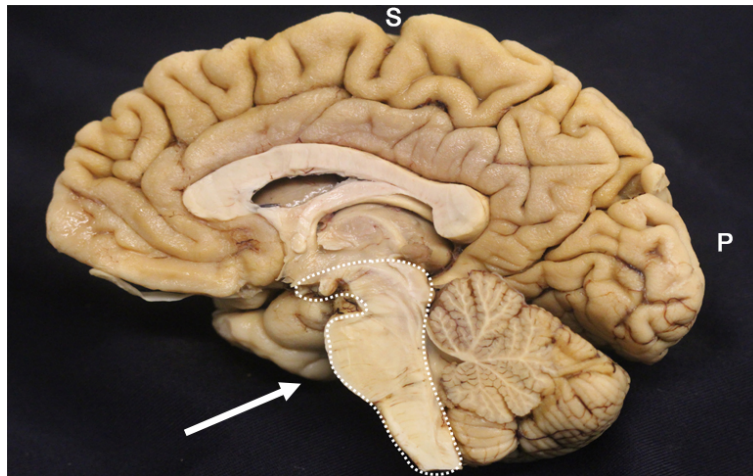


FIGURE 2.15 – **Tronc cérébral** Vue de profil des 3 étages du tronc cérébral, de haut en bas : le mésencéphale, le pont et la moelle allongée - *personal data* -

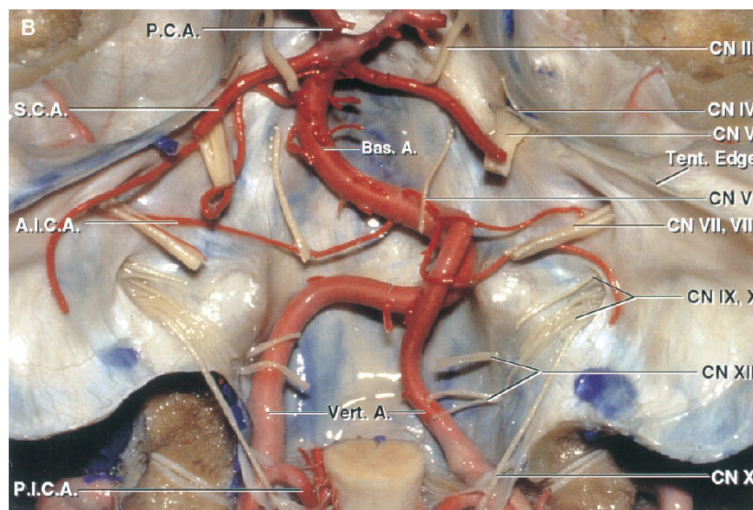


FIGURE 2.16 – **Foramen de la base du crâne**, d'après Rhoton et al. [78]

avec un premier relai dans le bulbe olfactif. Le nerf olfactif dans son segment cisternal chemine sur l'étage antérieur de la base du crâne, avec un trajet horizontal et droit, vers l'arrière, pour rejoindre l'espace perforé antérieur. Sa forme est plate et il mesure ~2 mm de plus grand diamètre pour ~30 mm de longueur. [13] Il se sépare en 3 stries olfactives qui se distribuent vers le cortex pré-frontal, l'aire septale et l'amygdale.[79]

## 2.8.2 Nerf optique - II

Le nerf optique est sensoriel pour la vision. Les cellules spécialisées de la rétine reçoivent le signal lumineux puis envoient des fibres qui se réunissent en regard de la papille pour se connecter au nerf optique. Celui-ci traverse l'orbite puis le canal optique et entre dans son segment



cisternal au dessus de la selle turcique. A ce niveau, le nerf optique mesure  $\sim 4.5$  mm de diamètre pour une longueur pré chiasmatique variable de  $\sim 20$  mm avec une section ovale.[71, 79] Les 2 nerfs optiques prennent une direction oblique vers l'arrière et l'intérieur puis fusionnent pour former le chiasma optique, suivi des *tractus* optiques qui contournent les pédoncules cérébraux pour rejoindre les corps géniculés latéraux au arrière des *thalamus*. De là, les radiations optiques enrobent les cornes temporales des ventricules latéraux puis atteignent le cortex "visuel" occipital.

### 2.8.3 Nerf oculomoteur - III

Le nerf oculomoteur est moteur pour le mouvement oculaire avec un contingent parasympathique. Son noyau se situe dans la partie haute du mésencéphale et en avant de l'aqueduc. Il existe un noyau accessoire parasympathique d'Edinger-Westphal. Les axones traversent vers l'avant pour émerger dans la fosse inter pédonculaire. Le segment cisternal est alors oblique en avant et en dehors, avec une longueur de environ  $\sim 14,6$  mm pour un diamètre de  $\sim 2.1$  mm et une forme tubulaire.[73] Ce segment passe d'abord entre la pince vasculaire formée par les artères cérébrale postérieure et cérébelleuse supérieure, puis se dirige vers le bas pour percer le toit du sinus caverneux au niveau du triangle oculomoteur (**Figure 2.16 et 2.17**).[81] Il traverse le sinus caverneux, puis la base du crâne via la fissure orbitaire supérieure, et l'orbite. Il se divise en rameau supérieur et inférieur, et se distribue aux muscles oculomoteurs.

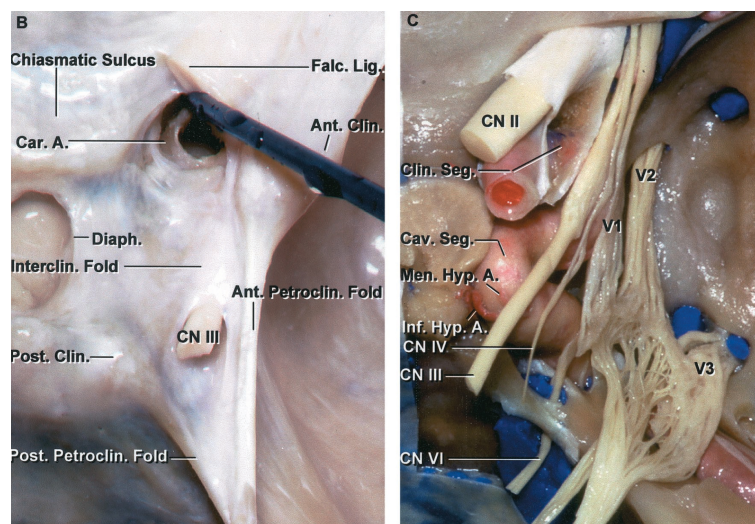


FIGURE 2.17 – **Sinus caverneux et triangle oculomoteur**, visualisation des nerfs II à VI, d'après Rhoton et al. [79]

### 2.8.4 Nerf trochléaire - IV

Le nerf trochléaire est moteur pour le mouvement oculaire vers le bas et le dehors. Son noyau est situé dans la partie basse du mésencéphale en avant de la substance grise périaqueducale. Ses fibres ont la particularité de croiser la ligne médiane pour émerger à la face postérieure du mésencéphale, juste au dessous des *colliculus* inférieurs. Son trajet cisternal est le plus long avec ~35.6 mm et son diamètre est le plus fin avec ~0.9 mm pour une forme aplatie.[47] Il contourne le mésencéphale à l'aplomb de l'incisure tentorielle puis pénètre dans le sinus caverneux et traverse la base du crâne via la fissure orbitaire supérieure. Il rejoint l'orbite et innerve le muscle oculomoteur oblique supérieur.

### 2.8.5 Nerf trijumeau - V

Le nerf trijumeau est mixte, en majorité sensitif pour la face avec une petite racine motrice pour les muscles masticateurs. Son noyau sensitif est étendu sur l'ensemble des 3 étages du tronc cérébral avec 4 noyaux principaux : spinal, bulbaire, pontique et mésencéphalique. Les axones convergent pour émerger ensemble à la face latérale du pont en un nerf trijumeau. Son segment cisternal est court, ~12 mm de long, et volumineux, ~5 mm de diamètre[48] avec une forme mutli-tubulaire. Il se dirige en haut et en avant vers l'apex pétreux où il pénètre dans le sinus caverneux et le cavum de Meckel. A ce niveau, il donne un ganglion trijeminal ou de Gasser et se divise en 3 branches : ophtalmique (V1), maxillaire (V2) et mandibulaire (V3) (**Figure 2.18**). Ces racines traversent alors la base du crâne par la fissure orbitaire supérieure, le foramen *rotundum* et le foramen *ovale*, respectivement. La branche V1 se divise dans l'orbite (rameaux frontal, lacrymal et nasociliaire) puis atteint la partie supérieure frontale de la face. La racine V2 se divise dans la fosse pterygopalatine (rameaux infra orbitaire et zygomatique) puis se distribue à la partie moyenne de la face (entre les commissures palpébrales et labiales). La branche V3 plonge dans la fosse infra temporale (rameaux lingual, buccal, alvéolaire, auriculo-temporal) puis se divise pour atteindre la partie inférieure de la face ; elle est accompagnée d'une petite racine motrice, supérieure et médiane (rameaux massétérique, temporal profond, ptérygoïdien, tenseur du tympan, tenseur du voile du palais) ([www.chups.jussieu.fr/ext/neuranat](http://www.chups.jussieu.fr/ext/neuranat)).

### 2.8.6 Nerf abducens - VI

Le nerf abducens est moteur pour les mouvements oculaires vers l'extérieur. Son noyau est situé au tiers moyen du 4<sup>e</sup> ventricule. Ses fibres émergent en avant, au niveau du sillon bulbo-pontique, de part et d'autre de la ligne médiane. Son segment cisternal est oblique vers le haut et l'extérieur, avec ~1.3 mm de diamètre pour ~15.8 mm de longueur et une forme légèrement aplatie. Il traverse le clivus moyen via le canal de Dorello, puis poursuit son trajet dans le sinus caverneux au contact de l'artère carotide interne. Il traverse la base du crâne au niveau de la fissure orbitaire supérieure pour rejoindre le muscle oculomoteur droit externe dans l'orbite.[49]

### 2.8.7 Paquet acoustico-facial - VII/VIII

Le nerf facial, son nerf intermédiaire de Wrisberg, le nerf cochléaire et les nerfs vestibulaires supérieur et inférieur sont regroupés dans leur trajet cisternal : on parle de paquet acoustico-facial.

#### 2.8.7.1 Nerf facial - VII

Le nerf facial est moteur pour la mimique du visage. Son noyau est situé au tiers moyen du plancher du 4<sup>e</sup> ventricule. Les axones émergent à la partie latérale du sillon bulbo-pontique dans l'angle ponto-cérébelleux (ou fossette latérale, **Figure 2.19**). Son segment cisternal présente une direction latérale, avec un diamètre de ~1 mm pour une longueur de ~16 mm et une forme

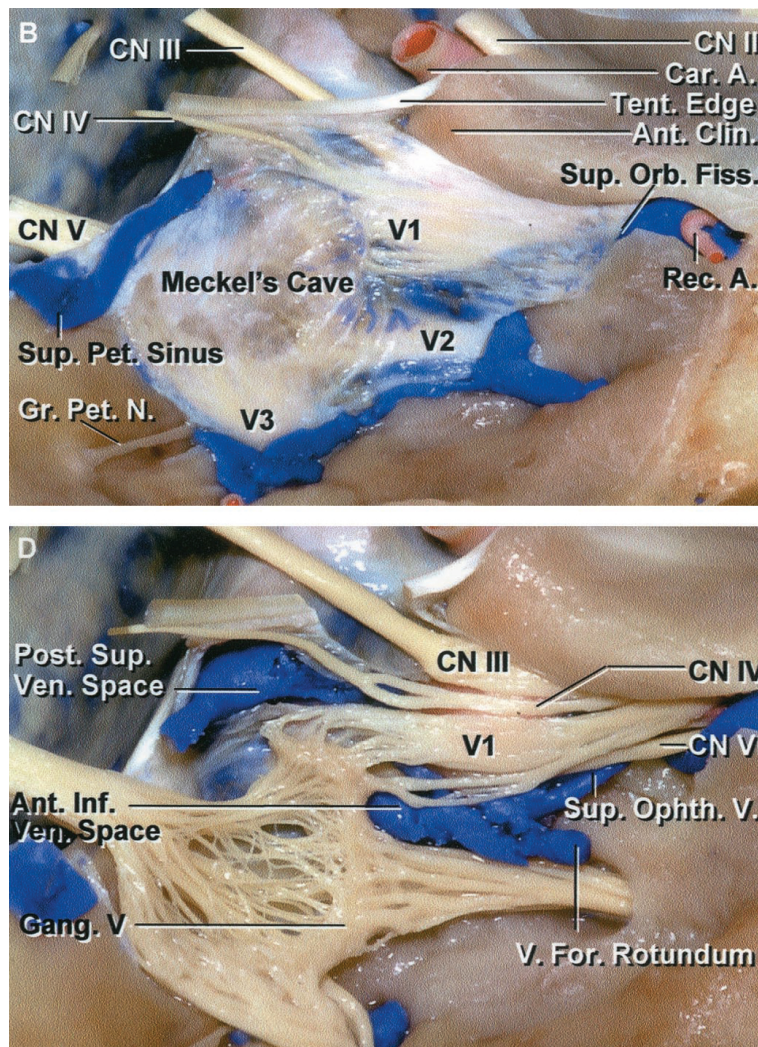


FIGURE 2.18 – Sinus caverneux et cavum de Meckel, visualisation du ganglion trijéminal et des branches du nerf V, d'après Rhoton et al. [80]



tubulaire.[38] Il rejoint le méat acoustique interne, puis traverse la base du crâne via un trajet complexe dans la mastoïde, pour sortir par le foramen stylo-mastoïdien, transpercer la glande parotide, se diviser en rameaux supérieur et inférieur, et enfin se distribuer aux muscles peauciers de la face.

Il existe un nerf intermédiaire de Wrisberg, sensitif, sensoriel et végétatif, qui accompagne le nerf facial. Il joue un rôle dans la sécrétion salivaire et la gustation pour les 2/3 antérieurs de la langue.[53]

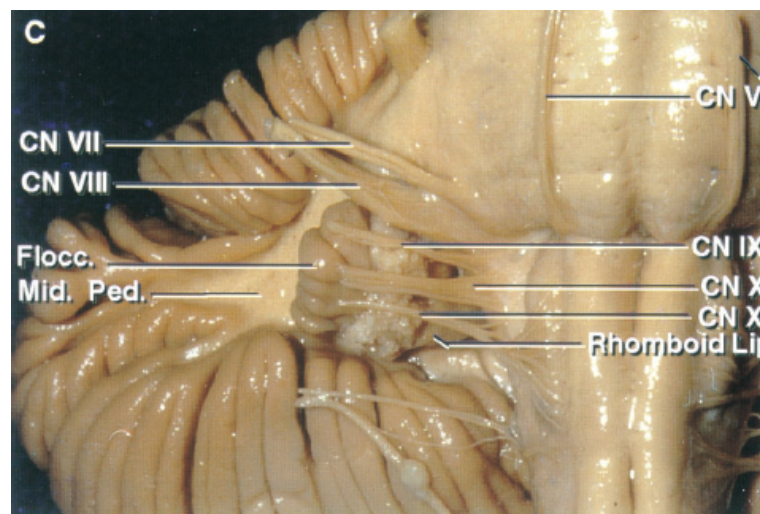


FIGURE 2.19 – **Angle ponto-cérébelleux**, où émergent les éléments du paquet acoustico-facial et des nerfs mixtes, d'après Rhoton et al. [78]

### 2.8.7.2 Nerf cochléo-vestibulaire - VIII

Le nerf cochléo-vestibulaire est sensoriel pour l'audition et l'équilibre. Il est constitué de 2 nerfs : le nerf cochléaire et le nerf vestibulaire. Le noyau cochléaire est situé dans la partie haute du pont ; le noyau vestibulaire est situé en regard, au niveau du plancher du 4<sup>e</sup> ventricule. Ces 2 noyaux envoient des axones qui se rejoignent pour former le nerf cochléo-vestibulaire. Celui-ci émerge à la partie latérale du sillon bulbo-pontique juste en arrière du nerf facial (**Figure 2.19**). Son segment cisternal a une direction similaire à celle du nerf facial, pour un diamètre de ~1.4-2.3 mm, une longueur de ~16.5 mm[38] et une forme tubulaire. Le nerf vestibulaire se divise dans sa partie cisternale en nerf vestibulaire supérieur et inférieur. Les nerfs cochléaire et vestibulaire se séparent dans le méat acoustique interne pour rejoindre respectivement la cochlée, responsable de l'audition, et le système vestibulaire, responsable de l'équilibre. Ce dernier regroupe l'utricule, le saccule, et les canaux semi circulaires.

### 2.8.8 Nerfs mixtes - IX/X/XI

Les nerfs mixtes regroupent le nerf glosso-pharyngien, vague et accessoire. Ils ont la particularité d'être dispersés en nombreuses radicelles à leur émergence au tronc puis de se regrouper à leur traversée de la base du crâne par le foramen jugulaire (**Figure 2.20**).

#### 2.8.8.1 Nerf glosso-pharyngien - IX

Le nerf glosso-pharyngien est mixte. Ses noyaux sont situés au tiers inférieur du plancher du 4<sup>e</sup> ventricule, avec un noyau moteur « ambigu », un noyau sensoriel « solitaire », un noyau végétatif « salivaire inférieur ». Ses fibres convergent, puis émergent à la face latérale de la moelle allongée, en arrière de l'olive. Le segment cisternal est dirigé en dehors et en bas, constitué de 10 à 20 radicelles qui se réunissent en un nerf de ~0.4-1.1 mm de diamètre et une longueur de ~15 mm.[60] Il traverse la base du crâne via le foramen jugulaire et rejoint le carrefour laryngo-pharyngé pour activer les muscles de la déglutition. Il transporte également les fibres de la sensibilité du 1/3 postérieur de la langue, de l'oro-pharynx, du naso-pharynx. Il permet la gustation pour le 1/3 postérieur de la langue. Son rôle parasympathique est de stimuler la sécrétion salivaire de la glande parotide.

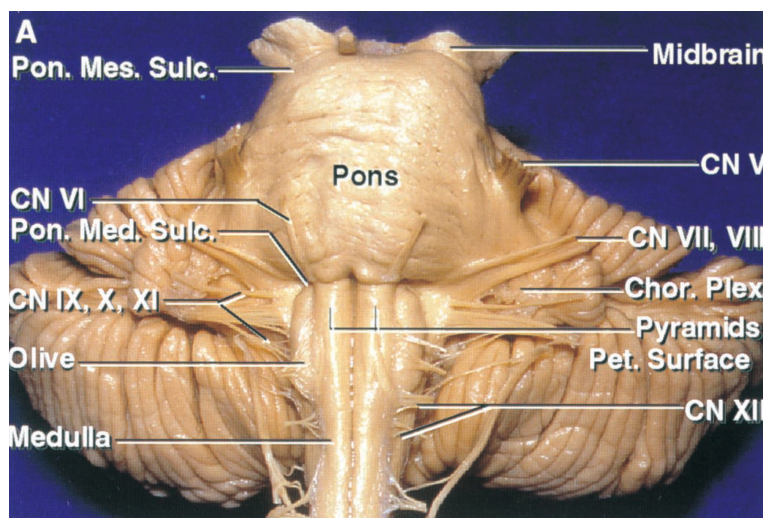


FIGURE 2.20 – **Tronc cérébral de face**, visualisation de nerfs crâniens V à XII, d'après Rhoton et al. [78]

#### 2.8.8.2 Nerf vague - X

Le nerf vague est mixte. Ses noyaux sont situés au niveau du plancher du 4<sup>e</sup> ventricule, avec un noyau moteur « ambigu », un noyau sensitif « spinal », un noyau viscéro-moteur « dorsal du vague » et un noyau viscéro-sensitif « solitaire ». Les fibres convergent puis émergent à la face latérale de la moelle allongée, en arrière de l'olive, sous le nerf IX. Le segment cisternal

accompagne le IX avec une direction similaire. Il est constitué de 4 à 10 radicelles qui se réunissent en 2 paquets supérieur et inférieur pour un diamètre de ~1-1.5 mm et une longueur également de ~15 mm.[60] Il traverse la base du crâne via le foramen jugulaire et rejoint le carrefour laryngo-pharyngé pour activer les muscles de la phonation. Il transporte les fibres de la sensibilité de la base de la langue. Son rôle parasympathique concerne, entre autres, les poumons (bronchoconstriction), les gros vaisseaux (vasodilatation), le cœur (bradycardie), l'estomac, l'œsophage, l'intestin grêle et le colon (accélération du péristaltisme).

### **2.8.8.3 Nerf accessoire - XI**

Le nerf accessoire est moteur pour les mouvements de la tête par rapport au cou. Il présente un rameau bulbaire et un rameau médullaire. Son noyau est situé au tiers inférieur du plancher du 4<sup>e</sup> ventricule. Les fibres émergent en arrière de l'olive, sous le nerf X, pour suivre le même trajet cisternal que le IX et le X jusqu'au foramen jugulaire : constitué de 6-16 radicelles regroupées en 4-5 paquets dont le diamètre global est ~1 mm pour une longueur également de ~15 mm.[60] Le rameau médullaire, issu des cornes ventrales des segments médullaires cervicaux C2 à C5, remonte en arrière du ligament dentelé pour rejoindre le rameau bulbaire au foramen jugulaire. L'ensemble se distribue aux muscles du cou : trapèze et sterno-cléido-mastoïdien.

### **2.8.9 Nerf hypoglosse - XII**

Le nerf hypoglosse est moteur pur la langue. Son noyau est à la partie la plus inférieure du plancher du 4<sup>e</sup> ventricule, dans une région appelée "trigone de l'hypoglosse". Les fibres émergent à la face latérale de la moelle allongée en avant de l'olive, dans le sillon pré-olivaire. Le segment cisternal se dirige de façon oblique en avant et en dehors, avec un diamètre de ~0.8-1.2 mm et une longueur de ~12.7 mm.[43] Il est constitué de 6-14 radicelles qui se réunissent en 2-4 troncs pour traverser la base du crâne via le canal de l'hypoglosse puis descendre dans le cou jusqu'à la langue.



## ETAT DE L'ART

**A**près avoir rappelé les principales notions qui permettent de comprendre la création du tractogramme, depuis la récupération du signal IRM, jusqu'aux algorithmes mathématiques de reconstruction pas-à-pas ou par probabilité d'orientation des fibres, j'établis l'état de l'art en tractographie des nerfs crâniens. Une revue ciblée de la littérature scientifique permet de sélectionner 21 études publiées et d'en extraire les données cliniques, les détails techniques d'acquisition et de post traitement, le placement, le nombre et la forme des ROIs, ainsi que les méthodes de filtration. L'ensemble des paramètres utilisés dans le pipeline de tractographie n'est pas rapporté dans chaque étude mais la combinaison de toutes les études permet de donner un aperçu étonnant de la variabilité de ces paramètres. De là, j'esquisse les défis de la tractographie des nerfs crâniens qui proviennent à la fois des caractéristiques anatomiques des nerfs crâniens et de la technique de tractographie elle-même. Tout ceci permet de mieux comprendre la tractographie des nerfs crâniens et d'envisager son application en pratique clinique.



# Overcoming Challenges of Cranial Nerve Tractography : A Targeted Review

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## 3.1 Abstract

**Background :** Diffusion imaging tractography caught the attention of the scientific community by describing the white matter architecture in vivo and non-invasively but its application to small structures such as cranial nerves remains difficult. The few attempts to track cranial nerves presented highly variable acquisition and tracking settings. **Objective :** We propose a targeted review collecting all technical details and pointing out challenges and solutions in cranial nerve tractography. **Methods :** A “targeted” review of the scientific literature was carried out using the MEDLINE database. We selected studies that reported how to perform the tractography of cranial nerves, and extracted the following : clinical context; imaging acquisition settings; tractography parameters; regions of interest (ROIs) design; and filtering methods. **Results :** Twenty-one published articles were included. These studied the optic nerves in supra-sellar tumors, the trigeminal nerve in neuro-vascular conflicts, the facial nerve position around vestibular schwannomas, or all cranial nerves. Over time, the number of MRI diffusion gradient directions increased from 6 to 101. Nine tracking software packages were used which offered various types of tridimensional display. Tracking parameters were disparately detailed except for fractional anisotropy, which ranged from 0.06 to 0.5, and curvature angle, which was set between 20 and 90°. ROI design has evolved towards a multi-ROI strategy. Furthermore, new algorithms are being developed to avoid spurious tracts and improve resolution. **Conclusion :** This review highlights the variability in the settings used for cranial nerve tractography. It points out challenges that originate both from cranial nerve anatomy and the tractography technology, and allows a better understanding of cranial nerve tractography.

## 3.2 Introduction

Cranial nerve anatomy has long been described from post mortem brain dissections by eminent anatomists.[98] Latter, white matter fibers were described with specific specimen

preparation and advancing anatomical knowledge.[61] In the 1980's, the development of magnetic resonance imaging (MRI) allowed the visualization of the central nervous system architecture in vivo, and more recently heavily-weighted T2 sequences have depicted small neurological structures, such as cranial nerves in their skull base cisterns segment.[86] However, the description of the trajectory of certain thin nerves is still difficult, particularly their course within the brainstem, through skull base foramina, or around tumors.[42, 50] Advances in diffusion imaging have led to the development of tractography which is capable of tracking brain white matter fibers.[7, 67, 68] This new imaging method uses the unequal diffusion of water molecules along white fibers to extract their principal direction and then reconstruct white matter tracts. Combining a dedicated diffusion acquisition and specific tracking parameters allows reconstruction of large white fiber groups [67, 68] such as cortico-spinal tracts,[20] optic radiations,[56] corpus callosum, and superior longitudinal fasciculus.[16] Nonetheless, tracking of small-scaled structures, such as cranial nerves, remains an ongoing challenge because of their small size, an intricate anatomical environment sensitive to susceptibility artifacts, and a limited MRI resolution.[17, 111] Recent studies have reported effective tracking of large cranial nerves such as the optic nerve, trigeminal nerve, or acoustic-facial bundle.[29, 41, 50, 51] Efforts to achieve tracking of the thinner cranial nerves are currently driven by skull base tumor studies since predicting the position of cranial nerves displaced around tumors could be a significant asset in neurosurgery.[19, 36, 39, 82, 88, 102, 111] Many different acquisition settings, tracking software and parameters, regions of interest (ROIs), and filtering methods have been used so far to address the entire "tractography" pipeline (**Figure 3.1**). Herein, we propose a targeted review of all technical aspects used in cranial nerve tractography. We compare these parameters and aim to provide a better understanding of this imaging tool for future routine clinical use.

### 3.3 Material and Methods

A "targeted" review of the scientific literature was carried out using the MEDLINE database with the following keywords : tractography, cranial nerves, diffusion imaging. Seventy-seven studies were identified. Original articles in English published in international peer-reviewed journals published up to October 1, 2017 were included. Case reports were excluded since they did not provide enough the tracking details. Because of a different anatomical environment and subsequently a variable tracking strategy, studies focused on brain white matter pathways or peripheral nerves or extra-cranial segments of cranial nerves were excluded. For all studies selected, we extracted all parameters

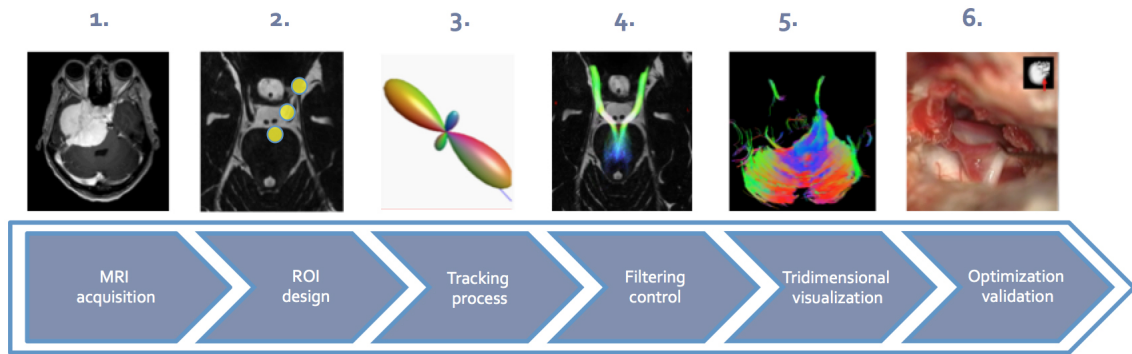


FIGURE 3.1 – **Visual summary of the tractography processing pipeline.** The tracts corresponding to the white fibers are reconstructed following seven steps : 1 – dedicated cerebral MRI acquisition with a diffusion sequence, 2 – geometric distortions correction, 3 – region of interest (ROI) design, 4 – tractography with specific parameters, 5 – anatomical control and filtering of spurious tracts, 6 – appropriate tridimensional visualization, 7 – surgical application and ground truth correlation.

used along the tractography processing pipeline (**Figure 3.1**), including clinical context (number of patients ; pathological condition or type of tumor ; cranial nerve studied ; visualization rate), MRI acquisition setup (magnetic field ; number of gradient directions ; slice thickness ; b-value ; voxel size ; sequence of reference), software and computational parameters (fractional anisotropy threshold ; maximal curvature angle ; minimal length), region of interest (ROI) design strategy, and filtering and validation methods.

### 3.4 Results

#### 3.4.1 Clinical context and visualization rate

Twenty-one studies, published between 2006 to 2017, were included ; among theses 2 included healthy subjects and 19 focused on various types of tumors and neurological diseases : vestibular schwannomas (n=9), cerebellopontine angle tumors (n=4),[39, 82] brain tumors or supra-sellar tumors (n=3),[83] trigeminal neuralgia (n=2),[35, 41] and deafness (n=1).[99] (**Table 3.1**) Ten studies focused on displacement of the acoustic facial bundle by vestibular schwannomas, which makes this condition the most frequently found in cranial nerve tractography. The studies included between 3 and 30 patients and obtained a visualization rate of cranial nerves that ranged from 62.5% to 100%. This visualization rate reflected the percentage of cranial nerves successfully tracked for each subject. Studies that focused on a single cranial nerve (13/21 studies targeted the acoustic facial bundle) reported a visualization rate greater or equal to 81.8%.[111] The lowest visualization rates – respectively 62.5% and 63.6% – were found for the

very early study published in 2006,[92] and for the first study that targeted all cranial nerves which was published in 2010.[42] Zolal et al. reported a tracking success rate of 30-70% considering the whole group of 10 cranial nerves tracked in 5 skull base tumor cases.[118] It is noteworthy that two research teams appeared as the most dynamic in cranial nerve tractography : the fiber tractography lab in Pittsburgh, USA[110, 111] and the Hodaie lab in Toronto, Canada.[41, 42]

| Date | Authors                | Patients  | Pathology                     | CN studied                  | Visualization rate |
|------|------------------------|-----------|-------------------------------|-----------------------------|--------------------|
| 2006 | <i>Taoka et al.</i>    | 8         | Vestibular schwannomas        | VII/VIII                    | 62.5%              |
| 2007 | <i>Kabasawa et al.</i> | 4         | Healthy subjects              | V, VIII                     | 100%               |
| 2009 | <i>Salmela et al.</i>  | 2 +10 HS  | Supra sellar tumor            | II                          | 100%               |
| 2010 | <i>Hodaie et al.</i>   | 4         | “Neurosurgical patients”      | II, III, V, VI, VII/VIII, X | 63.6%              |
| 2011 | <i>Chen et al.</i>     | 3         | Vestibular schwannomas        | VII/VIII                    | 100%               |
| 2011 | <i>Fujiwara et al.</i> | 13 + 14HS | Trigeminal neuralgia          | V                           | 100%               |
| 2011 | <i>Gerganov et al.</i> | 22        | Vestibular schwannomas        | VII/VIII                    | 90.9%              |
| 2012 | <i>Hodaie et al.</i>   | 5         | Trigeminal neuralgia          | V                           | 100%               |
| 2012 | <i>Roundy et al.</i>   | 5 +1HS    | Cerebellopontine angle tumors | VII/VIII                    | 100%               |
| 2013 | <i>Zhang et al.</i>    | 8         | Vestibular schwannomas        | VII/VIII                    | 87.5%              |
| 2014 | <i>Choi et al.</i>     | 11        | Vestibular schwannomas        | VII/VIII                    | 100%               |
| 2015 | <i>Vos et al.</i>      | 5 + 5HS   | Deafness                      | VIII                        | 100%               |
| 2015 | <i>Wei et al.</i>      | 23        | Vestibular schwannomas        | VII/VIII                    | 91.3%              |
| 2015 | <i>Yoshino et al.</i>  | 22        | Vestibular schwannomas        | VII/VIII                    | 81.8%              |
| 2016 | <i>Borkar et al.</i>   | 20        | Vestibular schwannomas        | VII/VIII                    | 95%                |
| 2016 | <i>Song et al.</i>     | 15        | Vestibular schwannomas        | VII/VIII                    | 100%               |
| 2016 | <i>Hilly et al.</i>    | 28 + 13HS | Cerebellopontine angle tumors | VII/VIII                    | 95,20%             |
| 2016 | <i>Zhang et al.</i>    | 30        | Vestibular schwannomas        | VII/VIII                    | 96.7%              |
| 2016 | <i>Yoshino et al.</i>  | 3 + 4HS   | « Brain tumors », HCP atlas   | All CNs I to XII            | 100%               |
| 2017 | <i>Zolal et al.</i>    | 5 + 30HS  | Skull base tumors             | II, III, V VII/VIII         | 30-70%             |
| 2017 | <i>Behan et al.</i>    | 10        | Cerebellopontine angle tumors | V, VII/VIII                 | 100%               |

*CN = cranial nerves, NR = not reported, HS = healthy subjects*

TABLE 3.1 – Clinical context : number of patients, pathology, studied cranial nerves and visualization rate.

### 3.4.2 Imaging settings

MRI machine constructors were General Electric (General Electric Healthcare, Milwaukee, WI, USA), Philips (Philips Medical System, Best, Netherland), and Siemens (Siemens Medical Solutions, Erlangen, Germany); machines had a permanent magnetic field of 3 Tesla (T) with the exception of two earlier studies that used a 1.5T magnetic field (**Table 3.2**). [21, 92] MRI diffusion parameters varied and the spatial resolution increased over time. The number of gradient directions ranged from 6 to 101, and most of the studies (n=11) reported between 20 to 32 gradient directions. The b-value was almost always 1000 s.mm-2 except for two studies for which the b-value was 800 s.mm-2. [11, 50] Slice thickness ranged from 3 to 1.2 mm and voxel size from 2.5 to 0.6 mm. Voxel was not systematically isometric and gap intersection rarely specified. Repetition and echo time were not collected since these were never the same as they depend on the MRI machine settings. Other parameters such as matrix size, field-of-view, and the number of slices would have been interesting to compare but they were poorly detailed. An anatomical sequence was always superimposed on the diffusion sequence to initiate the tracking process from ROI and verify the tract reconstructed on the basis of the known anatomy. This reference was preferentially a T2 sequence in constructive interference steady state such as CISS (Siemens), FIESTA (General Electric) and THRIVE/bFFE (Philips). Two authors chose T1 post-contrast weighted sequence (T1W) as a reference and two studies did not report any anatomical reference. [21, 116] Only five studies reported distortion correction before tracking, but provided little technical detail. [8, 19, 50, 99, 111]

### 3.4.3 Tractography software

Tractography can be performed with different algorithms divided into two different categories : deterministic and probabilistic. On the one hand, deterministic tractography relies on streamlined algorithms and reconstructs fibers step-by-step from a seed by using the local tract direction defined by the major eigenvector of the diffusion tensor. The earlier deterministic algorithm used non-constant integration steps, [65] but more recent deterministic algorithms were streamlined using different interpolation methods (tri-linear, second, or fourth order Runge-Kutta), tensor deflection, or tensor line. [6, 57, 103] On the other hand, probabilistic algorithms [9, 34, 74] consider the multiple fiber orientation at each voxel and uncertainties due to diffusion acquisition or diffusion model deficiencies. It results in a map of fiber orientation probability allowing the reconstruction of fibers regarding a specific seed.

| Year | Author                 | Machine          | Field (T) | Gradient Directions | Slice thickness (mm) | b-value (s/mm <sup>2</sup> ) | Anatomical Ref.  | Acquisition Voxel size |
|------|------------------------|------------------|-----------|---------------------|----------------------|------------------------------|------------------|------------------------|
| 2006 | <i>Taoka et al.</i>    | Siemens          | 1.5       | 6                   | NR                   | 1000                         | T2 CISS          | NR                     |
| 2007 | <i>Kabasawa et al.</i> | General Electric | 3         | 6                   | 3                    | 800                          | T2 FLAIR         | NR                     |
| 2009 | <i>Salmela et al.</i>  | Philips          | 3         | 6                   | 2                    | 1000                         | T2               | 1.9x2x2                |
| 2010 | <i>Hodaie et al.</i>   | General Electric | 3         | 25                  | 3                    | 1000                         | T1 and T2 Fiesta | NR                     |
| 2011 | <i>Chen et al.</i>     | General Electric | 3         | 25                  | 3                    | 1000                         | T1 and T2 Fiesta | NR                     |
| 2011 | <i>Fujiwara et al.</i> | General Electric | 3         | 6                   | 1.2                  | 1000                         | 3D-bSSFP         | 1,6x1,6x1,2            |
| 2011 | <i>Gerganov et al.</i> | Siemens          | 3         | 12                  | 1.6                  | 1000                         | T2 CISS          | NR                     |
| 2012 | <i>Hodaie et al.</i>   | General Electric | 3         | 25                  | 3                    | 1000                         | T2 and T1W       | NR                     |
| 2012 | <i>Roundy et al.</i>   | Philips          | 3         | 32                  | 1.2                  | 1000                         | T2 FIESTA        | 0.78x0.78x1.2          |
| 2013 | <i>Zhang et al.</i>    | Siemens          | 3         | NR                  | 3                    | 1000                         | NR               | NR                     |
| 2014 | <i>Choi et al.</i>     | Philips          | 1.5       | 32                  | 2.5                  | 1000                         | NR               | 2,5x2,5x2,5            |
| 2015 | <i>Vos et al.</i>      | Philips          | 3         | 22                  | 1.8                  | 1000                         | T2 DRIVE         | NR                     |
| 2015 | <i>Wei et al.</i>      | Siemens          | 3         | 30                  | 2                    | NR                           | T2 CISS          | 0.6x0.6x0.6            |
| 2015 | <i>Yoshino et al.</i>  | General Electric | 3         | 30                  | 2.5                  | 1000                         | T2 FIESTA        | NR                     |
| 2016 | <i>Borkar et al.</i>   | Philips          | 3         | 15                  | 1.5                  | 800                          | T1W              | 0.78x0.78x1,5          |
| 2016 | <i>Song et al.</i>     | General Electric | 3         | 30                  | 1.2                  | 1000                         | FIESTA           | NR                     |
| 2016 | <i>Hilly et al.</i>    | Philips          | 3         | 32                  | 2                    | NR                           | T2 CISS          | 2x2x2                  |
| 2016 | <i>Zhang et al.</i>    | General Electric | 3         | 64                  | 2                    | 1000                         | T2 FIESTA        | NR                     |
| 2016 | <i>Yoshino et al.</i>  | Siemens          | 3         | 101                 | 2.4                  | 12 B-values                  | T1W              | 2,4x2,4x2,4            |
| 2017 | <i>Zolal et al.</i>    | Siemens          | 3         | 20                  | 2                    | 800                          | 2x2x2            | T1 or T2 CISS          |
| 2017 | <i>Behan et al.</i>    | General Electric | 3         | 60                  | 3                    | 1000                         | 0.9375x0.9375x3  | T1                     |

TABLE 3.2 – **MRI Acquisition setups : MRI machine, permanent field strength, number of gradient directions, slice thickness, b-value, anatomical reference and acquisition voxel size.**

Nine different software packages were used (**Table 3.3**) ; most were based on a deterministic algorithm. Mrtrix3 was the only one that was based on a probabilistic algorithm. The more frequently used software was 3DSlicer (n=5) and dTV (n=4), followed by IPlan (n=3), Philips Extended Workspace (PEW, n=3), DSI studio (n=2), ExploreDTI (n=1), DynaSuite (n=1), XST[76](n=1), and Mrtrix3 (n=1). In more details, 3DSlicer implemented Runge-Kutta interpolation, dTV implemented tensor line, and iPlan implemented tensor deflection. Some studies used the MRI machine constructor software (PEW), which allowed tractography to be performed directly on the MRI console. In other studies, the tracking process required a series of remote computational tools – including format conversion, overlaying, distortion correction, etc. – before reconstruction of the final tracts. The tridimensional (3D) rendering of the software packages was variable in approach, displaying the tracts, the tumor, or the neurovascular environment (**Figure 3.2**). The most recent studies used “open source” software packages, such as DSI Studio,

FSL or Mrtrix3, which are constantly evolving and supported by computer scientist communities.

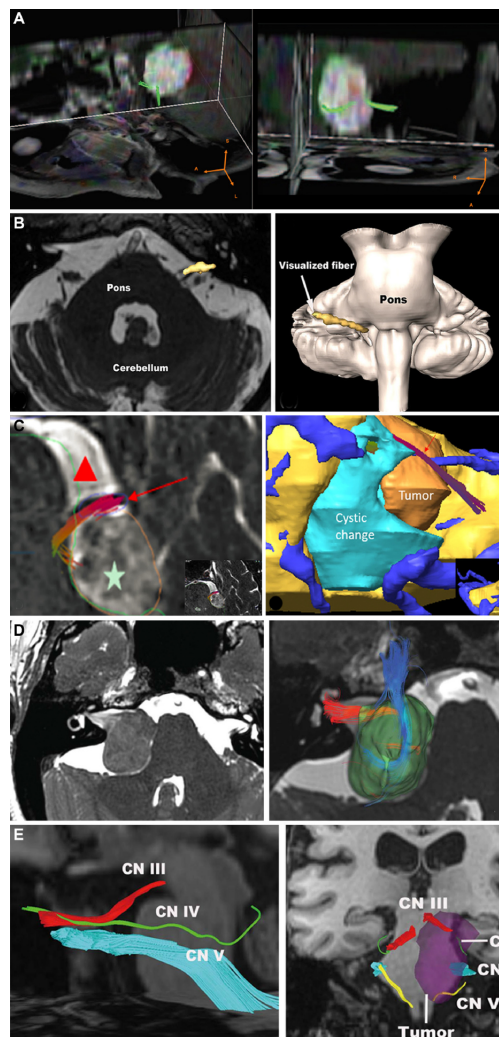
| Year | Author                 | Software                    | FA threshold | Curvature threshold | Min length (mm) |
|------|------------------------|-----------------------------|--------------|---------------------|-----------------|
| 2006 | <i>Taoka et al.</i>    | dTV + Volume One            | 0.1          | NR                  | NR              |
| 2007 | <i>Kabasawa et al.</i> | dTV + Volume One            | 0.1-0.18     | NR                  | NR              |
| 2009 | <i>Salmela et al.</i>  | Philips Extended Workspace  | 0.15         | 27                  | 10              |
| 2010 | <i>Hodaie et al.</i>   | 3DSlicer                    | 0.2          | 0.8 rad             | NR              |
| 2011 | <i>Chen et al.</i>     | 3DSlicer                    | 0.2          | 0.8 rad             | NR              |
| 2011 | <i>Fujiwara et al.</i> | dTV + Volume One            | 0.1          | NR                  | NR              |
| 2011 | <i>Gerganov et al.</i> | iPlan                       | 0.1          | NR                  | 5               |
| 2012 | <i>Hodaie et al.</i>   | 3DSlicer                    | 0.2          | 0.8 rad             | 2               |
| 2012 | <i>Roundy et al.</i>   | Philips Extended Workspace  | 0.15         | NR                  | NR              |
| 2013 | <i>Zhang et al.</i>    | NR                          | 0.1          | NR                  | NR              |
| 2014 | <i>Choi et al.</i>     | DSI studio                  | 0.15         | 70°                 | NR              |
| 2015 | <i>Vos et al.</i>      | ExploreDTI                  | 0.06-0.14    | 20°                 | 0.5             |
| 2015 | <i>Wei et al.</i>      | iPlan                       | 0.06-0.2     | NR                  | 5               |
| 2015 | <i>Yoshino et al.</i>  | dTV + Volume One            | Upper limit  | 30°                 | NR              |
| 2016 | <i>Borkar et al.</i>   | DynaSuite                   | 0.12         | 60 °                | NR              |
| 2016 | <i>Song et al.</i>     | 3DSlicer                    | 0.1          | 0.8 rad             | 5               |
| 2016 | <i>Hilly et al.</i>    | Philip's Extended workspace | 0.1          | 90°                 | 1               |
| 2016 | <i>Zhang et al.</i>    | iPlan                       | 0.06-0.2     | NR                  | 5               |
| 2016 | <i>Yoshino et al.</i>  | DSI Studio                  | 0.02-0.5     | 60° to 70°          | 2 to 20         |
| 2017 | <i>Zolal et al.</i>    | DSI studio                  | Upper limit  | 80°                 | 0               |
| 2017 | <i>Behan et al.</i>    | 3D slicer, XST, Mrtrix3     | 0.15         | 0.8 rad, 90°        | 5               |

TABLE 3.3 – **Fiber tracking context : software, fractional anisotropy threshold, curvature angle and minimal length.**

### 3.4.4 Tracking parameters

Although tracking parameters were numerous and critical to reproduce tractography results, they were not always detailed in the included studies. The minimum fiber length ranged between 1 to 20 mm but was often unspecified. This was also the case for the curvature angle, the threshold of which varied from 27 to 90°. It should be noted that the latter parameter can be specified in radians (3D slicer) or degrees (other software). The threshold on fractional anisotropy (FA) was highly variable between the studies, ranging from 0.05 to 0.5. Some studies used an FA threshold of 0.2, which is classical for the pyramidal tract,[55] with satisfactory results.[19, 42] Nonetheless, the most frequently used FA threshold was 0.1 and provided successful tracking in particular for the acoustic facial bundle even when displaced by tumors such as vestibular





**FIGURE 3.2 – Software rendering from selected studies : various insights of fiber tracking superimposed on anatomical reference, with tridimensional reconstruction of tumor or anatomical environment.** Tridimensional (3D) rendering is highly variable depending on software : Philips Extended Workspace (PEW) (A, reprinted from Roundy et al. 2012 : tracking of the facial nerve in a left vestibular schwannoma, no 3D reconstruction); Volume One/dTV (B, reprinted from Yoshino et al. 2015 : tracking of the right acoustic facial bundle in a healthy subject, good 3D insight of the anatomical environment but no tumor, unusual orientation); iPlan (C reprinted from Wei et al., 2015 : tracking of the facial nerve in a left vestibular schwannoma, low resolution of the 3D reconstruction); 3DSlicer (D, reprinted from Chen et al., 2010 :, tracking of the trigeminal nerve and the facial-vestibular complex in a right vestibular schwannoma, only 3D reconstruction of the tumor); and DSI Studio (E, reprinted from Yoshino et al., 2016 :, tracking of the cranial nerves III to VI in a left petroclival meningioma, no accurate 3D reconstruction of the environment). Some offer poor visualization of the anatomical environment (iPlan), the tumor (Volume One/dTV) or the tracts (PEW Portal). An optimal rendering should superimpose in 3D the entire neurovascular environment, the tumor shape and the cranial nerves reconstructed.



schwannomas.[36, 50, 82, 88, 92] One study assessed the FA threshold value adaptively, gradually increasing it to an upper limit before fibers disappeared ; the FA “upper limit” was tailored to each patient and reported to be  $0.10 \pm 0.04$ .[111] Another study stated an adjustment to individual variation by using variable values of FA from 0.06 to 0.20 ; this strategy improved both the visualization rate of cranial nerve trajectories and decreased spurious tracts.[115]

### 3.4.5 Region of interest design

The placement of ROI and the associated working view were detailed in various contexts, particularly for the acoustic facial bundle in vestibular schwannomas. The earliest studies placed ROI at the fundus of the internal acoustic meatus (IAM) on a sagittal cross section [92] or at the IAM on an axial cross section.[50] Subsequent studies placed their ROI in the “intra-canalicular compartment”[8, 19] while others chose the IAM “on the best aspect on 2 dimensional cross section”[42]. Other authors preferred to hand-draw a ROI on the nerve passing through the middle of the cistern on a sagittal cross section or through the tumor.[82] More recently, effective placement of ROI for the VII-VIII nerves was at the porus of the IAM on a plane perpendicular to its trajectory. (**Table 3.4**) [111] Over time, the use of two ROIs has been related to a greater tracking accuracy : one ROI was placed in the IAM and a second ROI at the brainstem root-entry-zone of the facial nerve.[88, 118] Similarly, a ROI within a track line that passed through the anterior-superior part of the IAM was used to specifically detect the facial nerve.[102] For the other cranial nerves, ROIs were often placed “where the cranial nerve can be best visualized on anatomic images”. [8, 42] A second or third ROI was then added along the intra-cerebral pathways if possible : [110, 111] the occipital lobe for the optic nerve, the posterior wall of the brainstem for the oculomotor nerve, the facial colliculus in the brainstem for the facial nerve,[105] and the anterior wall of the medulla for lower nerves.[42] The working view to place ROIs was rarely reported, although a common strategy was to draw the ROI in a plane perpendicular to the anatomical cisternal trajectory of the targeted nerve : the sagittal cross section for the facial nerve,[82, 92, 111] and the coronal cross section for the trigeminal nerve.[50] Furthermore, ROI size was never detailed with the exception of one study which reported ROI that should not exceed a size of 20 voxels.[8] In order to increase the success rate of the tracking, some authors reported adding “4 pixels of shell to the hand-painted area”[88] while others used a single voxel seed with subsequent expanded tracking along the course of the nerve.[39] Only one study pointed out the feasibility of tracking all cranial nerves and thoroughly reported the ROI placement strategy using multiple ROIs

for each nerve.[110]

| Year | Author                 | ROI placement                                                                                                                                                      | ROI number | Point of view                                   |
|------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------|-------------------------------------------------|
| 2006 | <i>Taoka et al.</i>    | Anterior superior part of the IAM                                                                                                                                  | 1          | sagittal cross section.                         |
| 2007 | <i>Kabasawa et al.</i> | Around the trigeminal nerve in the pre-pontine cistern                                                                                                             | 1          | on coronal section                              |
| 2009 | <i>Salmela et al.</i>  | Chiasma and occipital lobe                                                                                                                                         | 2          | on coronal section                              |
| 2010 | <i>Hodaie et al.</i>   | IAM on the best aspect                                                                                                                                             | 1          | on 2 dimensional cross sections                 |
| 2011 | <i>Chen et al.</i>     | Intra-canalicular compartment of VII/VIII complex                                                                                                                  | 1          | NR                                              |
| 2011 | <i>Fujiwara et al.</i> | Midpoint of the cisternal segment of V                                                                                                                             | 1          | NR                                              |
| 2011 | <i>Gerganov et al.</i> | IAM and facial nerve entry area at the brainstem                                                                                                                   | 2          | NR                                              |
| 2012 | <i>Hodaie et al.</i>   | Radio surgical target and trigeminal root entry zone                                                                                                               | 2          | NR                                              |
| 2012 | <i>Roundy et al.</i>   | Hand-drawn through the tumor in a mid-cisternal plane                                                                                                              | 1          | in a sagittal cut                               |
| 2013 | <i>Zhang et al.</i>    | IAM and FN entry at the brainstem                                                                                                                                  | 2          | NR                                              |
| 2014 | <i>Choi et al.</i>     | IAM and facial nerve entry area at the brainstem                                                                                                                   | 2          | NR                                              |
| 2015 | <i>Vos et al.</i>      | Cochlea                                                                                                                                                            | 1          | NR                                              |
| 2015 | <i>Wei et al.</i>      | IAM                                                                                                                                                                | 1          | NR                                              |
| 2015 | <i>Yoshino et al.</i>  | Porus of the IAM                                                                                                                                                   | 1          | in a plane perpendicular to VII VIII trajectory |
| 2016 | <i>Borkar et al.</i>   | Around the IAM and around the facial nerve entry at the brainstem                                                                                                  | 2          | NR                                              |
| 2016 | <i>Song et al.</i>     | IAM and the FN root entry zone at the Ponto medullary sulcus                                                                                                       | 2          | NR                                              |
| 2016 | <i>Hilly et al.</i>    | Single voxel seed with subsequent expanded tracking along the course of the nerve                                                                                  | 1          | NR                                              |
| 2016 | <i>Zhang et al.</i>    | Small ROIs [...] from the brainstem to the internal auditory canal                                                                                                 | Multiple   | NR                                              |
| 2016 | <i>Yoshino et al.</i>  | ROIs were placed on the generalized fractional anisotropy map at the area of the CN that could best be identified or the area that the CN was found to run through | Multiple   | NR                                              |
| 2017 | <i>Zolal et al.</i>    | CN cisternal segment and brainstem                                                                                                                                 | 2          | NR                                              |
| 2017 | <i>Behan et al.</i>    | Where CN is most identifiable                                                                                                                                      | 1          | NR                                              |

TABLE 3.4 – ROI design : placement, number and point of view.

### 3.4.6 Filtering strategy

Since tractography remains difficult to apply to cranial nerves, downstream improvements are required both for greater accuracy and better selectivity in the reconstructed tracts. A common strategy was to eliminate spurious tracts that did not match with current anatomical knowledge :[36, 116] crossing the midline such as ponto-cerebellar tracts, descending in to the brainstem such as sensory-motor tracts, or circling into the tumor. This filtering strategy was achieved by deleting each fiber that showed aberrant trajectory,[9, 118] or using “regions of exclusion” to avoid tracts coursing in the cerebellum or the temporal lobe. Some studies reported a “super selective” method which used primary tracts to place small ROIs and then initiate a second more accurate fiber tracking.[102, 111, 115, 116] To overcome the limitations of the diffusion imaging based

on a single tensor model, new acquisition or reconstruction methods, such as diffusion spectral imaging,[101] q-ball imaging,[107] q-sampling imaging,[109] and constrained spherical deconvolution[94, 95] have been proposed. They use an orientation distribution function (ODF) that could detect several fiber directions within the same voxel to provide a high angular resolution diffusion imaging (HARDI). Another study proposed a multiple-step pipeline called “high definition fiber tracking” (HDFT) reporting the first efficient fiber tracking of each cranial nerve.[110] Last but not least, probabilistic algorithms could yield more accurate results in the depiction of cranial nerve tracts than standard deterministic tractography,[118] as it has also been demonstrated for cortico-spinal pathways.[30]

| Parameters                      | Value/Comment                                                                                                                                       |
|---------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------|
| <b><i>MRI acquisition</i></b>   |                                                                                                                                                     |
| Magnetic field (T)              | 3                                                                                                                                                   |
| Diffusion gradient directions   | 32 or higher                                                                                                                                        |
| Diffusion slice thickness (mm)  | 2 or lower                                                                                                                                          |
| Diffusion slice gap             | 0                                                                                                                                                   |
| Diffusion voxel reconstruction  | Isotropic                                                                                                                                           |
| Anatomical reference(s)         | High resolution T1 <u>AND</u> T2                                                                                                                    |
| Additional sequences            | Sequences AP-PA                                                                                                                                     |
| Box size                        | Optic chiasma to <i>foramen magnum</i>                                                                                                              |
| <b><i>Tracking</i></b>          |                                                                                                                                                     |
| Geometric distortion correction | Eddy & topup FSL® tools                                                                                                                             |
| Software                        | Easy-to-use, “the one you better know”                                                                                                              |
| 3D rendering                    | CNs <u>AND</u> tumor <u>AND</u> environment                                                                                                         |
| Fractional anisotropy threshold | 0.1 or “upper limit”                                                                                                                                |
| Curvature threshold             | 70° or 0.8 rad                                                                                                                                      |
| Minimal length                  | 5-10 mm                                                                                                                                             |
| ROI placement                   | Best point of view onto anatomical images,<br>one, two or more ROIs:<br>mid-cisternal point, skull base foramen,<br>brainstem entry zone or nucleus |

*AP-PA: anterior-to-posterior – posterior-to-anterior, CN: cranial nerve, FSL: FMRIB (Functional Magnetic Resonance Imaging of the Brain) Software library, ROI: region of interest, T: Tesla,*

TABLE 3.5 – **Best set of acquisition and tracking parameters for routine practice.**

| Nerve                         | ROI placement                              |
|-------------------------------|--------------------------------------------|
| Olfactory nerve I             | Olfactory groove                           |
| Optic nerve II                | Intra-orbital optic nerve, chiasma +/- LGB |
| Oculomotor nerve III          | Mid-cisternal point                        |
| Trochlear nerve IV            | Inferior colliculus, cavernous sinus       |
| Trigeminal nerve V            | Mid-cisternal point                        |
| Abducens nerve VI             | Dorello canal entrance                     |
| Facial nerve VII              | IAC, facial brainstem nucleus              |
| Vestibulo-cochlear nerve VIII | IAC +/- cochlea                            |
| Lower nerves IX, X, XI        | Jugular foramen, post-olivary sulcus       |
| Hypoglossal nerve XII         | Hypoglossal canal +/- olive                |

*IAC: internal auditory canal, LGB: lateral geniculate body, ROI: region of interest.*

TABLE 3.6 – **Practical guide of ROI placement for each cranial nerve.**

## 3.5 Discussion

The main finding of this targeted review is that the result of tracking depends strongly on the anatomy of the cranial nerve tracked, its environment, and the post-processing steps. From this we identified two challenges, one related to the anatomy of cranial nerves and the other to the tractography technique, and we provide suggestions for best strategies to overcome them in routine neurosurgical practice (**Table 3.5 and 3.6**).

### 3.5.1 challenges from cranial nerve anatomy

#### 3.5.1.1 Cranial nerve features

Beyond the small size of cranial nerve fibers (between 0.1 to 5 mm),[47–49, 77] tracking is limited by certain tortuous trajectories in skull base cisterns or dura folds (trochlear and abducens nerves), splayed fibers within bundles (acoustic facial bundle and lower nerves), or flattened nerves around large tumors.[19] The vagus, accessory, or hypoglossal nerves are also dispersed into rootlets from the brainstem to their foramen that makes the tracking even more difficult.[42] In the same way, distinguishing between cochlear and vestibular nerves remains difficult[19, 36, 102] while the acoustic facial bundle is always reconstructed.[42, 92, 111] Therefore, each cranial nerve has anatomical specificities to be taken into account (**Table 3.6**). Tracking parameters should be tailored to each cranial nerve : a high angle of curvature for the optic chiasma, a precise ROI placement for the oculomotor nerve in its vascular clamp, a lower FA for the narrow

trochlear and abducens nerves, multiple ROIs for the trigeminal nerve if including of its three branches, a lower FA and a “nucleus” brainstem ROI for the acoustic facial bundle, a lower FA and a “brainstem emerging point” ROI for the vagus nerve fibers with its dispersed rootlets,[110] etc.

### **3.5.1.2 Tumor features**

In case of skull base tumor, its morphological and radiological characteristics influence the cranial nerve tractography. Authors reported inability to perform the tracking when the tumor volume was large,[36, 92] when the tumor was mostly cystic,[19, 92] and when the tumor diffusion signal was close to that of cranial nerves.[19] This is the case for schwannomas that grow from the nerve sheath and present a T2 or diffusion signal similar to that of the nerve itself. Furthermore, the tracking was limited when the tumor modified the anatomical environment and displaced the cranial nerves away from their known trajectory. The ROIs are hard to draw, and hence the reconstruction can be invalid. In parallel, arachnoid membranes or postoperative changes can hamper the tracking. Last but not least, tracking is even more difficult when large tumors lead cranial nerves to merge with the tumor membrane, to cross into it, and to be highly stretched.[102]

### **3.5.1.3 Fiber crossing**

The main difficulty in tractography remains fiber crossing. At fiber crossing points where fiber orientation is multiple, algorithms have to continue the reconstruction in the initial direction without joining a larger fiber bundle that cross tangentially and falsifying the reconstruction of tracts.[95] Regarding the cranial nerves anatomical environment, the brainstem presents a complex architecture with large white matter tracts crossing in the three dimensions : anterior-posterior such as the cerebellar peduncles, medial-lateral such as the transverse tracts or “deep” connections, and inferior-superior as the sensorimotor tracts.[64, 106] Thus, small fibers of cranial nerves arising from the pons cross tangentially large brainstem tracts and the tractography can provide spurious fibers if these brainstem tracts are recruited.[19, 42] By assuming a single anisotropic Gaussian distribution of fibers, the single tensor model fails to extract the true fiber diffusion profile within a voxel containing a crossing, branching, or merging configuration of fibers.[50] Recent technical advances overcame these issues using the orientation distribution of fibers (ODF) model providing a high angular resolution imaging (HARDI) : diffusion spectral imaging,[101] q-ball imaging,[107] q-sampling imaging,[109] and constrained spherical deconvolution.[25, 94, 95] Interestingly, while these limitations of the single tensor model have been acknowledged in brain white matter tractography,[30] most

software packages still used it in the included studies. This is probably because HARDI methods require longer MRI scans and complex post-processing steps, which may be difficult to implement in a routine clinical practice.

#### 3.5.1.4 Geometric distortions

Diffusion imaging is associated with geometric distortions caused by three different factors : (1) the magnetic susceptibility distribution of the subjects' head, (2) eddy currents from the rapid switching of the diffusion weighting gradients, and (3) the slight movements of the subjects' head during the long MRI acquisition protocol. Furthermore, these distortions are frequent at the skull base because of the close interface of air, bone, and soft tissues.[17] Thereby, distortion explains the failure to track cranial nerves at the skull base, both in their cisternal segment and through skull base foramina.[42] Artifacts caused by intra-petrous mastoid cells around the internal auditory canal hampers the tracking of the facial or cochlear nerve.[68] The trochlear and the abducens nerves are incompletely tracked due to susceptibility artifacts near facial regions.[110] Cerebrospinal fluid (CSF) pulsation also alters the diffusion signal around cranial nerves in cisterns[92] and causes a partial volume effect that reduces angular resolution.[67, 111] Few distortion correction methods were reported. These required additional computational steps, such as using “eddy” and “topup” tools in FSL software (FMRIB's - Functional Magnetic Resonance Imaging of the Brain - Software Library). It is of note that the “topup” method corrects geometric distortions through two extra acquisitions with opposing polarities of the phase encoding direction : e.g. posterior-to-anterior and anterior-to-posterior.

### 3.5.2 Challenges from tractography

#### 3.5.2.1 Validation and ground-truth control

The whole tractography processing pipeline requires many steps and settings (**Figure 3.1**) that could lead to many different results. Subsequently, there is a high inter-patient (tumor features, histology), inter-exam (MRI acquisition), and inter-observer (experience, skill) variability. The reproducibility and the reliability of this technique have to be tested by “ground-truth” controls. In earlier studies on intra-cranial white matter pathways, the anterior commissure was used as a reliability test on the basis of the anatomical coherence of tracts reconstructed from a single voxel ROI placed at this well-known anatomical landmark.[19, 42] In selected studies, no reliability control was detailed : only the “known anatomy” was referred to when excluding spurious tracts, also called “false continuations”. A recent study compared its tracking results with the human

connectome project atlas although half of the nerves could not be tracked because of a lack of diffusion data in the brainstem and skull base cisterns.[110] Surprisingly, no study used the contralateral normal side to validate the tracking around tumors. Only one study tested the reproducibility by repeating three times the entire tracking procedure.[82] Also, the visualization rate appeared as a subjective qualitative measure indicating whether the cranial nerve was reconstructed or not, and therefore objective quantitative markers are required to assess the quality of the tractography. The number, the density and the dispersion of fibers reconstructed could be tested for this purpose.

### **3.5.2.2 Anatomical reference**

Since MRI diffusion images have a low-resolution, an anatomical reference is needed to depict the neurovascular environment and the tumor morphology, draw the ROIs for initiation of the tracking, and validate the reconstructed tracts and exclude spurious fibers according to the known anatomy.[19, 111] A T2 sequence is used classically since it is the most appropriate to show the brainstem and CSF skull base cisterns properly.[11, 110] In case of tumor, a T1 post-contrast weighted sequence can correctly reconstruct the tumor shape and show its vascular supply.[19] Thus, the anatomical reference plays a crucial role to show the tumor, its anatomical environment, and the reconstructed tracts. It has to be accurately merged with the diffusion pictures on which the tracking process is performed.

### **3.5.2.3 Technical expertise and time**

Most authors concede that a successful cranial nerve tractography requires robust abilities in anatomy, radiology and computer science, and above all several years of tractography experience.[8, 110] Some confess a variable ability of operators to discern fibers from artifacts;[102] others state that methods of analysis generally involved user expertise regarding ROI design.[17] Nonetheless, the post-processing of tractography was always performed by the same operator(s) (one or two operators) in the selected studies. The learning curve can be shortened by helpful workshops dedicated to teach basics in diffusion imaging, tracking parameters, and software use (Natbrainlab under the direction of Pr M. Catani, London, UK). Any clinician who wants to use the tractography in his/her daily practice would benefit from close collaboration with a radiologist and a computer scientist. The acquisition time was reported in only 2 studies and was 9 and 17 min for the only diffusion sequence.[8, 88] In addition, only 2 studies estimated a calculation time, which was between 2h and 28h.[8, 118] This emphasizes that the

cranial nerve tractography requires a long imaging and post-processing time and gives directions for further research.

#### 3.5.2.4 Improvements

To overcome some of the challenges posed by cranial nerve tractography, authors have proposed improvements in both acquisition and tracking steps.

First, the resolution of diffusion images could be increased by a higher number of diffusion gradient directions[115] or higher magnetic field strength, at the cost of longer machine time and more geometric distortions.[17, 19, 88] A minimum of six gradient directions is required for a single tensor model tractography, however no study has defined an optimal number of gradient directions. This review leads us to propose an MRI acquisition protocol (**Table 3.5**) with thinner contiguous slices, isotropic voxels - equal length on all sides -, and a voxel size of 2 mm or smaller.[42, 111] New acquisition techniques, such as multiband acquisition, compressed sensing[54] or readout segmentation of long variable echo-trains (RESOLVE) sequence,[114] are under development providing a better resolution and shorter acquisition time.

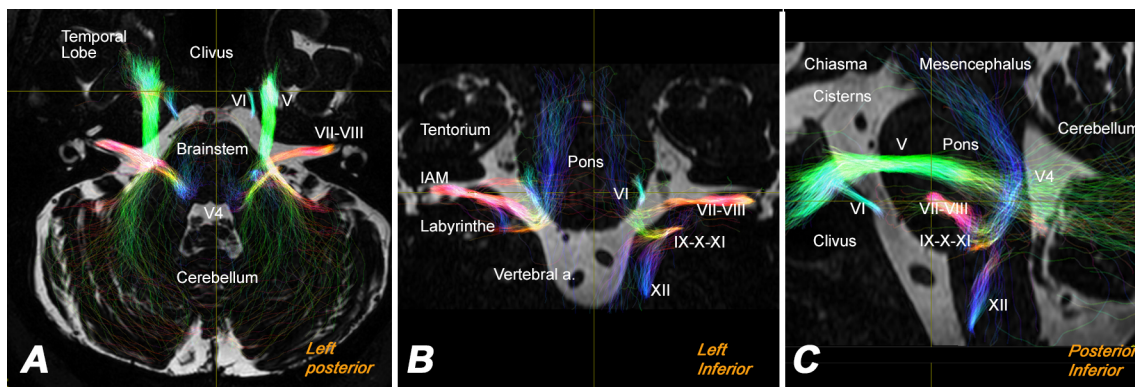
Second, tracking parameters and ROI design could be gathered in an atlas to provide an optimal fiber tracking of each cranial nerve. Beyond the new “HARDI” post-processing methods, new probabilistic algorithms[59, 95, 118] would improve the cranial nerve tracking accuracy particularly in very small or highly modified nervous structures despite a longer calculation time (**Figure 3.3**). Last but not least, tract reconstruction based on fiber density – track density imaging – could be a path to provide very high definition maps to perform a highly selective tracking.[12, 40]

#### 3.5.3 Perspectives

Beyond all the mentioned challenges, being able to produce an accurate fiber tracking of cranial nerves could be a significant asset in various medical fields. Accurately predicting cranial nerve displacement around skull base tumors will make surgery safer and faster.[17, 67, 68, 110] Other diseases could also benefit from this tool as an objective marker of white fiber damage that is not visible by conventional imaging. Affected nerves could have lower fiber density than healthy ones,[42] for example, in peripheral neuropathy, multiple sclerosis,[90] or nerve entrapment syndromes.[17] Also, tractography has the potential to visualize a continuum of cranial nerve trajectories from their brainstem nucleus to the skull base foramina in normal and pathological conditions. Subsequently, it could be a very interesting tool for the teaching of neuroanatomy as opposed to post mortem dissections. Last but not least, the integration of reconstructed tracts into the



neuronavigation device could help both the preoperative planning and the intraoperative neurosurgical work.[11, 36] Further technical advances would be helpful to overcome some of the challenges described. Our team is working on a standard tractography pipeline, detailing all steps from acquisition to post-processing parameters, using a high definition probabilistic algorithm.[94] We aim to provide a reliable and reproducible cranial nerve tractography pipeline that would be easy-to-use in the routine clinical practice (**Table 3.5 and 3.6**).



**FIGURE 3.3 – Cranial nerve tractography with probabilistic tractography algorithm.** As depicted on axial (A), coronal (B) and sagittal (C) views, the probabilistic cranial nerve tractography reconstructs the trajectory of most of the cranial nerves I to XII in healthy conditions. Though, the trochlear nerve is often too thin to be tracked. Probabilistic methods could reconstruct not only cranial nerve cisternal segment but also that within the brainstem or through skull base foramina. Testing the reliability of this technology requires robust anatomical knowledge in particular the neurovascular environment of the skull base including : brainstem (midbrain, pons and medulla), cerebellum, fourth ventricle (V4), tentorium, labyrinth, clivus, optic chiasma, and cerebro-spinal fluid cisterns. Personal data based on the constrained spherical deconvolution model with Mrtrix3 software ([www.mrtrix.org](http://www.mrtrix.org))

### 3.6 Conclusion

Tractography has already caught the attention of the scientific community since it allows the non-invasive in vivo description of brain white matter connections. This technology is still difficult to apply to small neurological structures such as cranial nerves. In the present paper, we review technical details of the whole tractography pipeline and we demonstrate the paramount importance of the tracking parameters that depend on the features of each cranial nerves, anatomical environment and tumor morphology, and above all a tailored design of ROI. As this targeted review points out,

applying tractography to cranial nerves demands advanced anatomical, radiological, and computational skills to achieve correct fiber tracking and to avoid spurious tracts. Nevertheless, advances such as faster imaging acquisition, high resolution post-processing, and multi-ROI tracking may help to overcome challenges, address the reconstruction of all cranial nerve trajectories, and promise new perspectives in neuroradiology, skull base surgery, and neuroanatomy.



## SÉRIE DE CAS

**A**pres avoir détaillé l'état de l'art en tractographie des nerfs crâniens, je développe ici un *pipeline* de tractographie dédié à la détection de la trajectoire des nerfs crâniens II à XI en conditions saines et tumorales. J'évalue son efficacité à travers une série de 62 patients présentant des tumeurs complexes variées de la base du crâne. Chaque étape de la tractographie est décrite depuis l'acquisition IRM jusqu'à la visualisation des tractogrammes et leur confrontation à la vérité-terrain, en passant par l'optimisation des paramètres de tracking, l'algorithme probabiliste et le *design* des ROIs. Les difficultés et les échecs sont analysés, tandis que l'impact de la technique sur la stratégie chirurgicale est rapporté. Une approche « par nerf » est préférée ici puisqu'elle cible électivement les nerfs considérés comme déplacés par les tumeurs. Cette étude clinique montre ainsi de manière originale l'application d'un algorithme probabiliste de tractographie aux nerfs crâniens déplacés par des tumeurs variées de la base du crâne, ainsi que son impact sur la stratégie chirurgicale.

# Probabilistic tractography to predict the position of cranial nerves displaced by skull base tumors : value for surgical strategy through a case series of 62 patients.

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## 4.1 Abstract

**Background :** Predicting the displacement of cranial nerves by tumors could make surgery safer and the outcome better. Recent advances in imaging and processing have overcome some of the limits associated with cranial nerve tractography, such as spatial resolution and fiber crossing. Among others, probabilistic algorithms yield to a more accurate depiction of cranial nerve trajectories. **Objective :** To report how cranial nerve probabilistic tractography can help the surgical strategy in a large series of various skull base tumors. **Methods :** After distortion correction and region of interest (ROI) seeding, a probabilistic tractography algorithm used the constrained spherical deconvolution model and attempted the reconstruction of cranial nerve trajectories in both healthy and displaced conditions. **Results :** Sixty-two patients were included and presented : vestibular schwannomas (n=33); cerebellopontine angle meningiomas (n=15); arachnoid or epidermoid cysts (n=6); cavernous sinus and lower nerves schwannomas (n=4); other tumors (n=4). For each patient, at least one ‘displaced’ cranial nerve was not clearly identified on classical anatomical MRI images. All 372 cranial nerves were successfully tracked on each healthy side; among the 175 cranial nerves considered ‘displaced’ by tumors 152 (87%) were successfully tracked. Among the 127 displaced nerves of operated patients (n=51), their position was confirmed intraoperatively for 118 (93%) of them. Conditions that led to tractography failure were detailed. On the basis of tractography, the surgical strategy was adjusted for 44 patients (71%). **Conclusion :** This study reports a cranial nerve probabilistic tractography pipeline that can : predict the position of

most cranial nerves displaced by skull base tumors, help the surgical strategy, and be a pertinent tool for future routine clinical application.

## 4.2 Introduction

Skull base tumor surgery remains a challenge since it requires complex surgical approaches sparing the brain and reaching deep-seated tumors within a dense anatomical environment that includes many cranial nerves and vessels.[1, 84] Even though the cerebral vascular supply or drainage is assessed adequately by cerebral magnetic resonance imaging (MRI) or angiography, depicting the whole cranial nerve trajectory from the brainstem to their target through the skull base and around tumors is not yet achievable in the routine clinical practice; high-resolution T1 or T2 classical MRI sequences can describe only the cisternal segment of the largest cranial nerves in normal conditions.[113]

Advances in diffusion magnetic resonance imaging (MRI) have used the unequal movement of water molecules along axons to reconstruct white matter fibers through a new post-processing called “fiber tracking” or “tractography”.[67] This technique has gained the enthusiasm of the scientific community as it has brought a novel way to explore the in vivo brain white matter architecture.[14, 16, 32] Nonetheless, tractography involves a complex multi-step processing pipeline and is still difficult to apply in fiber crossing areas[100] or to small-scale structures such as cranial nerves. These aspects have been overcome by progress made both in imaging acquisition and computational post-processing. Diffusion spectrum imaging,[101] q-ball[107] or q-sampling imaging,[109] and high definition fiber tracking (HDFT)[110] are options now available for high angular resolution diffusion imaging (HARDI) that provides more accurate and selective tracking results. Beyond the initial deterministic methods using a single diffusion tensor,[97] fiber tracking is evolving towards a fiber orientation distribution function (ODF) method that can detect several orientations of fibers in the same voxel.[9, 94] Furthermore, probabilistic algorithms with a constrained spherical deconvolution method provide a better depiction of crossing or small white matter tracts.[30, 59, 63, 95]

Predicting cranial nerve trajectories that are displaced by skull base tumors could be of help for surgery, as attested by recent studies focusing on the facial nerve course in vestibular schwannomas surgery using tractography.[11, 19, 21, 36, 39, 88, 102, 115] However, most cranial nerve tractography studies have focused on a single cranial nerve and a particular type of tumor, and have used a deterministic algorithm.[46] We report herein our experience through this large series of various skull base tumors for which all

displaced cranial nerves were depicted using a probabilistic tractography algorithm. We describe how this technique can help the surgical management of such tumors and we detail the whole tractography processing pipeline, including MRI acquisition settings, tracking parameters, and the crucial placement of regions of interest (ROIs).

## **4.3 Material and Methods**

### **4.3.1 Demographics, tumor, and follow-up**

The study was carried out in a skull base surgery department between December 2015 and December 2017. Patients were consecutively included if they : were aged 18 years or more ; had legal capacity ; had a history of skull base tumor displacing one or multiple cranial nerves ; provided consent after having been informed of the study. Those who were opposed were excluded without any change to their neurosurgical care. The institutional review board approval was obtained, and the study was registered in the worldwide database of clinical studies of the U.S. national library of medicine : <https://clinicaltrials.gov/>. In the case of vestibular schwannomas, the classification described by Koos et al. was used.[104] The follow-up after surgery was at least six months and concerned mostly cranial nerve palsy. The whole tractography pipeline is described hereafter.[46]

### **4.3.2 Imaging acquisition**

MRI images were acquired using a 3-Tesla (T) Ingenia machine (Philips Medical Systems, Beth, The Netherlands) with a 32-channel head coil. Diffusion images were acquired with following settings : b-value 1000s/mm<sup>2</sup> ; 32 directions ; TE/TR 102/3956ms, voxel size 2mm isotropic ; slice thickness 2mm ; no slice gap ; 26 slices ; single-shot spin-echo sequence ; and scan time 9min52s. The limits of the acquisition box were the optic tracts superiorly and the foramen magnum inferiorly. A T2 steady state and T1 post-contrast weighted sequence (T1W) were added for anatomical reference and tumor morphology assessment, respectively. A time-of-flight (TOF) sequence was also added to describe the vascular environment and distinguish the vessels from the nerves. According to Andersson et al.,[2] two sequences with two images for each diffusion gradient and opposed polarities of the phase encoding direction were used for distortion correction : posterior-to-anterior (PA) and anterior-to-posterior (AP). The whole MRI protocol was based on prior probabilistic tractography studies of the extracranial portion of the facial nerve,[3] lasted around 30 minutes, and was kept unchanged along the study.

### 4.3.3 Pre-processing

A brain mask defined the processing workspace for tractography and included the whole brainstem, the cerebrospinal fluid cisterns and the skull base foramina in which cranial nerves course. Subsequently, supra-tentorial structures were excluded. ‘Eddy’ and ‘topup’ FSL (FMRIB software library) functions, and AP-PA sequences were used to correct geometric distortions. The ROIs design involved a superimposition of the ODF map onto anatomical T2 pictures. ROIs were placed on the best identifiable aspect of the cranial nerve in its cisternal segment in the three dimensions : axial, sagittal, and coronal (**Figure 4.1**). For each cranial nerve, a single ROI was used ; ROIs were volumes (cube or sphere) and tailored to the anatomical features of each cranial nerve before initiating the tracking (**Table 4.1**). A region of exclusion (ROE) was drawn at the roof of the fourth ventricle in the coronal plane. Sometimes, another ROE was used within the tumor.

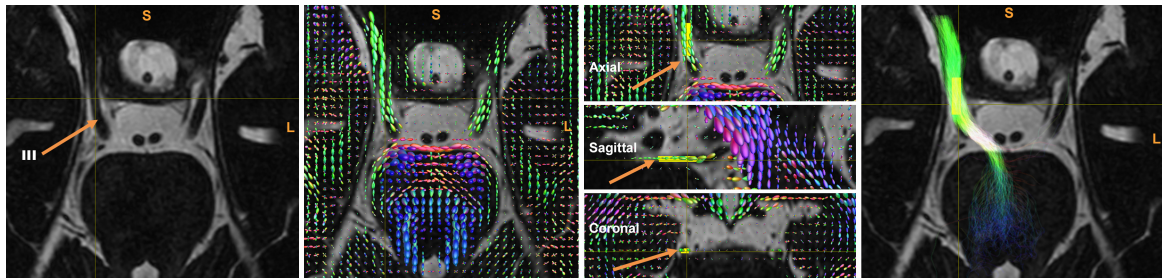


FIGURE 4.1 – **Strategy of the region of interest placement.** To overcome the residual distortion between anatomical and diffusion images at the skull base, the orientation distribution function (ODF) map was superimposed onto anatomical T2 sequence (A-B). For example, to track the right oculomotor nerve (orange arrow, A), a single ROI (in yellow) was used here with a volumic (cubic) shape. Its position was adjusted at the *best aspect* of the cranial nerve cisternal segment in the three dimensions : axial, sagittal, and coronal (orange arrows, C). The final reconstructed tracts show the cranial nerve trajectory from the brainstem to the skull base foramen (D).

### 4.3.4 Tractography

The Tractography process used the MRtrix3 software ([www.MRtrix.org](http://www.MRtrix.org), J-D Tournier, Brain Research Institute, Melbourne, Australia[93]) (**Appendice C**). For each voxel of the brain mask, the fiber population was estimated by a response function (“dwi2response” in MRtrix3), and then a constrained spherical deconvolution (6 spherical harmonic terms) was used to create a fiber orientation distribution function (ODF) map



(“dwi2fod” in MRtrix3). A probabilistic streamline tracking was performed (“tckgen” in MRtrix3) with the optimized parameters : minimum fiber length 10mm ; maximal curvature angle  $45^\circ$  ; and FA cut-off 0.3 (0.2 for cranial nerves VI and IX/X/XI) (Supplemental content 2). Fibers that crossed towards the cerebellum were excluded using a region of exclusion (ROE). The acoustic facial complex was tracked as a bundle, as were the lower nerves. Six cranial nerves and groups were thus considered : II, III, V, VI, VII/VIII, and IX/X/XI. The number of fibers of each nerve to be reconstructed was set according to the nerve diameter, respectively : 1000, 500, 700, 100, 300, 200 (**Table 4.1**). The olfactory and hypoglossal nerves were most often outside of the acquisition box. The trochlear nerve was too thin to be seen in the anatomical T2 sequence and tracked. Both sides were analyzed for each patient. Cranial nerves were considered displaced by tumors when they were in contact with or pushed/encased by the tumor. The tracking parameters were adjusted using data collected from the first ten included patients to improve the tractographic aspect even if the predicted position was not modified. Thereafter, data were collected and analyzed prospectively. The complete post-processing lasted around 30 minutes using a multi-core processor computer (Intel Core® i7, 2.3 GHz, Intel Corporation®, Santa Clara, CA, USA).

| Group | Nerve                           | ROI placement                            | Tracking parameters |                  |                 |
|-------|---------------------------------|------------------------------------------|---------------------|------------------|-----------------|
|       |                                 |                                          | FA threshold        | Number of Fibers | Other           |
| 1     | Optic nerve II                  | Whole optic chiasma                      | 0.3                 | 1000             | Maximal         |
| 2     | Oculomotor nerve III            | Cisternal segment before cavernous sinus | 0.3                 | 500              | curvature angle |
| 3     | Trigeminal nerve V              | Mid-cisternal point                      | 0.3                 | 700              | = $45^\circ$    |
| 4     | Abducens nerve VI               | Dorello canal entrance                   | 0.2                 | 100              |                 |
| 5     | Acoustic facial bundle VII-VIII | Whole Internal Acoustic Canal            | 0.3                 | 300              | Minimal length  |
| 6     | Lower nerves IX, X, XI          | Cisternal segment at the flocculus level | 0.2                 | 200              | = 10mm          |

TABLE 4.1 – **Strategy of ROI placement and tracking parameters.**

#### 4.3.5 Control and surgical validation

The reliability of tractography was assessed by comparing the healthy-side reconstructed tracts and cranial nerve cisternal trajectories on anatomical T2 constructive interference steady state (CISS) images. The ‘radiological’ position of the displaced cranial nerve was compared to its ground-truth ‘operative’ position through direct visualization on the surgical microscope. Furthermore, intraoperative electromyographic monitoring confirmed which cranial nerve was displaced by direct electric monopolar stimulation (Nerve Integrity Monitoring® system, Medtronic, Minneapolis, MN, USA) with the following settings : 100 microV and 0.03 mA. This control was enabled for cranial nerves with motor function : the oculomotor ; the trigeminal (motor root) ; the

abducens; the facial; the vagus; and the hypoglossal nerves. The position of the acoustic facial bundle around the tumor used the six divisions described by Sampath et al.[85] The concordance between the ‘radiological’ and the ‘surgical’ position of cranial nerves was determined using Cohen’s Kappa coefficient and interpreted according to the Landis and Koch criteria; the facial nerve was assessed alone since its positioning was more precise.

## 4.4 Results

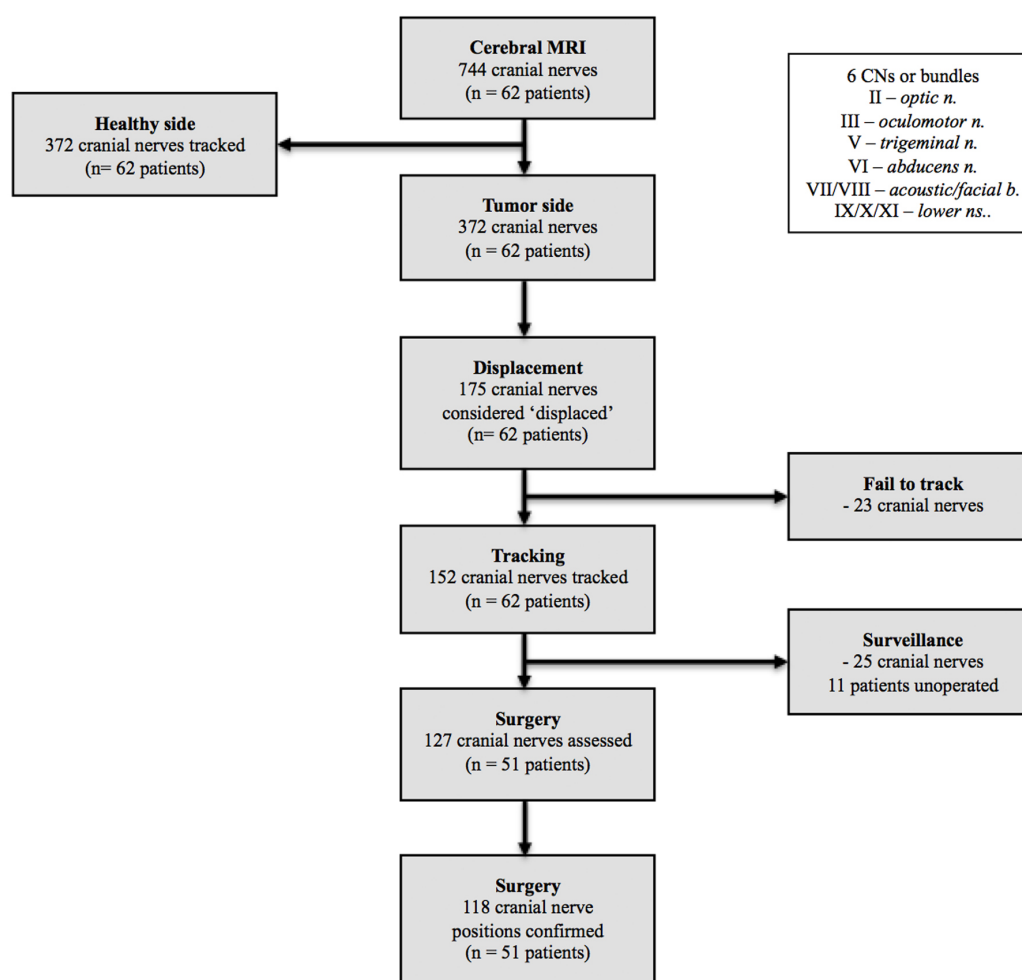
### 4.4.1 Patients

Sixty-two patients were included; 36 were female, and the mean age was 51 years (SD : 15, range : 19 to 79). They presented various types of tumors : vestibular schwannomas (n=33); cerebellopontine angle meningiomas (n=15); arachnoid or epidermoid cysts (n=6); cavernous sinus or lower nerves schwannomas (n=4); one chondrosarcoma; one nasopharyngeal carcinoma; one choroid papilloma, and one melanoma metastasis. The mean tumor size was 30 mm (SD : 12) while vestibular schwannomas were most frequently classified as Koos III (n=10) or IV (n=14). In view of operative risks, non-invalidating symptoms and the lack of radiological growth, 11 patients did not undergo surgery but were subjected to a “wait-and-see” attitude. For each patient, at least one ‘displaced’ cranial nerve was not clearly identified on classical anatomical MRI images.

### 4.4.2 Tractograms

A total of 744 cranial nerves were tracked on both sides in the 62 patients (**Figure 4.2**). On the contralateral healthy side, all 372 cranial nerves were tracked. Among the 175 displaced cranial nerves, 152 (87%) were successfully tracked, i.e. 23 of these nerves were not tracked. Conditions that led to tractography failure (n=23) were : nerve encasement (n=11), cystic tumor (n=6), large tumor (n=4), and very small-sized nerve (n=2). Because of their thinness, the abducens nerve and the acoustic facial bundle were the more difficult to track contrary to the optic, the oculomotor, and the trigeminal nerves (**Figure 4.3**). Noteworthy, the hypoglossal nerve was successfully tracked in the 3 tumors in which it was considered displaced. Reconstructed fibers of cranial nerves always stopped at the entry of skull base foramina due to a diffusion signal drop. No nuclei or segments were clearly identified in the brainstem either. Regarding the 52 acoustic-facial bundles displaced around tumors, the facial nerve was often distinguished and its most frequent position was anterior (n=17; 33%) or anterior-superior (n=14; 27%) according to Sampath et al.(Sampath, Rini, et Long 2000) The posterior position was

rare (n=4 ; 8%) and never concerned vestibular schwannomas. The facial nerve coursed within the tumor in one case and was unidentified in 7 cases. For cases of trigeminal nerve displacement (n=45), its most frequent positions were superior (n=25 ; 56%) and lateral (n=10 ; 22%) along the tentorium, while the lower nerves were mostly pushed inferiorly by tumors.



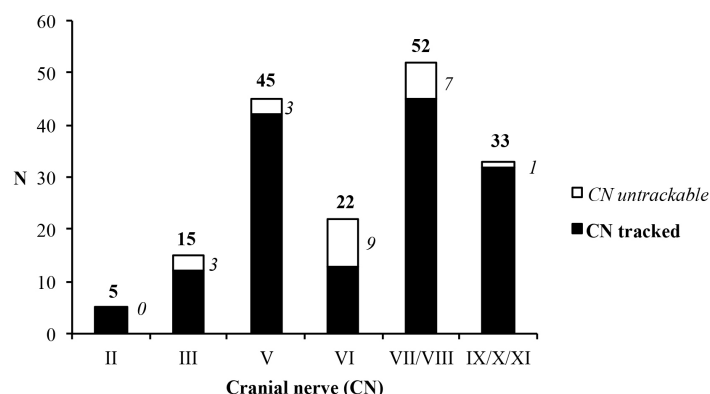
**FIGURE 4.2 – Study diagram.** Having acquired a cerebral MRI in 62 patients, 744 cranial nerves were tracked. At each side, six nerves or groups were considered : the optic nerve, the oculomotor nerve, the trigeminal nerve, the abducens nerve, the acoustic-facial bundle (VII, VIII), and the lower nerves (IX, X, XI). The olfactory and hypoglossal nerves were often out of the acquisition box. The trochlear nerve was too thin to be ever seen onto anatomical images. At the tumor side, 175 cranial nerves were considered 'displaced', among which 152 were successfully tracked. Regarding operated patients (n=51), the position of 118 (94%) cranial nerves was confirmed intraoperatively.

### 4.4.3 Surgical findings and outcome

Among the 51 patients who had surgical removal of their skull base tumor, 7 different approaches were used (**Table 4.2**). The most frequent route was the translabyrinthine approach (n=31) followed by the retrosigmoid approach (n=10); the least used were the subtemporal approach (n=3), the anterior petrosectomy (n=3), the orbitozygomatic trans-sylvian approach (n=1), the endoscopic endonasal approach (n=1), and combined approaches (n=2). Forty-three percent of the resections were complete (n=22), while the removal was considered gross total in 17 (33%) of procedures and subtotal and 11 (22%). One surgery was a simple fenestration of a large cerebellopontine arachnoid cyst. Forty-seven patients had a pre-operative cranial nerve palsy that was most often a loss of hearing (n=34, 72%) in case of vestibular schwannomas. Other pre-operative dysfunctions concerned the oculomotor (n=2), the trigeminal (n=6), and the abducens (n=5) nerve depending on the tumor site. After surgery, five patients recovered from their prior cranial nerve palsy, 27 were clinically stable, whereas 19 patients had an additional palsy that was frequently a facial palsy (grade II to VI as described by House and Brackmann (House et Brackmann 1985)). Among the 127 cranial nerves displaced that were identified by tractography in surgical patients, 118 (93%) had their position confirmed by operative findings. Nine patients had one cranial nerve for which the ‘surgical’ position was not in accordance with the ‘radiological’ position predicted by tractography because of large tumor (n=4), cystic tumor (n=3), or nerve encasement (n=2). According to the Cohen’s Kappa coefficient assessing the concordance between these two positions, there was an almost perfect agreement for all cranial nerves ( $K = 0.94$ ) while there was a moderate agreement considering the single facial nerve ( $K = 0.47$ ). There was no complication or adverse event due to the tractography. Three patients, for whom the ‘wait-and-see’ attitude was decided, were lost to follow-up.

| Surgical approach                      | Total population, n = 51 |
|----------------------------------------|--------------------------|
| Trans labyrinthine approach, TLA (%)   | 31 (61%)                 |
| Retro sigmoid approach, RSA (%)        | 10 (20%)                 |
| Sub temporal approach, STA (%)         | 3 (6%)                   |
| Anterior petrosectomy, AP (%)          | 3 (6%)                   |
| Orbito-zygomatic approach, OZA (%)     | 1 (2%)                   |
| Endoscopic endonasal approach, EEA (%) | 1 (2%)                   |
| Combined or multi step approach (%)    | 2 (4%)                   |

TABLE 4.2 – Surgical approaches to skull base tumors

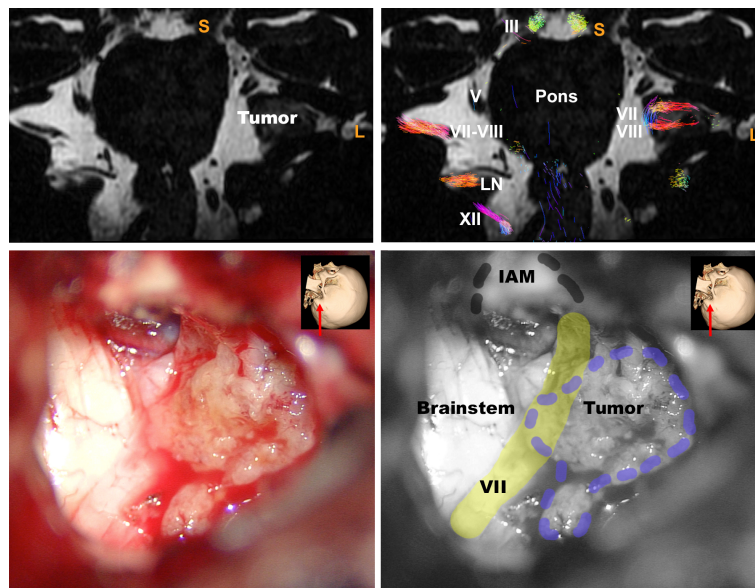


**FIGURE 4.3 – Distribution of the cranial nerves considered displaced around skull base tumors.** The cranial nerves most frequently displaced around tumors were the acoustic-facial bundle, the trigeminal, and the lower nerves followed to a lesser extent by the abducens, the oculomotor, and the optic nerves. Regarding the 54 facial nerves displaced, their most frequent position was anterior-superior (n=17) and anterior (n=11) as described by Sampath et al., while seven facial nerves were unidentifiable.

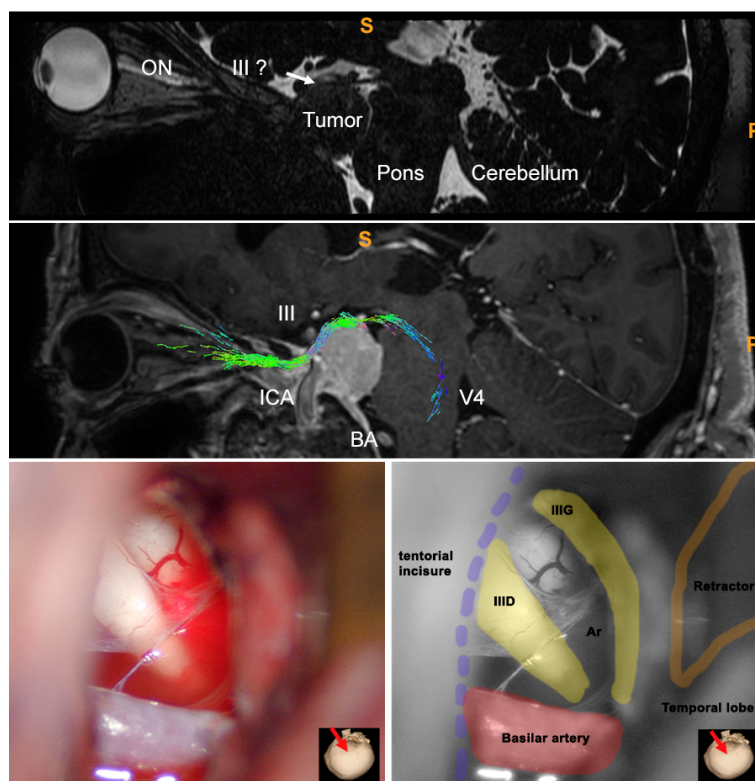
#### 4.4.4 Surgical strategy

On the basis of tractography, the surgical strategy was adjusted for 71% of the patients (n=44). The value of tractography was illustrated through several cases of the series (**Figures 4.4-7**). The operative risk was considered too high and surgery was not performed for 7 patients. In these cases, tractography depicted one or more cranial nerves severely distorted or completely encased by solid tumors while tumor growth was no evident and poor symptoms. For example, an asymptomatic young man with a lower nerve schwannoma was directed to a radiologic follow-up. The same decision was taken for a 70-years old woman that presented a giant bilateral clival meningioma with multiple cranial nerve encasement and minimal clinic impact. A different surgical approach was chosen for 10 patients for which tractography revealed cranial nerve crossed the surgical path selected. This corridor was tailored not to cross cranial nerves, or as less as possible. As such, the tracked position of the trigeminal nerve within a petroclival chondrosarcoma led to prefer a lateral subtemporal approach rather than an anterior endoscopic transnasal one (**Figure 4.7**). In another case of choroid papilloma of the right cerebellopontine angle, tractography identified the lower nerves pushed superiorly against the acoustic-facial bundle, which helped both the craniotomy and the release of cranial nerves from the tumor capsule (**Figure 4.7**). In addition to most patients in which the approached was tailored, 27 patients had their tumor resection

steps optimized thanks to tractographic inputs. For any type of tumor, to know the position of cranial nerves before operating allowed the surgeon to create a mental map of the patient's specific anatomy (tumor, cranial nerves, and environment) and then alternating fast safe debulking and high-precision dissecting of the cranial nerves attached to the tumor (**Figure 4.7**). The advantage of tractography was found for almost all meningiomas (n=14), all cystic tumors (n=6), and all cavernous sinus or lower nerve schwannomas (n=4). Though, tractography helped the surgical strategy for only 19 of vestibular schwannomas (58%).

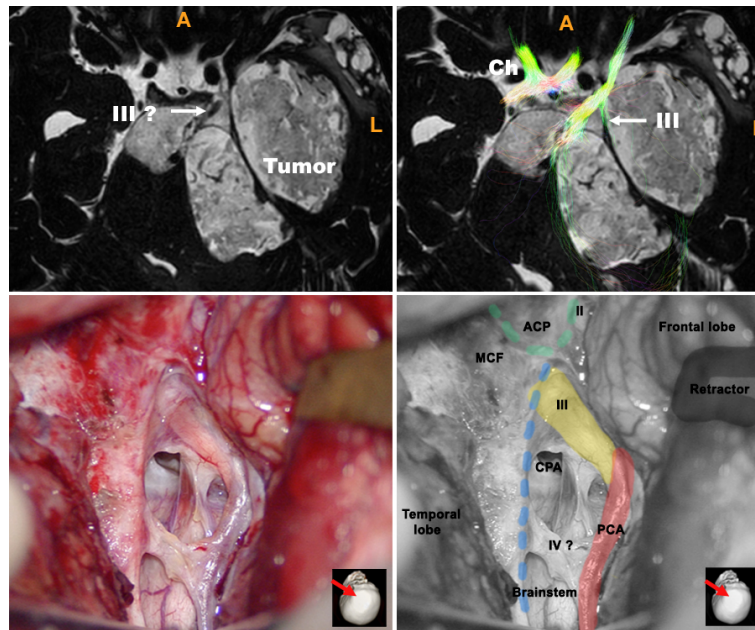


**FIGURE 4.4 – Illustrative case 1.** A 42-year-old man presented with a left-sided hearing loss and tinnitus. The cerebral MRI found a large right Koos-3 vestibular schwannoma with significant brainstem contact. The tumor diameter was 23 mm with full but heterogeneous enhancement; and it filled the internal acoustic canal. The acoustic facial bundle was not identified on classical T2 images while the trigeminal nerve was pushed superiorly and the lower nerves were in close contact inferiorly (axial view, A). Tractography depicted the acoustic facial bundle flattened at the anterior-superior tumor surface and confirmed the position of cranial nerves V and IX/X/XI (tractography overlaid on T2 sagittal views, B). Cranial nerves II to XII were correctly tracked on the contralateral healthy side except for the trochlear nerve. Because of the volume and the hearing status, a translabyrinthine approach was performed resulting in a gross total resection with perioperative confirmation of the anterior-superior position of the facial nerve by both visualization and electromyographic monitoring (microscopic view of the translabyrinthine approach and anatomical landmarks, C-D). The patient was discharged home after a week; he presented a House-Brackmann-4 facial palsy that disappeared after 3 months. The tractography was useful in this case to know the position of the facial nerve before surgery which allows surgeons to rapidly and safely debulk the tumor; and then to work cautiously removing the most adherent residue attached to this nerve.



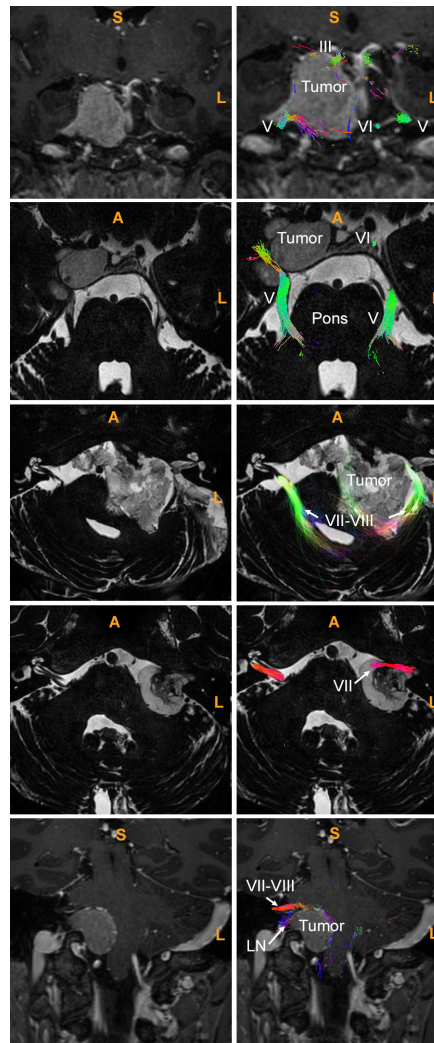
**FIGURE 4.5 – Illustrative case 2.** A 69-year-old woman reported a slight balance disorder and diplopia in the left gaze. The ophthalmological examination did not report any other abnormality. A cerebral MRI found a left upper petroclival meningioma of 24 mm in diameter, which was in contact with the trigeminal nerve although the abducens and oculomotor nerve were not identified in classical T2 anatomical images (axial view, A). The tractography displayed the course of the oculomotor nerve stretched at the superior pole of the tumor (tractography overlaid on sagittal and coronal T2 views, B) while the abducens nerve was not displaced but passed across the inferior medial side of the tumor. A subtemporal approach was chosen not to cross any cranial nerves and led to a gross total resection leaving a tumor fragment around the trigeminal porus and the dural entry point of the abducens nerve. The operative findings confirmed the position of cranial nerves III to VI. At the end of the surgery, the oculomotor bifurcation is seen in the interpeduncular fossa (microscopic view and anatomical landmarks, C-D). The patient did not have any postoperative neurological deficit. The tractography, in this case, oriented the choice of the surgical corridor by depicting the position of cranial nerves displaced, superiorly or inferiorly, by the tumor. The tractography, in this case, oriented the surgical approach and made the surgery safer by predicting the position of cranial nerves III to VI around the tumor. *Ar : arachnoid sheet, BA : basilar artery, ICA : internal carotid artery, V4 : fourth ventricle, III (G and D) : oculomotor nerve (left and right).*





**FIGURE 4.6 – Illustrative case 3.** A 43-year-old man who had a known history of an epidermoid cyst with multiple prior surgeries performed in Romania, presented with headache. A cerebral MRI found a left large supra-infra-tentorial cystic lesion with severe brainstem compression and encasement of multiple cranial nerves. The restriction of the apparent diffusion coefficient confirmed a giant epidermoid cyst recurrence. The cranial nerves were unidentifiable because of anatomical changes from previous surgical procedures and the presence of many tumor membranes (arrow, T2 axial view, A). The tractography allowed the distinction of nerves from membranes and showed the oculomotor nerve pushed inferiorly and medially (arrow, tractography overlaid on T2 axial views, B). Surgery was performed in two steps : a first retrosigmoid approach to release the compression effect, and then an orbitozygomatic route to optimally remove the supratentorial content. The position of the oculomotor nerve was confirmed by both visualization and electric stimulation (microscopic view and anatomical landmarks, C-D). The patient was then discharged home without any cranial nerve palsy. He was to have an annual MRI follow-up to detect tumor recurrence. The probabilistic tracking was, in this case, a useful tool to differentiate cranial nerves from other anatomical structures, and it thus helped the surgical resection steps. ACP : anterior clinoid process, CPA : cerebellopontine angle, MCF : middle cranial fossa, PCA : posterior cerebral artery, II : optic nerve, IV : trochlear nerve.





**FIGURE 4.7 – Examples of surgical strategy adjustments using cranial nerve tractography according to the tumor histological type.** In a case of right large petroclival meningioma, tractography allowed to identify the oculomotor nerve coursing at the superior margin of the tumor and the trigeminal nerve pushed inferiorly; the approach was oriented hence to an anterior petrosectomy (coronal T1W views without and with tractography, A and B). In a case of right petrous apex chondrosarcoma, tractography visualized the trigeminal nerve that was displaced superiorly and laterally; the approach was then adjusted to a subtemporal corridor (axial T2 views without and with tractography, C and D). In a case of a large left cerebellopontine angle epidermoid cyst, tractography confirmed the posterior position of the acoustic-facial bundle and helped both the approach and the decompression (axial T2 views without and with tractography, E and F). In a case of a left multi-cystic vestibular schwannoma, tractography distinguished the facial fibers within an anterior cyst that made the removal safer (axial T2 views without and with tractography, G and H). In a case large right choroid papilloma appended to the jugular foramen, tractography showed both the acoustic facial and lower nerves displaced at the superior pole of the tumor that helped the surgeon to tailor the approach and the resection steps (coronal T1W views without and with tractography, I and J). *III : oculomotor nerve, V : trigeminal nerve, VI : abducens nerve, VII : facial nerve, VII-VIII : acoustic facial bundle, LN : lower nerves.*

## 4.5 Discussion

The present work reports a large skull base tumor case series in which probabilistic tractography was applied to cranial nerves. On the healthy side, tractography was able to reconstruct cranial nerves II, III, V, VI, the acoustic-facial bundle, and the lower nerves. On the tumor side, tractography depicted the majority of ‘displaced’ cranial nerve trajectories that led to adjust the surgical strategy.

### 4.5.1 A new cranial nerve tractography insight

We designed an original study based on a large series of various skull base tumors using a probabilistic tractography algorithm to depict the elective position of cranial nerves ‘displaced’ by tumors and report how tractography helped the surgical strategy. Although 14 cranial nerve tractography case series were published between 2011 and 2017 (**Table 4.3**), [8, 11, 21, 36, 39, 82, 88, 102, 110, 112, 115, 116, 118] they included little samples of patients (from 3 to 30) or healthy subjects. Among these studies, 10 attempted to predict the position of the single facial nerve in a single type of tumor : vestibular schwannomas. The remaining four tracked several cranial nerves in “skull base” or “cerebellopontine angle” tumors. Nine different tractography software packages were used. Most studies used a deterministic algorithm (n=11), however Zolal et al. and Behan et al. recently compared deterministic and probabilistic algorithms in case series of 5, 10, and 21 patients. [8, 117, 118] They concluded that probabilistic tractography yielded more accurate depictions of cranial nerves than deterministic methods [117, 118] by avoiding the manual elimination of spurious fibers while conceding an increased calculation time. [8] It is of note that Yoshino et al. achieved the tracking of all cranial nerves from I to XII using a combined method called high definition fiber tracking (HDFT). [110] Despite a user-related and multi-step tracking process, the authors demonstrated the most accurate tracking of each cranial nerve detailing tracking parameters and ROI placement amidst anatomical landmarks in healthy patients. In addition, they successfully applied their method in 3 “skull base tumor” cases for which they were the only ones detailing the impact of tractography on the surgical strategy.

### 4.5.2 Optimization of the ROI design

We faced and overcame several challenges during the development of the tractography pipeline. For instance, distortions were frequent at the skull base because of the interface of different magnetic susceptibility tissues, eddy currents, and movement of the subjects’ head. Even though a correction was performed thanks to “eddy” and “topup” tools of

| Date | Authors                | Number of patients | Tumors                        | CN studied           | Visualization rate | Software               | Algorithm                       |
|------|------------------------|--------------------|-------------------------------|----------------------|--------------------|------------------------|---------------------------------|
| 2011 | <i>Gerganov et al.</i> | 22                 | Vestibular schwannomas        | VII/VIII             | 90.9%              | iPlan                  | Deterministic                   |
| 2012 | <i>Roundy et al.</i>   | 5 (1*)             | Cerebellopontine angle tumors | VII/VIII             | 100%               | PEW                    | Deterministic                   |
| 2013 | <i>Zhang et al.</i>    | 8                  | Vestibular schwannomas        | VII/VIII             | 87.5%              | NA                     | Deterministic                   |
| 2014 | <i>Choi et al.</i>     | 11                 | Vestibular schwannomas        | VII/VIII             | 100%               | DSI Studio             | Deterministic                   |
| 2015 | <i>Wei et al.</i>      | 23                 | Vestibular schwannomas        | VII/VIII             | 91.3%              | iPlan                  | Deterministic                   |
| 2015 | <i>Yoshino et al.</i>  | 22                 | Vestibular schwannomas        | VII/VIII             | 81.8%              | dTV/VolumeOne          | Deterministic                   |
| 2016 | <i>Borkar et al.</i>   | 20                 | Vestibular schwannomas        | VII/VIII             | 95%                | DynaSuite              | Deterministic                   |
| 2016 | <i>Song et al.</i>     | 15                 | Vestibular schwannomas        | VII/VIII             | 100%               | 3DSlicer               | Deterministic                   |
| 2016 | <i>Hilly et al.</i>    | 28 (13*)           | Cerebellopontine angle tumors | VII/VIII             | 95.2%              | PEW                    | Deterministic                   |
| 2016 | <i>Zhang et al.</i>    | 30                 | Vestibular schwannomas        | VII/VIII             | 96.7%              | iPlan                  | Deterministic                   |
| 2016 | <i>Yoshino et al.</i>  | 3 (4*, HCP**)      | Skull base tumors             | I to XII             | 100%               | DSI Studio             | Deterministic                   |
| 2016 | <i>Zolal et al.</i>    | 5 (30*)            | "Skull base tumors"           | II, III, V, VII/VIII | 30-70% $\Psi$      | DSI Studio, FSL        | Deterministic and Probabilistic |
| 2017 | <i>Behan et al.</i>    | 10                 | Cerebellopontine angle tumors | V, VII/VIII          | 100%               | 3D slicer, XST, Mtrix3 | Deterministic and Probabilistic |
| 2017 | <i>Zolal et al.</i>    | 21                 | Vestibular schwannomas        | VIII, VII            | 33-81%             | FSL                    | Probabilistic                   |

\*Healthy volunteers, \*Human connectome project (HCP) Atlas,  $\Psi$  "success rate" considering all ten cranial nerves tracked together, NR: Not reported, PEW: Philips extended workspace (Portal), FSL: FMRIB software library, XST: eXtended streamline tractography.

TABLE 4.3 – Reported case series using cranial nerve tractography

FSL® (FMRIB software library[70]), a slight shift often persists between anatomical and diffusion images. Consequently, a ROI placed in the anatomical image could, in some instances, not correspond to the same area on the diffusion image. The tract reconstruction could thus provide false continuations or misleading information. We used the T2 anatomical map superimposed on the ODF map to visualize both anatomical landmarks and local fiber orientations (ODF) on which the tracking was initiated. Our strategy was then to draw ROIs at the point where each nerve can be best seen regarding its cisternal segment in the three dimensions. The ROI shape was a volume (cube) and its size was tailored to the anatomical feature of each nerve : not too small as to avoid missing fibers and not too big so as to prevent recruitment of other cranial nerves or pontocerebellar tracts (**Figure 4.1**). Likewise, the ROI placement should not be too medial or too lateral to avoid either recruitment of brainstem fibers or a drop of the diffusion signal.

#### 4.5.3 Limitations and future directions

In the present study, tractography described only six groups of cranial nerves since the cisternal segment of the trochlear nerve was never seen on T2 to initiate the tracking, the olfactory and the hypoglossal nerve were often out of the acquisition box, and the

lower nerves were not separable. Considering the 23 failure cases in which tractography failed to detect the displaced nerve or the 9 erroneous cases in which tractography was not in accordance with surgical findings, we identified issues because of the following :

- a) Tumor features : cyst, large volume, internal acoustic canal filling, diffusion signal similar to the nerve (schwannoma)
- b) Cranial nerve modifications : flattening like “candy wrapper”, encasement within the tumor, displacement far away from its known position, merging with the tumor capsule
- c) Anatomical environment : confusion with arteries, veins or arachnoid/tumor membranes ; artifacts or drop of the diffusion signal at the skull base ; false continuations when brainstem tracts recruiting

In an attempt to solve these issues, news methods could be developed, such as upsampling,[87] track-density imaging,[12] length-based tracking,[10] full-brain tracking[22], multiple-ROI strategy or super selective filtering methods.[102]

The heterogeneity of the skull base tumors presented herein could represent a limitation of the present study, yet the variety of tumors does allow the consideration of tractography aspects among different histological types, and it is of note that the impact of tractography varied according to tumors. Surprisingly, while the management of all meningiomas and epidermoid cysts was helped by tractographic input, around half of the vestibular schwannomas did not derive any clear benefit from tracking of the facial nerve. This could be explained by the high probability of displacement of the facial nerve at the anterior or superior-anterior tumor margin, as it was the case in the present study for 70% of vestibular schwannomas with an almost perfect agreement. However, in cases of unusual position of the facial nerve, tractography may play an important role in reducing the risk of facial palsy in vestibular schwannoma surgery. In order to validate a potential implementation of the tractography in routine clinical practice, further studies would be required to assess the reproducibility by blind comparison between several users, the reliability by objective markers (quantitative anisotropy[108] or track density and distribution[27]), and the impact on patients (operative time, length of hospital stay, long-term clinical follow-up, quality of life, etc.).

## **4.6 Conclusion**

Probabilistic tractography showed a promising ability to predict the position of displaced cranial nerves around skull base tumors. Along with advances in imaging acquisition, reconstruction methods, and tridimensional rendering of the anatomical environment, this technique could be an effective tool in routine surgical practice.



## CLINICAL IMAGES

L'application de la technique de tractographie aux nerfs crâniens est ici illustrée par 2 vignettes cliniques successives. La première est le cas d'une paralysie isolée post traumatique du nerf oculomoteur où la tractographie confirme la section du nerf crânien invisible en imagerie IRM classique avec un impact diagnostic et pronostic. La seconde est le cas d'une volumineuse tumeur kystique compressive de l'angle ponto-cérébelleux où la tractographie décrit la position des nerfs crâniens invisibles en imagerie IRM classique pour guider les étapes clés de la chirurgie à travers les nerfs crâniens.

### 5.1 Case 1 - Tractography for cranial nerve injury prognosis in an isolated post-traumatic palsy of the oculomotor nerve

DTI tractography detecting isolated oculomotor nerve damage after traumatic brain injury.

**Timothee Jacquesson, Carole Frindel, Francois Cotton**

*Published in World Neurosurgery 2017[45] doi :10.1016/j.wneu.2017.01.082.*

#### Legend

A 24 year old woman was a victim of a severe car crash. She initially presented a Glasgow Coma Score of 8 (E2V2M4), a left hemiparesis (3/5) and a left pupil that was unreactive and dilated (11mm). She also had a superficial wound of the left 4th finger and multiple subcutaneous hemorrhages. After orotracheal intubation, she was transferred

to our trauma center. Blood tests did not reveal any metabolic disorders or intoxications. The body-scan found only disseminated petechial cerebral hemorrhages without any fractures or other abnormalities. In particular, no skull base fractures were detected (**Figure 5.1**). The transcranial doppler did not show signs of intracranial hypertension. After a few hours of surveillance in ICU, the patient quickly awoke without any remaining motor deficit. Surprisingly, she kept a total intrinsic and extrinsic oculomotor nerve palsy that was confirmed by a thorough ophthalmological examination. She had no other neurological symptom.

A dedicated cerebral MRI (Achieva 3T, Philips medical system, Best, Netherland) showed petechial cerebral hemorrhages that spared the brainstem (**Figure 5.2**). T2 CISS suggested a partial sectioning of the left oculomotor nerve just before entering the superior orbital fissure but the left posterior communicating artery hampered the radiological analysis (**Figure 5.3**). DTI fiber tracking (Mrtrix3 package software, J.D. Tournier, Brain Research Institute, Melbourne, Australia[93]) was performed with the following parameters : fractional anisotropy threshold 0.3, curvature angle 0.45, minimum length 10 mm, ROI seeding oculomotor nerve cisternal segment on coronal cross section.

Tractography confirmed a sharp arrest of oculomotor fibers at this precise point (**Figure 5.4**). Since the clinical trend has been favorable, the woman was discharged home. However, there was no evolution of the left third cranial nerve palsy 6 months later. This case indicates that isolated cranial nerve palsy can occur in severe traumatic brain injury and could benefit from specific high resolution imaging to refine potential damages and future outcome.

5.1. CASE 1 - TRACTOGRAPHY FOR CRANIAL NERVE INJURY PROGNOSIS IN AN  
ISOLATED POST-TRAUMATIC PALSY OF THE OCULOMOTOR NERVE

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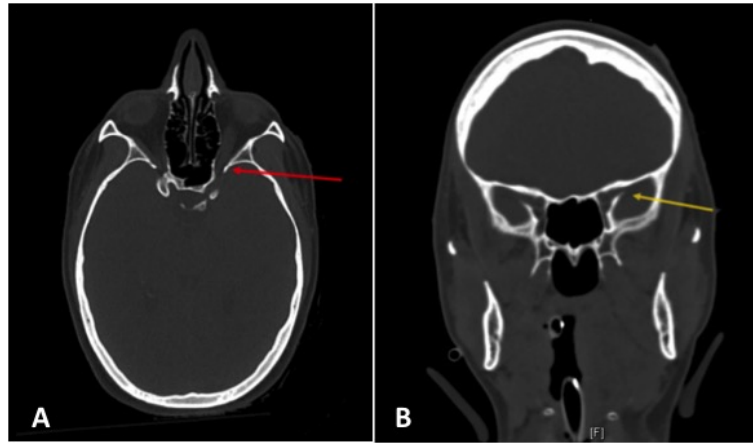


FIGURE 5.1 – **Cerebral CT-scan in axial (A) and coronal (B) views.** No visible skull base fracture particularly in the para sellar area (red arrow) and the superior orbital fissure (yellow arrow).

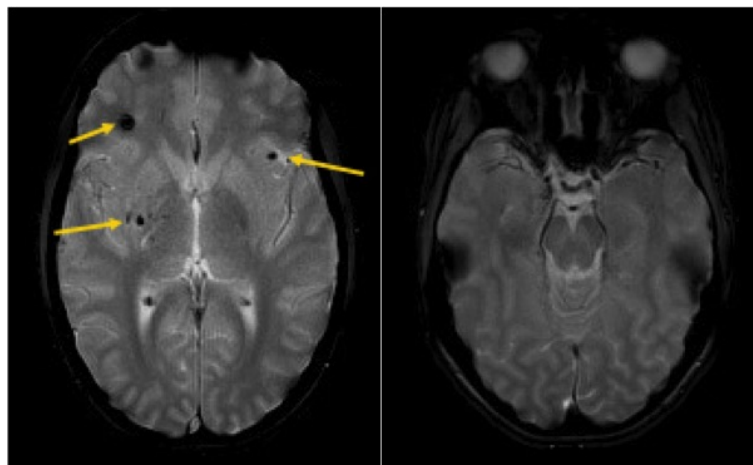


FIGURE 5.2 – **Cerebral MRI in axial view and T2\* sequence.** Petechial cerebral hemorrhages (A, yellow arrows) that spare cranial nerves and the brainstem (B).





FIGURE 5.3 – **Cerebral MRI in axial view and T2 CISS sequence.** Partial sectioning of the left oculomotor nerve in its cisternal segment just before entering the superior orbital fissure (yellow \*). The posterior communicating artery courses posteriorly from the carotid artery termination, pinching the oculomotor with the superior cerebellar artery and hiding its trajectory (red arrow).

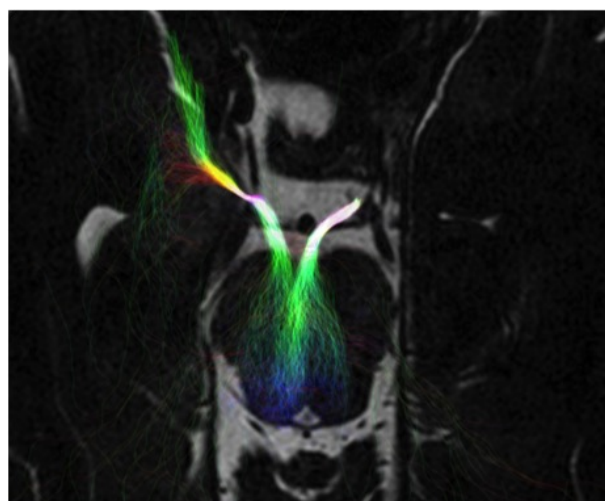


FIGURE 5.4 – **DTI tractography of the two oculomotor nerves superimposed on axial T2 CISS sequence.** Sharp arrest of left oculomotor nerve.

## 5.2 Case 2 - Tractography for surgical strategy in case of severe cranial nerve displacement by a large skull base cyst

MRI tractography detecting cranial nerve displacement in a cystic skull base tumor.

**Timothee Jacquesson, Francois Cotton, Carole Frindel**

*Published in World Neurosurgery 2018[44] doi : doi :10.1016/j.wneu.2018.06.182.*

Legend

A 37-year-old man was addressed to our neurosurgical department with a 2-month history of a progressive invalidating balance disorder. A first ear examination did not find any auditory deficit but a single right vestibular areflexia. There was no other neurological abnormality. A cerebral magnetic resonance imaging (MRI) found a T2 hyper signal lesion of the right cerebellopontine angle that severely compressed the brainstem. A typical arachnoid cyst was assumed owing to the absence of either gadolinium enhancement or restriction in the apparent diffusion coefficient. A surgical fenestration was proposed ; however, the position of cranial nerves was not clearly identified (**arrows, Figure 5.5**). An additional MRI diffusion sequence allowed the use of a recent imaging tool called ‘tractography’, which extracts the preferential orientation of water molecules along tissues to reconstruct white matter tracts. On the basis of the orientation distribution function (ODF) of fibers at each voxel (**Figure 5.5**), a probabilistic algorithm used the spherical deconvolution method (Mrtrix3 package software - J-D Tournier, Brain Research Institute, Melbourne, Australia[93]) to reconstruct the trajectories of cranial nerves. In the present case, their position was subsequently depicted : the acoustic facial was severely flattened posteriorly and superiorly, while the lower nerves were pushed inferiorly (**Figure 5.6**). The trajectory of the trigeminal, abducens, and hypoglossal nerves were also described. Furthermore, the tridimensional distribution of the cranial nerves in this modified anatomical environment helped the surgical strategy (**Figure 5.7**). Effective neurosurgical decompression was performed and confirmed the position of cranial nerves V to XII. The patient was discharged and returned home without any cranial nerve deficit. This case illustrates how advances in imaging can now better describe the anatomy surrounding brain tumors and make surgery safer to the benefit of patients.

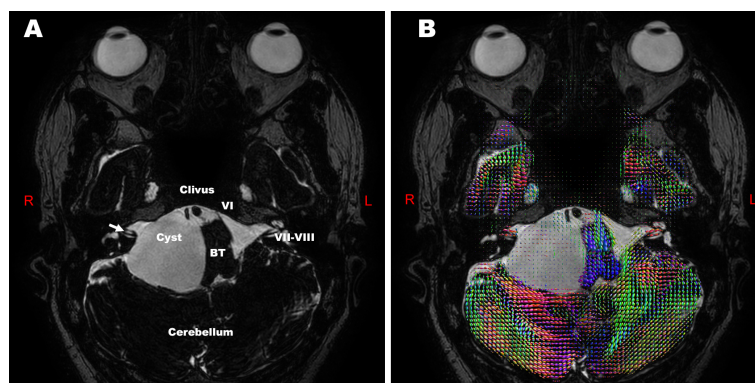


FIGURE 5.5 – **Axial T2 cerebral MRI image (A) and ODF map superimposition (B) that show a large cystic tumor of the right cerebellopontine angle.** The position of cranial nerves is difficult to predict accurately. The ODF reflects the probability of several fiber orientations at each voxel that allows a high angular resolution diffusion imaging (HARDI).

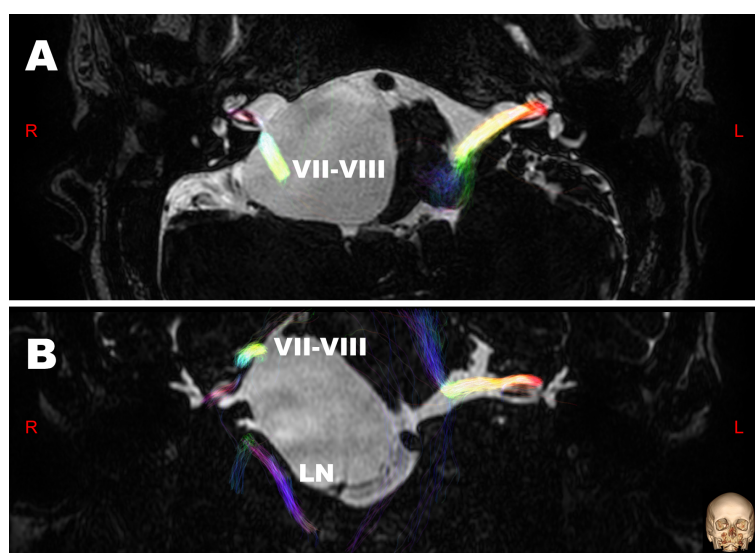


FIGURE 5.6 – **Tractography overlaid on T2 cerebral MRI in axial (A) and coronal (B) views.** The acoustic facial bundle appears displaced posteriorly and superiorly, while the lower nerves are pushed inferiorly.

5.2. CASE 2 - TRACTOGRAPHY FOR SURGICAL STRATEGY IN CASE OF SEVERE CRANIAL NERVE DISPLACEMENT BY A LARGE SKULL BASE CYST

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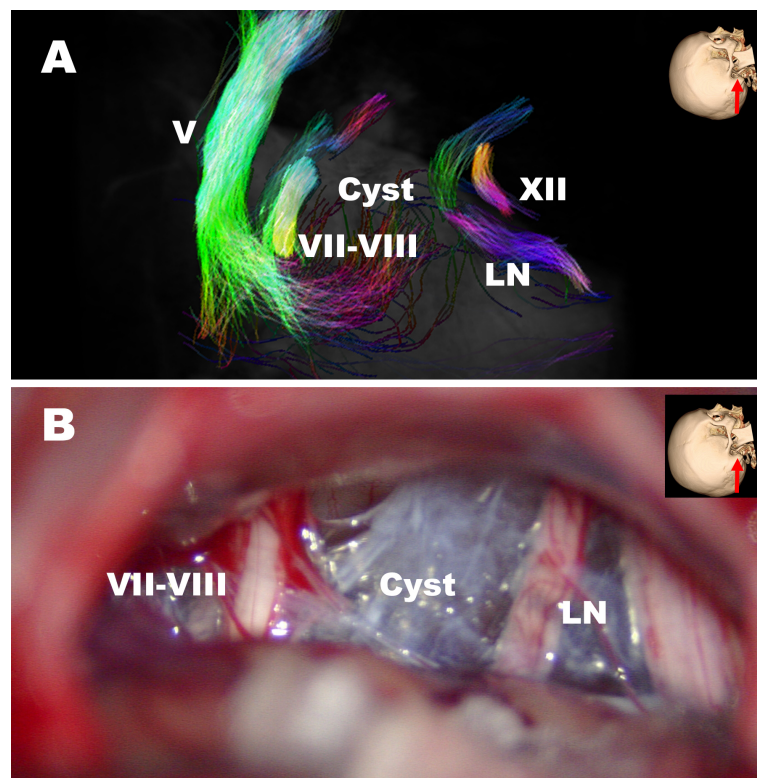


FIGURE 5.7 – **Tridimensional rendering of tractography in surgical position (A) and operative view of the retro-sigmoid approach (B).** Displaying the reconstructed tracts in three-dimensions can help the surgery since it simulates the surgical approach and the predicted position of cranial nerves displaced by the tumor.



## FULL TRACTOGRAPHY

**D**e nouvelles approches sont nées de l'évaluation de l'"état de l'art" en tractographie des nerfs crâniens et de notre expérience de développement d'un *pipeline* dédié utilisant un algorithme probabiliste : ce sont la *full tractography*, le *clustering* et l'*upsampling*. Aussi, la première étude utilisant la technique déterministe *HDFT* (*high definition fiber tracking*) capable de suivre la totalité des nerfs crâniens en condition saine, a été publiée en parallèle de mes travaux, en 2016, par l'équipe du Dr Juan Fernandez-Miranda de Pittsburgh, USA. Cela a motivé mon départ en mobilité internationale pendant un an, dans le *Neuroanatomy and Fiber Tract Lab* de Pittsburgh, USA. Cette méthode *HDFT* s'est révélée efficace mais au prix d'un post-traitement long, complexe et opérateur-dépendant. De plus, notre pipeline probabiliste souffrait d'un mauvais rendu tridimensionnel des tractogrammes. C'est pourquoi, je propose ici une nouvelle approche de *full tractography* ou *full seeding* qui s'affranchit du *design* des ROIs et offre une visualisation tridimensionnelle efficace. Grâce au logiciel DSI Studio, elle permet une reconstruction rapide par algorithme déterministe (*generalized q-ball imaging, GQI*),[109] une segmentation tumorale facile, le *design* d'une région d'exclusion unique et réutilisable, ainsi qu'un filtrage aisé et simple. Le développement de cette nouvelle approche a été facilité par une collaboration étroite avec son développeur, le Dr Yeh. L'application directe en pratique clinique est illustrée ici à travers 2 exemples de tumeurs complexes de la base du crâne.

# Full-brainstem tractography for routine pre-operative planning in skull base surgery.

**Timothee Jacquesson, Fang-Chang Yeh, Sandip Panesar, Jessica Barrios, Arnaud Attyé, Carole Frindel, Francois Cotton, Paul Gardner, Emmanuel Jouanneau, Juan C. Fernandez-Miranda**

*Revision in progress in Journal of Neurosurgery 2018*

## 6.1 Abstract

**Background :** Diffusion imaging tractography has allowed the in vivo description of brain white matter. One of its applications is presurgical planning for brain tumor resection. Due to a limited spatial and angular resolution, it is difficult for fiber tracking to delineate fiber crossing areas and small-scale structures, in particular brainstem tracts and cranial nerves. New methods are being developed but these involve extensive multi-step tractography pipelines including the patient-specific design of multiple regions of interest (ROIs). **Objective :** We propose a new practical full-brainstem tractography method that could be implemented in routine presurgical planning for skull base surgery. **Methods :** A Philips MRI machine provided diffusion-weighted and anatomical sequences for two healthy subjects and two skull base tumor patients. Tractography of the full brainstem, the cerebellum and cranial nerves was performed using the software DSI studio, generalized-q-sampling reconstruction, orientation distribution function (ODF) of fibers, and quantitative anisotropy-based generalized deterministic algorithm. No ROI or extensive manual filtering of spurious fibers was used. Tractography rendering was displayed in a tridimensional space with directional color code. This approach was tested on diffusion data from the Human connectome project (HCP) database. **Results :** The brainstem, the cerebellum, and the cisternal segments of most cranial nerves were depicted in all participants. The tridimensional rendering permitted the visualization of cranial nerve displacement by skull base tumors, thus helping to plan the surgical strategy. **Conclusion :** As opposed to classical ROI-based methods, this novel full tractography approach could enable routine enhanced surgical planning or brain imaging for skull base tumors.

## 6.2 Introduction

The introduction of diffusion imaging tractography has caught the interest of the scientific community by describing for the first time in vivo brain white matter anatomy.[6, 65] The ability to reconstruct white matter fibers from the preferential orientation of water molecules on diffusion magnetic resonance images (MRI) has improved the understanding of both anatomy[32] and neurological disorders.[14, 41, 90] Visualizing the exact displacement of cranial nerves in skull base tumor cases would make surgery safer and, potentially, the clinical outcome better.[42] Though tractography has depicted most white matter tracts, applying this technique to small-scale structures such as cranial nerves and to crossing, merging, and branching fiber areas remains a great technical challenge in terms of spatial and angular resolution. Efforts are, however, currently being made to overcome these technical shortcomings, as is demonstrated by the increasing number of tractography studies attempting to detect facial nerve trajectory around vestibular schwannomas.[11, 19, 21, 36, 39, 88, 102, 115]

Advances in both imaging acquisition and post-processing have been developed to improve the tractography accuracy providing a high angular resolution diffusion imaging (HARDI); these include diffusion spectrum imaging,[101] q-ball imaging[75, 107] or generalized q-sampling reconstruction,[109] constrained spherical deconvolution,[94] and a combination of the aforementioned such as high definition fiber tracking (HDFT).[32] Since the single diffusion tensor model is limited to the detection of a unique fiber trajectory per voxel, tractography has evolved to other models, such as the orientation distribution function (ODF) that can represent several populations of fibers per voxel.[30, 54, 76] Furthermore, probabilistic algorithms yield more accurate depictions of cranial nerve trajectories than deterministic ones;[8, 118] however ‘false continuations’ have limited their application so far.[62]

Above all, accurate cranial nerve tractography requires high spatial resolution. The voxel acquisition size should thus approximate the anatomical diameter of most cranial nerves. However, a 0.5 mm or lower voxel size will reduce the signal-to-noise ratio and will increase both the scanning time and image distortions, particularly at the skull base area.[82, 117] Second, the tracking results would become more dependent upon the skills of the operator, especially the design of regions of interests (ROIs) and manual elimination of spurious fibers.[82, 117] Third, in addition to depicting multiple fiber populations at fiber crossing areas, this high-resolution tractography would involve new calculation methods and long multi-step post-processing.[8] A tractography pipeline for accurate high-resolution cranial nerve needs therefore to be simplified in order to



encourage its routine use for brain imaging and surgical planning.

In the present work, we propose a novel practical full-brainstem tractography approach that includes distortion correction, generalized q-sampling reconstruction, quantitative anisotropy-based deterministic fiber tracking, and tridimensional rendering. We illustrate its application in both healthy and skull base tumor participants.

## **6.3 Material and Methods**

### **6.3.1 Participants**

Two patients with a skull base tumor (one woman; age range : 22-69 years; one right Koss-IV vestibular schwannoma, one left petroclival meningioma), and two ‘healthy’ subjects were included in this study between November 2016 and May 2018. The institutional review board approval was obtained (IRB Number 2015-A01113-46). All participants gave informed consent. They were studied in 6 steps (**Figure 6.1**).

### **6.3.2 Imaging acquisition and pre-processing**

Data were acquired using a 3-Tesla (T) Ingenia (Philips Medical Systems, Best, The Netherlands) MRI machine with the following settings : 32 gradient directions, b-value 1000 s/mm<sup>2</sup>, 2 mm isometric voxels, slice thickness 2mm ; no slice gap, TE/TR 102/3956ms, 26 slices ; single-shot spin-echo sequence ; and scan time 9min52s. A T2 steady state sequence was added as anatomical reference, while a T1 post contrast weighted sequence was used in the cases of skull base tumor to allow manual tumor segmentation. Distortions were corrected using the top-up and eddy tools of the FMRIB software library (FSL) software. Diffusion data were reconstructed using a generalized q-sampling imaging method.(Yeh, Wedeen, et Tseng 2010) The ODF was extracted at each voxel with a mean diffusion scaling parameter of 1.2.

### **6.3.3 Fiber tracking**

A region of avoidance (ROA) was drawn to keep the whole brainstem, the cerebellum, and skull base cisterns and bones (**Figure 6.2**). All supra-tentorial fibers were hence excluded. If required, tumor segmentation was used as a second ROA. No ROI were used for either seeding or tract selection. A deterministic algorithm was applied using DSI Studio software (<http://dsi-studio.labsolver.org>). Fiber tracking used the following parameters : step size 0.1 mm ; fiber length from 10 to 300 mm ; angular threshold 90° ; ‘default’ anisotropy threshold that varied from 0.015 to 0.049. A total of 25,000 tracts

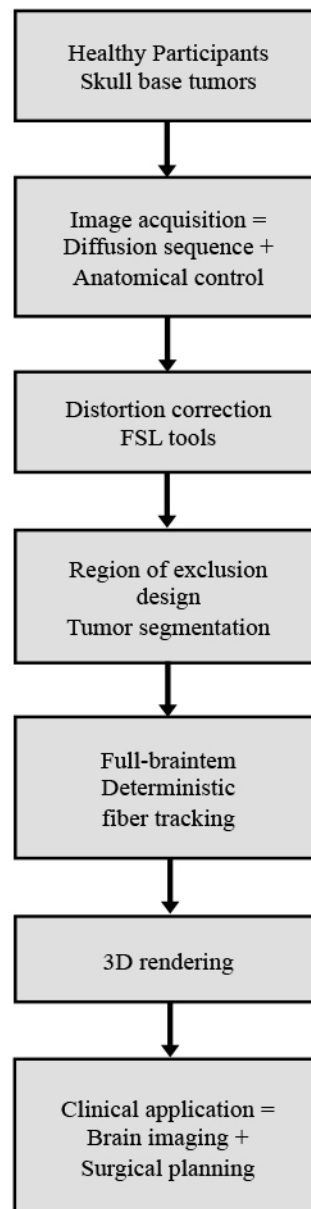


FIGURE 6.1 – **Study diagram.** From a Philips MRI machine and using a dedicated acquisition protocol, we applied a full-brainstem tractography approach that included : distortion correction, region of exclusion design, tumor segmentation if required, ODF-based generalized deterministic algorithm, tridimensional rendering.

were calculated. Fibers were displayed as tubes with a 0.1 mm diameter. The standard directional-encoded color of tractography was kept to incorporate fiber directionality information : The standard directional-encoded color of tractography was kept to incorporate fiber directionality information : ‘green’ for fibers passing anterior-posteriorly or posterior-anteriorly, ‘blue’ for fibers passing superior-inferiorly or inferior-superiorly, and ‘red’ for fibers passing lateral-medial or medial-lateral (**Figure 6.3**). Manual filtering of spurious fibers and false continuations was reduced to a 10-minute maximal time of cleaning. Post-processing in its entirety lasted approximately 20 minutes using a multi-core processor computer (Intel Core® i7, 2.3 GHz, Intel Corporation®, Santa Clara, CA, USA).

#### **6.3.4 Validation**

The final full-brainstem tractography was validated via expert comparison to the known anatomy from specimen dissection.(Ludwig, E. et Klingler, J. 1956; Rhoton 2000) Fiber tracking was performed by a neurosurgeon (T.J.) who had three years of tractography experience. The reliability of the tractography was assessed by a senior neurosurgeon with high-level experience in both neuroanatomy and tractography (J. F-M.). The tracking parameters were kept identical for all participants included in the study, aside from the fractional anisotropy threshold that varied on a subject-specific basis and was selected using a compromise value between maximum anatomical detail and minimum ‘noise’, i.e. false fibers. Last, to assess the reliability and reproducibility of this novel approach, the pipeline was tested on a healthy subject randomly extracted from the Human Connectome Database (HCP, Washington University, St. Louis, United States of America).

### **6.4 Results**

‘Full’ tractography depicting the brainstem, the cerebellum and most cranial nerves was performed in all 4 participants. The tridimensional view offered rotation and magnification on demand. We henceforth describe the findings in detail for healthy conditions followed by skull base tumor cases.

#### **6.4.1 Brainstem and cerebellum**

The three brainstem components were visualized from top to bottom : the mesencephalon with the oblique ‘violet’ fibers of the cerebral peduncles ; the pons with the red transversal pontocerebellar fibers that connect the cerebellum through the cerebellar

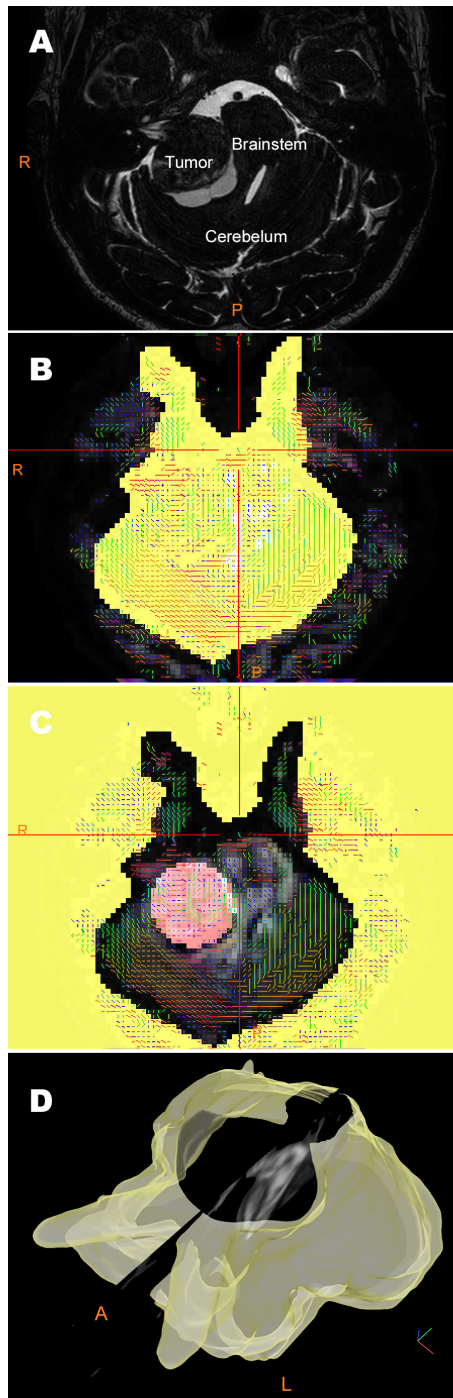


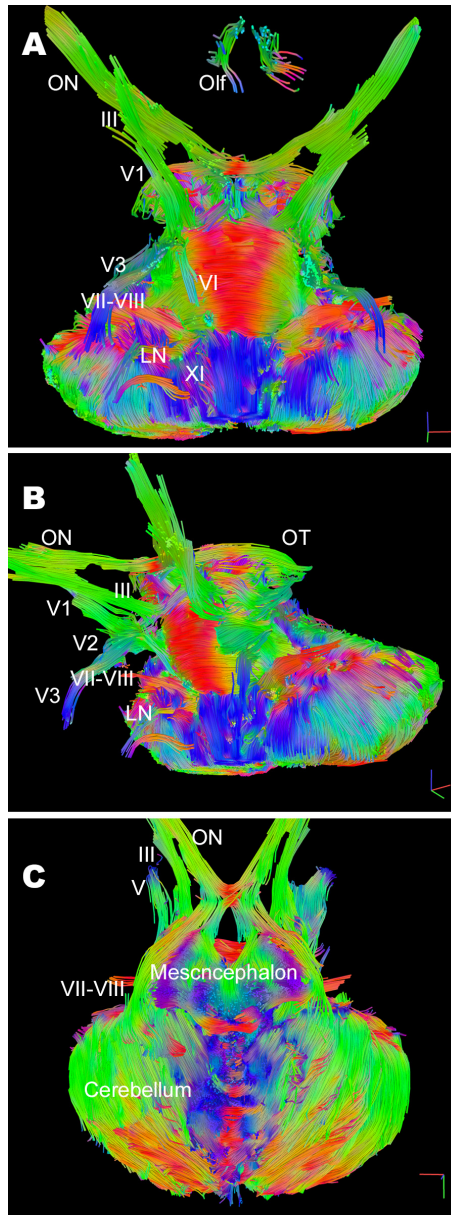
FIGURE 6.2 – **Region of avoidance design.** The brainstem, the cerebellum, and skull base cisterns are identified on T2 anatomical images (axial view, A), then a single ROI is drawn to include all of these on the orientation of distribution function (ODF) map (B) before being negated to create a region of avoidance (ROA) (C). Tumor segmentation was performed separately to add a second ROA if required. No ROI were used. Full-tractography was initiated out of the ROA(s) that reduced the manual step of multiple ROI design. The final workspace of full-tractography is displayed in an oblique tridimensional view (D).

peduncles; and the medulla with the ascending and descending 'blue' sensorimotor tracts (**Figure 6.3**). The pons was framed by the pontomesencephalic and the pontomedullary sulci. At the medulla stage, the 'blue' pyramids and the olives bulged and were separated by the ventral median, the pre- and post-olivary sulci. Superiorly, the mesencephalon was cut just before it connected to the diencephalic brain; its butterfly shape was seen, containing the 'violet' cerebral peduncles laterally, the 'blue' lemnisci medially, and the 'red' colliculus nuclei posteriorly (**Figure 6.3**). Inferiorly, the upper cervical spinal cord was continuous with the medulla 'blue' ascending or descending tracts, which were indistinguishable from one another. The anterior, posterior, and flocculonodular lobes of the cerebellum hemispheres were identified and built its pyramidal shape (**Figure 6.3**). At the midline, the median lobules of the cerebellar vermis were displayed in 'red'. At the cerebellopontine angle, the flocculus was identified just lateral to the emergence of the acoustic-facial bundle and lower nerves (**Figure 6.3 and 6.4**).

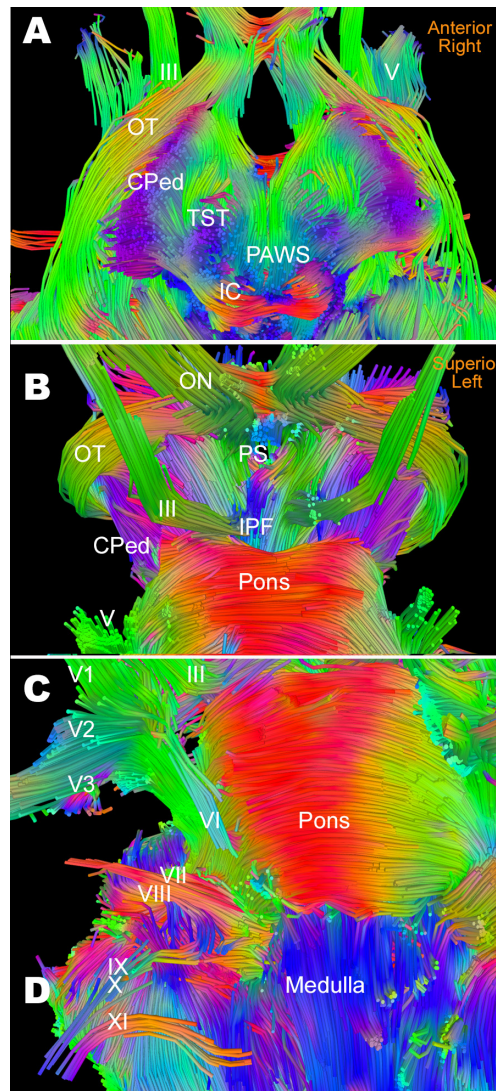
#### 6.4.2 Cranial nerves

The olfactory nerve was not identified aside from a few thin 'green' fibers separating from the optic nerves at a 45° angle and then coursing anteriorly (**Figures 6.3 and 6.5**). Conversely, the optic pathways were well depicted as was the characteristic "X" pattern corresponding to the optic nerves, chiasma, and optic tracts. The 'blue' pituitary stalk came from the posterior edge of the chiasma and dived to the pituitary gland in the homonym fossa. Optic tracts passed around the mesencephalon, though their connection to the lateral geniculate nucleus and colliculi was less depicted. Optic nerves were readily displayed in 'green', including their cisternal, intracanal and intraorbital segments. In the orbit, optic nerves merged with oculomotor and V1 nerves and fanned out within the ocular globe. All of these 'green' intraorbital nerve fibers may be confused with oculomotor muscles : rectus inferior, superior, lateral, or medial.

The oculomotor nerve was well depicted in 'green' from its emergence at the inferior lip of the interpeduncular fossa to its meeting of V1 at the superior orbital fissure (**Figure 6.4**). The trochlear nerve was hard to identify because of its very small relative diameter. A few fibers came from the posterior side of the mesencephalon to meet cranial nerves III and V1, and these corresponded to nerve IV (**Figure 6.6**). The trigeminal nerve emerged at the lateral side of the pons and coursed straight anteriorly. After the short straight 'green' cisternal segment, the trigeminal nerve flattened to assume the characteristic shape of the trigeminal ganglion, plated against the petrous apex and the lateral wall of the cavernous sinus. From a lateral view, its three glove-finger-like divisions were distinguished : the ophthalmic nerve (V1) crossed superiorly towards



**FIGURE 6.3 – Full-brainstem tractography of a ‘healthy’ subject.** These diffusion data acquired on a Philips MRI machine led to reconstruct a much longer segment of cranial nerves (inferior and oblique views, respectively A and B); for instance, the orbital portion of optic (ON) and oculomotor nerves (III) and the cavernous portion of the trigeminal nerve with its three branches (V1, V2 and V3). The third cranial nerve trajectory was first slightly descending, probably due to its usual course within the vascular pinch of basilar termination arteries, and was then oblique anteriorly and laterally, before entering the orbit. The right abducens nerve (VI) was identified; as well as thin fibers circumvented the cerebral peduncles that corresponded to the trochlear nerve (IV). Cranial nerves that belong to the acoustic-facial (VII-VIII) or lower bundles (LN) can be distinguished. A few fibers of the olfactory nerve can be found although its emergence at the anterior perforating space is not seen. Some rootlets of the hypoglossal nerve at the pre-olivary sulcus are observed, as well as the ascending branch of the accessory nerve (XI). Mesencephalon was correctly reconstructed (superior view, C) contrary to the medulla oblongata in which ascending/descending fibers were missing.



**FIGURE 6.4 – Full-brainstem tractography magnification of the mesencephalon contents, the interpeduncular fossa, and the cerebellopontine angle.** Full-brainstem tractography provided a unique insight of the true anatomy of the brainstem, the cerebellum, and cranial nerves. A sectional cut at the upper level of mesencephalon allowed visualization of its gross architecture, such as : oblique cerebral peduncles (CPed) in ‘violet’, ascending spinothalamic (STT) or descending corticospinal tracts in ‘blue’, colliculus nuclei (inferior colliculi : CI) in ‘red’, and fibers coursing anteriorly that could match with oculomotor nerves in ‘green’ (superior view, A). The interpeduncular fossa (IPF) is well identified between the 2 cerebral peduncles (CPed) and the chiasma (meeting point of optic tracts, OT, and optic nerves, ON) while the oculomotor nerves (III) emerge at the inferior edge of the triangle and the pituitary stalk (PS) dives anteriorly (anterior view, B). The cerebellopontine angle is drawn with the flocculus and the emergence of the acoustic-facial bundle (VII-VIII) and the lower nerves (LN). Above, the trigeminal nerve courses anteriorly and divides into three branches (V1, V2, and V3). The abducens nerve (VI) crosses from the pontomedullary sulcus just medially to the trigeminal nerve. The facial nerve can be distinguished from the cochlear nerve (anterior view, C). The accessory nerve (XI) can also be separated from the glossopharyngeal (IX) and the vagus nerves (X). A few fibers of the hypoglossal nerve (XII) can be seen at the pre-olivary sulcus.

the orbit; the maxillary branch (V2) went anteriorly towards the pterygopalatine fossa; the mandibular branch (V3) dived inferiorly towards the infratemporal fossa (**Figures 6.3-6**). In terms of diameter and length, the trigeminal nerve was the largest cranial nerve depicted.

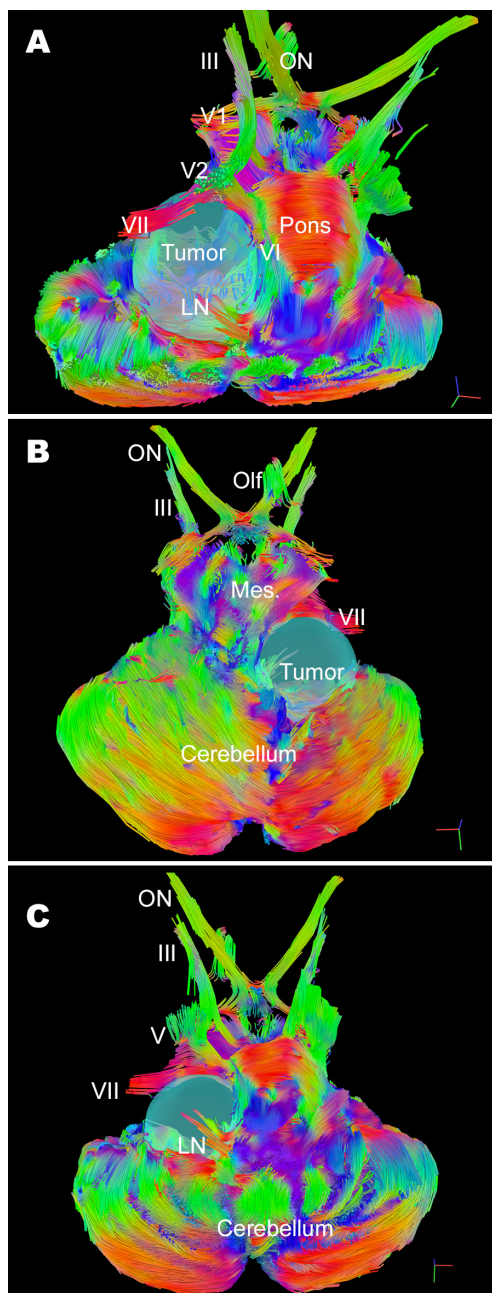
The abducens nerve was seen emerging from the median pontomedullary sulcus before coursing obliquely, superiorly and laterally, to join the V1 and the oculomotor nerves. Its 'blue' cisternal part was followed as it stayed close to the pons, but the trajectory was lost as the nerve entered within the dura fold of Dorello's canal. The components of the acoustic facial-bundle emerged at the cerebellopontine angle, just medial to the flocculus, and crossing laterally in 'red' towards the petrous pyramid. The cochlear and facial nerves could be less distinguished from one another (**Figures 6.4 and 6.6**), but the diffusion signal dropped at the porus of the internal acoustic meatus that made intracanalicular fibers difficult to detect.

The lower cranial nerves were displayed as a group of rootlets passing laterally and inferiorly, from 'red' to 'blue'. They left the post-olivary sulcus at the pontomedullary level to curve anteriorly and inferiorly into the jugular foramen (**Figure 6.4**). The glossopharyngeal and vagus nerves were not separated, although the ascending cervical root of the accessory nerve could be seen. Several rootlets of the hypoglossal nerve were observed between the olive and the pyramid (**Figures 6.3-5**).

#### 6.4.3 Illustrative case 1

A 22-year-old man presented with a large right Koos-4 vestibular schwannoma compressing the brainstem and expanding the internal acoustic meatus. The acoustic-facial bundle was not identified on T2 'constructive interference steady state' images. The trigeminal nerve seemed to be pushed superiorly while the lower nerves were displaced inferiorly, as it is usually the case in vestibular schwannomas. Full-brainstem tractography allowed the visualization of the facial nerve, which was completely flattened at the anterior-superior side of the tumor (**Figure 6.6**). The lower nerves were also identified at the anterior-inferior tumor margin, as well as the trigeminal nerve superiorly. Because of the large tumor volume and total right hearing loss, a surgical gross-total removal was performed using a trans-labyrinthine approach. The anterior-superior position of the facial nerve was confirmed intraoperatively by both visualization and electro-myographic monitoring. Postoperatively, the facial motor function was preserved while left-sided deafness resulted as expected. This illustrates the value of such a tridimensional (3D) view of a skull base tumor in its anatomical environment with displaced cranial nerve position, which would help the surgeon to create a mental map before the surgery and





**FIGURE 6.5 – Full-brainstem tractography of a large left vestibular schwannoma.** In this case, a large right Koos-4 vestibular schwannoma compressing the brainstem and expanding the internal acoustic meatus, the acoustic-facial bundle (VII-VIII) was not identified on T2 ‘constructive interference steady state’ images. The trigeminal nerve seemed to be pushed superiorly and the lower nerves (LN) displaced inferiorly (inferior view, A). Full-brainstem tractography allowed the visualization of the facial nerve at the anterior-superior side of the tumor (video and oblique view, B), while the lower nerves (LN) were pushed inferiorly (superior view, C). Relationships with the trigeminal branches (V1, V2 and V3) and the abducens nerve (VI) were also detailed while the optic (ON) and oculomotor nerves (III) are well identified.

to make it safer. He could adjust the resection steps taking care dissecting the tumor capsule when close to the expected position of the nerves (Supplemental content 1 : 3D stereoscopic view 1).

#### **6.4.4 Illustrative case 2**

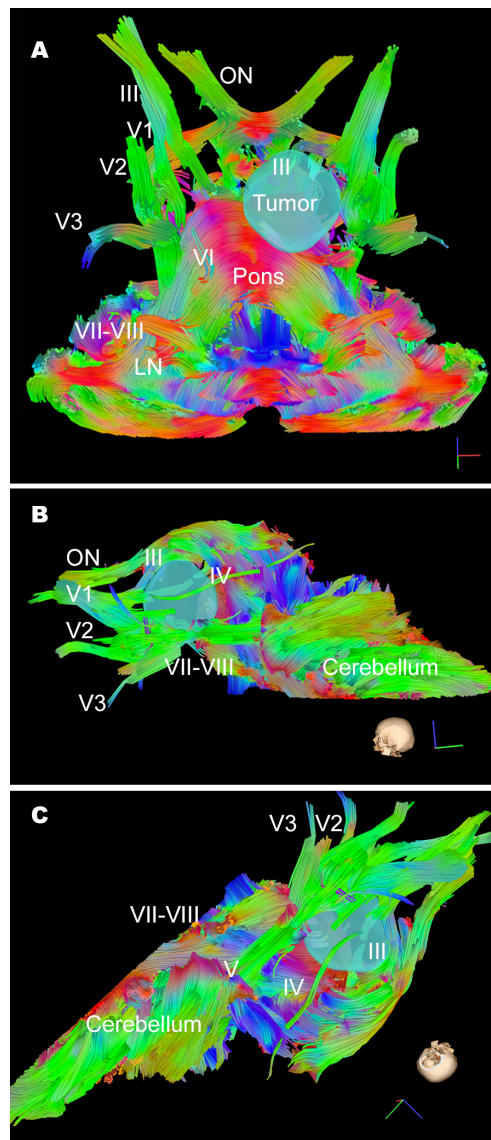
A left-sided upper petroclival meningioma was found in a 69-year-old woman with slight balance disorder and diplopia on the leftward gaze. On classical T2 images the oculomotor nerve was severely displaced but not identified, and the trigeminal and abducens nerves crossed closely at the inferior medial tumor margin. Full-brainstem tractography depicted the trajectory of the oculomotor nerve that was displaced superiorly while the position of cranial nerves V and VI was clearly defined (**Figure 6.7**). The 3D rendering allowed to choose the best surgical approach and to anticipate cranial nerve displacement. A safe gross-total removal was performed without any postoperative neurological deficit (Supplemental content 2 : 3D stereoscopic view 2).

#### **6.4.5 HCP database**

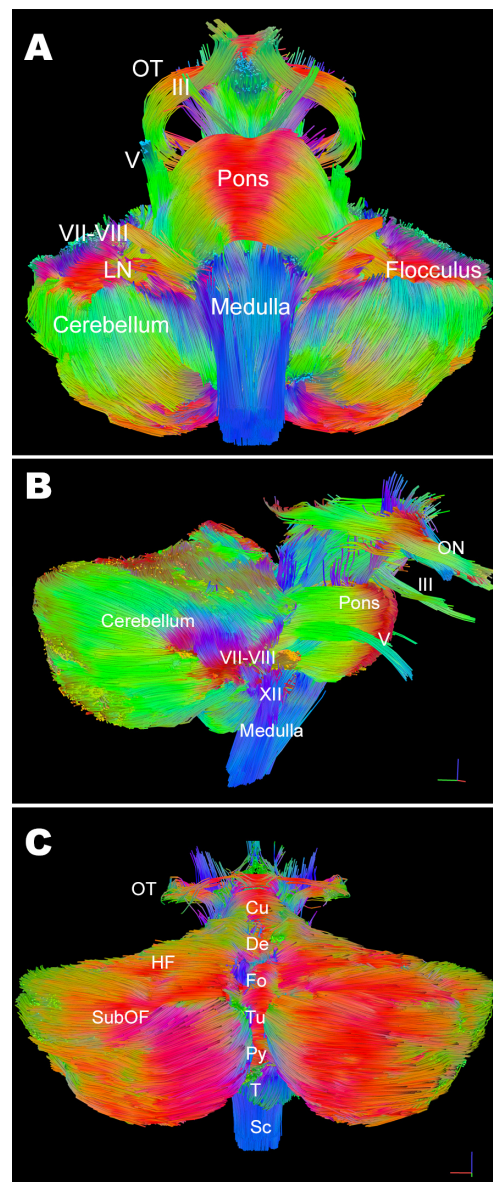
Using diffusion data of a random healthy subject from the HCP database, this full-brainstem approach provided more smoothed and adequate insight of the brainstem and the cerebellum (**Figure 6.7**). The three stages of the brainstem were well identified, in addition to the cerebellar lobes including the horizontal and sub-occipital fissures and their horizontal strips turning ‘red’ to ‘green’. However, loss of diffusion signal was found that resulted in a shortening of all cranial nerve trajectories after emerging the brainstem. The olfactory, trochlear, abducens, and hypoglossal nerves weren’t seen, although the cochlear and facial nerves could be distinguished from one another (**Figure 6.7**). The cerebral peduncles were trimmed because corticospinal tracts were cut over the design of the region of avoidance design.

### **6.5 Discussion**

This work presents a novel full-brainstem tractography approach using various MRI acquisition protocols and simplified post-processing without extensive manual filtering and ROI seeding. This approach provides an original tridimensional insight into in vivo anatomy of the brainstem, the cerebellum, and cranial nerves. For skull base tumors, the displacement of cranial nerves can be more adequately depicted to help surgical strategy. Furthermore, the rapid and accessible tractography pipeline proposed herein appears usable in a routine radiological and pre-surgical practice.



**FIGURE 6.6 – Full-brainstem tractography of a left petroclival meningioma.** In this case, a left-sided upper petroclival meningioma, the oculomotor nerve was not clearly identified on standard T2 images, even if the trigeminal and abducens nerves were guessed crossing at the inferior medial tumor margin. Full-brainstem tractography depicted the oculomotor nerve (III) trajectory superiorly and the relationships between the tumor and cranial nerves IV, V, and VI (inferior view, A). The three trigeminal branches (V1, V2, and V3) were recognized including their cavernous and foramen segments through the skull base, as well as the optic nerves including their intraorbital segment (ON). A few fibers of the trochlear nerve (IV) can be seen, circumventing the cerebral peduncles (lateral view, B). The acoustic-facial bundle (VII-VIII) and the lower nerves (LN) were identified and distinguished from one another on both sides. The tridimensional rendering allowed to mimic the surgical approach and choose the best one (oblique view, C).



**FIGURE 6.7 – Full-brainstem tractography approach applied on a healthy subject from the human connectome project database.** These data from the human connectome project database allowed visualization of the tridimensional anatomy of the brainstem and the cerebellum. The three stages of the brainstem were adequately seen despite the few fibers of the cerebral peduncles (anterior and lateral view, respectively A and B). The pyramidal shape of the cerebellum was reconstructed with many anatomical landmarks, such as : horizontal (HF) and sub-occipital fissures (SubOF), hemispheres, tonsils, median lobules (Cu : culmen, De : declive, Fo : folium, Tu : tuber, Py : pyramid, T : tonsils), flocculus and cerebellopontine angle (posterior view, C). The culmen presented an expected ascending orientation. The third (folium) was found as a groove between the cerebellar hemispheres. The cisternal portions of the oculomotor (III), trigeminal (V), acoustic-facial (VII-VIII), and lower nerves (LN) were displayed. Conversely, the olfactory, trochlear, abducens, and hypoglossal nerves were not tracked. At the superior part, the optic tracts (OT) and nerves (ON) were identified on both sides of the chiasma. At the inferior part, the reliefs of both the medulla and the spinal cord (Sc) were identified.

### 6.5.1 Trageted versus Full tractography

Although tractography is becoming more popular, as attests the increasing number of studies published in this field, only a few studies have focused on the tractography of all cranial nerve and brainstem.[42, 64, 91, 110] In 2010, Hodaie et al. reported the first attempt to track the all isolated cranial nerves. They were able to depict the cisternal trajectory of cranial nerves II, III, V, VI, VII/VIII and X, using multiple ROI seeds and multiple FA thresholds to reduce the discarding of erroneous tracts.[42] In 2016, Yoshino et al. described for the first time the cisternal trajectory of all cranial nerves in healthy subjects using a tractography pipeline named ‘high definition fiber tracking’ (HDFT). This method combined several HARDI ones and involved multiple ROI seeds and manual deletion of false fibers.[110] In 2016, Meola et al. provided the first tractography study of the brainstem excluding cranial nerves on the basis of a 488-subject atlas from the HCP database. They reported a deterministic Runge-Kutta interpolation followed by a super-selective fiber tracking with manual filtering according to the “known anatomical knowledge”. In addition to extensive user-related steps, this study did not depict cranial nerve trajectories or anatomical change induced by tumors.[64] In 2018, Tang et al. reported a probabilistic atlas of normal human brainstem pathways based on the HCP database. They used a multi-step post-processing pipeline including among others : track-density imaging, multiple ROIs manual delineation for each tract, ODF-based reconstruction, whole brain probabilistic algorithm, and filtering algorithm based on topographic regularity.[91] This brainstem tractography study provided a useful anatomical reference, although the complex post-processing did not allow its use in a clinical environment and no tumor case was included.

Finally, no study has focused on tractography of the brainstem, the cerebellum, and cranial nerves together; and none has provided a comprehensive, easy, and useful tridimensional rendering of the whole posterior cranial fossa tractography in both healthy and tumor conditions.

### 6.5.2 Towards routine tractograpy use

Most of recent studies of tractography used “research” MRI machines with acquisition protocol that could not be transferred in a clinical environment at this time. We thus limited the acquisition protocol to only a diffusion sequence and an anatomical T1 or T2 control, and we chose the settings that could be used in a clinical population (**Table 6.1**). Hence, 32 gradient directions were sufficient for tracing cranial nerve trajectories and to depict the gross anatomy of posterior cranial fossa contents. The acquisition time was

reduced secondary to faster methods, such as multiband acquisition[31] and to a smaller size of the acquisition box that can be tailored to exclude the supratentorial portion of the brain. Last, the correction of distortion was performed using FSL tools and then automated.

The post-processing time remains a key point of the tractography pipeline, which is infrequently reported possibly because it can take hours and even days. Among the numerous recent clinical tractography studies, only three detailed calculation time, which varied from 3 to 28 hours.[8, 118] The optimal trade-off between acquisition time, HARDI post-processing methods, and tracking results is not agreed upon for use in a clinical population.[8] Bearing these issues in mind, we propose to reduce the user-related steps of deterministic tractography : ROI design and manual elimination of spurious fibers. Subsequently, no ROIs were used but instead replaced by a large ROA to include only the brainstem, the cerebellum, and cranial nerves. The tracking parameters were adjusted to the anatomy of cranial nerves (usual length, maximal curvature) and then kept unchanged.

Tractographic rendering is highly variable depending on the ability of software to depict cranial nerves, anatomical environment, and tumor in three dimensions. Contrary to tracking results that are mostly obtained by experimented users,[11, 39, 82] we propose a simplified method that any surgeon or radiologist can understand and use. In addition to easy-to-use tractography steps, the software DSI Studio offers a tridimensional insight that displays effectively most cranial nerves trajectories in healthy subjects or when displaced around skull base tumors.

To summarize, the six points that helped us make both acquisition and post-processing simpler to allow a routine clinical use are : (1) a reduced number of acquisition sequences (diffusion and anatomical control), (2) an acquisition-box size limited to the posterior cranial fossa, (3) an automated correction of image distortion, (4) a single ROA without multiple ROIs, (5) optimized unchanged tracking parameters, and (6) a readable 3D tractography rendering.

### 6.5.3 Limitations and future directions

Given the size of cranial nerves, that ranges from 0.2 to 10 mm, and the potential modification of the anatomical features of cranial nerves flattened around tumors, the 2 mm voxel size of standard cerebral MRI diffusion sequence is not suitable for the thinnest nerves. However, both higher angular (gradient directions) and spatial resolutions (voxel size) would require specific MRI machines and extensive calculation time that do not match with a clinical use. Cranial nerve tractography, therefore, requires new

|                        | Parameters                      | Value/Comment                                                                             |
|------------------------|---------------------------------|-------------------------------------------------------------------------------------------|
| <b>MRI Acquisition</b> | MRI Machine                     | Philips                                                                                   |
|                        | Diffusion gradient directions   | 32                                                                                        |
|                        | Slice thickness (mm)            | 2                                                                                         |
|                        | b-value (s/mm <sup>2</sup> )    | 1000                                                                                      |
|                        | Magnetic field (Tesla)          | 3                                                                                         |
|                        | Voxel reconstruction            | Isotropic                                                                                 |
|                        | Anatomical reference(s)         | High-resolution T2-weighted imaging                                                       |
|                        | Box Anatomical limits           | Thalamus to <i>foramen magnum</i>                                                         |
| <b>Tracking</b>        | Geometric dist. correction      | Topup and eddy FSL tools                                                                  |
|                        | Basis of reconstruction         | ODF map                                                                                   |
|                        | Software                        | DSI Studio                                                                                |
|                        | Fractional anisotropy threshold | 'default' (0.015-0.049)                                                                   |
|                        | Curvature threshold             | 90°                                                                                       |
|                        | Minimal/maximal length          | 10-300 mm                                                                                 |
|                        | Step size                       | 0.1                                                                                       |
|                        | Algorithm                       | Euler / streamline deterministic                                                          |
|                        | ROI design                      | Negate a unique large ROI that encases the full brainstem, cerebellum, and cranial nerves |
|                        |                                 |                                                                                           |

*Dist.: distortion, ODF: Orientation distribution function.*

TABLE 6.1 – **Diffusion acquisition and tracking parameters.**

post-processing methods to increase the final working resolution, and one potentially interesting method is upsampling.[87] Furthermore, a 2-mm MRI resolution means that each voxel containing cranial nerves may also be occupied by cerebrospinal fluid or tumor, and this uncertainty is addressed by probabilistic algorithms. These use repetitive sampling to extract the probability of fiber ODFs to reconstruct white matter tracts and thus yield a better delineation of cranial nerve trajectories.[8, 59, 63, 118] Comparing full-brainstem deterministic tractography to a probabilistic algorithm could be of great interest for demonstrating the reconstruction of other segments of cranial nerves : through the skull base or within the brainstem.

Thanks to previous tractography studies of the brain white matter architecture,[32] this technique is becoming more familiar to the neurosurgical community. Nonetheless, the post-processing methods required for applying it to cranial nerves requires computer power and skills. In addition, tractography varies upon both MRI acquisition and tracking parameters, such as angle threshold, fractional anisotropy threshold, step size, algorithm, and 3D rendering.[118] Obviously, the neurosurgeon does not need to understand all

the subtleties of tractography to use it in a surgical strategy, and therefore advances in computer science are needed to help with post-processing, such as automation,[18] machine learning,[69] or artificial intelligence. The rendering of tractography is less readable for the neurosurgeon unfamiliar with it. Furthermore, providing an adequate tridimensional insight of cranial nerves within a normal or tumor environment requires multiple steps and considerable post-processing time.[42, 110, 118] The readability of tractography could be improved by providing, at the end of the post-processing pipeline, a simple 3D movie or 3D pdf file that could display the brainstem, the cerebellum, the tumor and cranial nerves. Consequently, understanding of the final results would be easier and this technique could thus be spread to the scientific community. Moreover, the tractographic results can potentially be incorporated into virtual reality simulation software for pre surgical planning, and into image guidance platforms for intraoperative use.

As only a limited number of participants in the present report, it is necessary to evaluate its value, particularly in a wider variety of tumor types, which have different cranial nerve displacement configurations, and by multiple operators with diverse backgrounds to assess its robustness for future clinical use.

## **6.6 Conclusion**

We propose herein a simplified full tractography approach that allows in vivo tridimensional visualization of the individual patient's anatomy of the brainstem, the cerebellum, and cranial nerves. This novel approach could allow routine enhanced surgical planning or brain imaging in case of variations induced by skull base tumors.





## DISCUSSION

**L**a discussion de ces travaux tient en 2 parties, la première justifie mes choix méthodologiques, notamment dans l'étude clinique, la seconde revient sur les obstacles et limites liés à la technique de tractographie.

## 7.1 Choix méthodologiques

### 7.1.1 Séquence d'acquisition IRM

En suivant l'exemple des études réalisées par l'équipe de Grenoble sur la tractographie de la portion extra-crânienne du nerf facial dans les tumeurs de la parotide,[3] j'ai pu d'emblée définir la séquence d'acquisition IRM utile et ajustée pour une machine « Philips 3T Achieva » : T1 avec injection de Gadolinium, 250 images, crâne entier, épaisseur de coupe 1mm (contrôle tumoral); T2 *THRIVE* 132 images, fosse crânienne postérieure (FCP), épaisseur de coupe 0.5 mm (contrôle anatomique), TOF Angio, 120 images, FCP (environnement vasculaire et distinction nerf-vaisseau); diffusion, 26 images 32 directions, épaisseur de coupe 2mm avec voxels isotropes (tractographie); 26 images *B0* dans les sens AP et PA (correction des distorsions). Cela m'a permis d'établir rapidement le protocole d'étude, de le soumettre au Comité de Protection des Personnes, puis de démarrer les premières inclusions de patients dont les résultats préliminaires ont permis d'optimiser les paramètres de *tracking*.

### 7.1.2 Logiciels de tractographie

Il existe de nombreux logiciels capables de réaliser le post traitement de tractographie. La plupart de ces logiciels ont été développés pour la tractographie des faisceaux de substance blanche du cerveau, avec souvent une reconstruction préalable d'un tractogramme du cerveau complet suivi d'une dissection virtuelle faisceau par faisceau (Trackvis, 3D slicer). Certains ont été développés par des industriels pour une application clinique directe avec un format propriétaire, d'autres sont en libre accès *online* et souvent portés par un ou plusieurs développeurs et/ou une communauté *web*.

Le logiciel **Mrtrix3** a été choisi initialement pour plusieurs raisons : il utilise un algorithme probabiliste qui a montré des aptitudes à surpasser les difficultés classiquement retrouvées en tractographie du cerveau,[94] il est disponible en accès libre gratuit, il présente des possibilités d'automatisation de l'ensemble du *pipeline* depuis la conversion des images sources DICOM jusqu'à la visualisation de la tractographie, son langage source est « ouvert » avec une communauté web de développeurs dynamiques (<http://community.mrtrix.org/>) qui ouvre des perspectives d'amélioration continue. toutefois, la visualisation tridimensionnelle des tractogrammes reste imparfaite et son utilisation enlignes de commandes nécessite des compétences informatiques.

Le logiciel **DSI Studio** a été retenu dans un second temps puisqu'il est développé dans l'équipe de Pittsburgh, leader de la tractographie, où j'ai réalisé une mobilité internationale. Ce logiciel permet le déroulement complet des étapes de la méthode *high definition fiber tracking* développée par cette équipe, la seule à avoir permis la description du trajet cisternal de tous les nerfs crâniens en condition normale/saine. DSI Studio apparaît complémentaire de Mrtrix3 puisqu'il utilise une approche déterministe rapide 'generalized q sampling imaging' avec un rendu tridimensionnel final très performant. Le développeur initial, le Dr. Frank Yeh [109] fait partie intégrante du Fiber tract lab de Pittsburgh, ce qui a permis de collaborer sur des pistes de développement potentiel pour l'application clinique de la tractographie des nerfs crâniens (cf. chapitre 6). Le Dr Yeh poursuit activement l'amélioration de son support avec des mises à jours parfois pluri-mensuelles, des tutoriels, des lignes de commandes et des liens vers d'autres plateformes notamment pour les analyses de connectométrie (*CIRCOS circular genome data visualization* [//www.circos.ca/](http://www.circos.ca/)). Néanmoins, la correction des distorsions n'est pas automatisée et moins performante.

### 7.1.3 Optimisation des paramètres de tracking

Les données issues des 10 premiers patients inclus dans l'étude clinique ont permis d'optimiser les paramètres de *tracking*. A l'aide de la *Virtual Imaging Platform* (VIP) hébergée par le laboratoire CREATIS, l'impact de chacun des paramètres sur le tractogramme final a été évalué. Grâce à la puissance de calcul offerte par la plateforme, plusieurs simulations ont été menées en même temps en faisant varier un seul paramètre à la fois selon un échantillon de valeurs possibles. Ainsi, les valeurs suivantes ont été testées : seuil de FA (0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.35, 0.4), angle maximal de courbure en degré (30, 40, 50, 60, 70, 80, 90), longueur minimale des fibres en mm (1, 5, 10, 15, 20), nombre de fibres à reconstruire (100, 200, 300, 500, 1000, 2000). Le nombre maximum de fibres à générer correspondait à  $10 \times$  nombre de fibres à reconstruire. Le meilleur paramètre a été retenu selon un compromis entre 3 critères : nombre de fibres obtenu, dispersion des fibres et cohérence anatomique. Le nombre de fibres devait se rapprocher de celui estimé en fonction du diamètre anatomique de la portion cisternale des nerfs crâniens (cf chapitre 4). La dispersion a été mesurée par la distance au centroïde établi comme le point central de la portion cisternale du nerf crânien. La dispersion était alors la moyenne des distances euclidiennes de chaque coordonnée de fibres au centroïde du nerf. La cohérence anatomique correspondait à la validité du tractogramme obtenu en fonction de l'anatomie connue du nerf crânien ciblé.[77]

### 7.1.4 Patients tests et patients non opérés

L'inclusion des 10 premiers patients de l'étude clinique pour l'optimisation des paramètres de tracking ainsi que celle des patients non opérés pourrait constituer un **biais de sélection**. En effet, des patients pour lesquels les paramètres de *tracking* n'étaient pas fixes ou pour lesquels il n'était pas possible d'avoir un contrôle de la vérité-terrain lors de la chirurgie ont été inclus. Néanmoins, la position détectée par la tractographie est restée globalement inchangée avant et après l'analyse *VIP*, et l'optimisation a permis de définir le meilleur jeu de paramètres en terme de visualisation et de précision anatomique. De plus, puisque la série de cas a permis de montrer l'impact de la tractographie sur la stratégie de prise en charge des tumeurs de la base du crâne, il est apparu intéressant de conserver les patients non opérés chez qui la technique avait justement orienté la décision chirurgicale vers une attitude de surveillance (cf chap. 4).

### 7.1.5 Groupes de nerfs crâniens

Les nerfs crâniens olfactif (I) et (XII) ont été exclus de l'analyse car trop souvent en dehors de la boîte d'acquisition IRM et peu concernés par les tumeurs de la base du crâne incluses dans la série de cas. Le nerf trochléaire a également été exclu de l'analyse car son diamètre très fin  $\sim 1\text{mm}$  ne permettait pas toujours de le voir en imagerie T2, même haute résolution. Il n'y avait donc pas de placement de ROI ni de contrôle anatomique fiable. Les nerfs crâniens ont été rassemblés en **6 groupes** ou paquets selon leur disposition anatomique : chiasma optique (II), nerf oculomoteur (III), nerf trijumeau (V), nerf abducens (VI), paquet acoustico-facial (VII-VIII), nerfs mixtes (IX-X-XI). Même si la précision de la tractographie s'est améliorée avec mon expérience à travers le temps, il n'était pas possible de discriminer les nerfs au sein des groupes VII-VIII et IX-X-XI au début de l'étude.

### 7.1.6 Objectifs et critères de jugement

2 objectifs ont été retenus pour la série de cas.

- **L'objectif 1** était l'étude de la fiabilité du *pipeline* de tractographie des nerfs crâniens, du côté controlatéral sain, pour chaque patient. Le critère de jugement 1 était le nombre de nerfs crâniens ( $n=1-6$ ) correctement identifiés du côté sain. Un nerf crânien était identifié si la tractographie représentait des fibres correspondant à sa position attendue selon l'IRM en pondération T2 haute résolution.
- **L'objectif 2** était l'étude de la faisabilité du *pipeline* de tractographie appliqué électivement aux nerfs crâniens modifiés par la tumeur (au contact, déplacé, étiré, ou englobé). Le critère de jugement 2 était le nombre de nerfs crâniens  $n$  correctement identifiés du côté pathologique, parmi le(s)  $X$  nerf(s) identifié(s) comme modifié(s) par la tumeur. Un **objectif 2 secondaire** était la comparaison entre la *position attendue* selon la tractographie IRM et la **position réelle** peropératoire des nerfs crâniens électivement modifiés, à l'aide du microscope et de la stimulation électrique.

### 7.1.7 Tests statistiques

La position des nerfs crâniens a été définie en 7 possibilités : antérieure, postérieure, supérieure, inférieure, latérale, médiale, non identifiable. Pour le nerf facial, la position était décrite selon la classification de Sampath,[85] classiquement utilisée dans les études de la position du nerf facial dans les schwannomes vestibulaires : antérieur, antéro-supérieur, antéro-inférieur et postérieur, intra-tumoral, non identifiable. Cette

nuance avait pour but de permettre une comparaison de mes résultats avec les autres études décrivant spécifiquement la position du nerf facial déplacé par les schwannomes vestibulaires. Les positions attendue et réelle ont été comparées via un **test statistique de concordance de Kappa** assorti de son test de Kappa de Cohen. La position des nerfs VII dans les schwannomes vestibulaires a été analysée à part. Les tests statistiques ont été conduits via le logiciel SPSS® avec au seuil de significativité de 5%.

### 7.1.8 Approche par nerf

J'ai choisi de rapporter la faisabilité et la précision de la tractographie selon une **approche par nerf**, c'est-à-dire en évaluant la technique de tractographie appliquée aux nerfs crâniens électivement modifiés par une tumeur de la base du crâne, et non en fournissant un taux de visualisation par patient pour un nerf crânien ciblé. Ce choix est venu du constat de l'hétérogénéité des critères de jugement dans les autres études de tractographie des nerfs crâniens. En effet, le **taux de visualisation** rapporté dans la majorité des études (cf chapitre 3) faisait référence soit au pourcentage de patients chez qui un nerf ciblé est correctement visualisé,[11, 39, 88] soit au pourcentage de nerfs crâniens correctement visualisés dans un pool de patients.[118] Cela a induit un **biais de mesure** avec une potentielle surestimation de l'efficacité de la technique. Néanmoins, cette approche par nerf rend plus difficile la comparaison de nos résultats avec les autres études.

### 7.1.9 Paquet acoustico-facial ou nerf facial

Dans les tumeurs de type schwannomes, la tumeur se développe à partir de la gaine du nerf constituée de cellules de Schwann. Dans le cas particulier des schwannomes vestibulaires, la croissance tumorale entraîne une destruction du nerf vestibulaire puis du nerf cochléaire au cours du temps, ce qui explique les symptômes les plus fréquemment associés : vertiges, acouphènes, troubles de l'équilibre, surdité. Le nerf facial est le plus souvent préservé ce qui en fait un enjeu majeur du pronostic fonctionnel pendant et après la chirurgie. Ainsi, le groupe « paquet acoustico-facial » devient celui du « nerf facial » dans les schwannomes vestibulaires. Ce qui n'est pas le cas pour les autres tumeurs où les 4 nerfs du paquet acoustico-facial restent groupés en cas de déplacement/étirement, sans destruction de l'un de ses composants. Il peut s'agir d'un **biais de confusion** qu'il convient de préciser.

## 7.2 Limitations liées à la tractographie

### 7.2.1 Variations inter- et intra-observateur

Une des principales limites inhérente à la technique de tractographie reste la dépendance à l'opérateur. Depuis le choix des paramètres de tracking jusqu'au positionnement des ROIs en passant par la lecture des tractogrammes, l'analyse peut largement varier d'un opérateur à l'autre. Du fait du niveau et de la multiplicité des compétences requises, il reste difficile de réunir plusieurs opérateurs à compétence comparable en tractographie. C'est pourquoi, l'analyse en aveugle avec plusieurs opérateurs n'a pas été possible dans notre étude. Il est à noter que la variation inter-observateur des résultats n'a été qu'exceptionnellement recherchée dans la littérature.[110] Par ailleurs, on peut aussi suspecter une variation intra-observateur au cours du temps selon l'inévitable courbe d'apprentissage. Par exemple, une différence de 1 cadran dans la position du nerf facial décrite dans les schwannomes selon la classification de Sampath est tout à fait possible, et ceci autant entre 2 mesures d'un même observateur que entre 2 observateurs pour une même mesure (**biais d'observation**). Afin de renforcer la reproductibilité et la puissance statistique de nos résultats dans de futures études de tractographie, il faudrait envisager une lecture en aveugle des tractogrammes par au moins 3 opérateurs avec des compétences comparables en tractographie.

### 7.2.2 Variations inter-constructeurs

Une seconde difficulté dans la réalisation de la tractographie est celle de la variabilité des machines IRM entre constructeurs. L'ensemble des études de ce travail a été mené sur des machines IRM **Philips Ingenia**. J'ai pu tester des paramètres similaires sur des machines **General Electric** mais l'ajustement des paramètres d'acquisition s'est révélé moins poussé, de même le nombre de directions possibles de la séquence diffusion était moins élevé. L'application du protocole sur une machine **Siemens 3T Prisma** a posé le problème d'une large perte du signal de diffusion exactement au centre de la boîte d'acquisition (**Figure 7.1**). Or celui-ci correspondait exactement au chiasma et à la partie antérieure du tronc cérébral où se trouvaient les segments cisternaux des nerfs crâniens. Ainsi, le signal de diffusion des nerfs crâniens était perdu juste après leur émergence du tronc cérébral. J'ai tenté de multiples approches sans parvenir à récupérer un signal correct : diminution de la taille de la boîte, acquisition dans le plan sagittal, réduction du nombre de directions, diminution de la valeur de  $b$  (9000, 2000, 1500, 1000, 800  $mm.s^{-2}$ ), essai de la séquence de Cook, essai de séquence DTI ou DSI, essai d'acquisition mono et bipolaire, etc. Il est à noter que ces différences dans la qualité

d'acquisition restent fortement dépendantes des paramètres de chaque machine IRM et des profils de sensibilité des antennes utilisées. Ces variations inter-machines et inter-constructeurs pourraient faire l'objet d'études comparatives intéressantes mais requièrent de toute façon une collaboration étroite avec les acteurs industriels et leurs ingénieurs pour pouvoir modifier en détails les réglages « machine » et proposer une acquisition IRM de diffusion de qualité pour les nerfs crâniens.

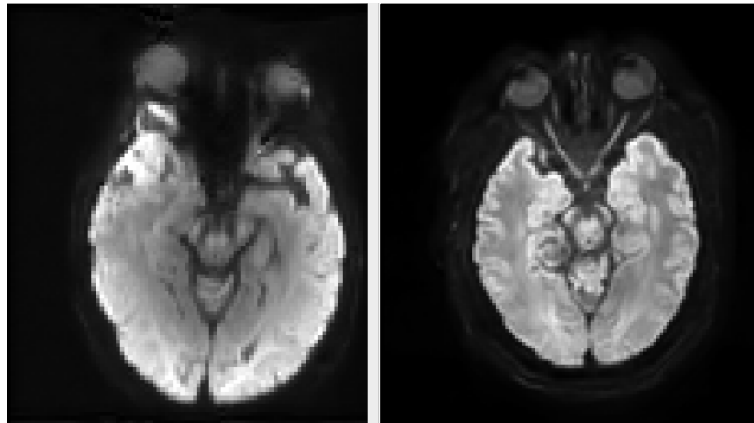


FIGURE 7.1 – **Variations inter constructeurs.** Entre une acquisition Siemens (gauche) et Philips (droite), on peut voir une large perte du signal de diffusion en avant du tronc cérébral au centre de la boîte d'acquisition pour la machine IRM Siemens du *Magnetic Resonance Research Center, Pittsburgh, USA.* - *personal data*-

### 7.2.3 Enjeu de la résolution spatiale ou angulaire

Un troisième obstacle à la technique de tractographie est celui de la possibilité d'acquérir des images de diffusion à haute résolution spatiale et angulaire. L'évolution matérielle des machines IRM et l'apparition des méthodes de post-traitement HARDI ont mené à l'obtention d'images de diffusion avec un nombre croissant de directions : 64, 101, 128, 256, etc. Cette augmentation de la résolution angulaire a permis d'améliorer les résultats de la tractographie dans les zones de croisement de fibres au prix d'un temps d'acquisition et de calcul prolongé. Ainsi, la séquence de diffusion avec 32 directions utilisée dans mes travaux ne paraît pas optimale, notamment elle n'autorise pas toutes les méthodes de post-traitement. Toutefois, la détection de la trajectoire des nerfs crâniens dans le cas des tumeurs de la base du crâne concerne en majorité leur segment cisternal qui ne croise pas d'autres groupes de fibres. Aussi, j'ai montré que les échecs de la tractographie étaient souvent liés à la petite taille des nerfs ou au petit nombre de fibres par voxel en cas d'écartèlement *candy-wrapper like* au contact de la tumeur. Les progrès semblent alors plutôt s'orienter vers l'augmentation de la résolution



spatiale ou du contraste. Néanmoins, si des études en IRM à haut champ magnétique ou avec une résolution spatiale d'acquisition élevée (1mm voire inférieure) paraissent prometteuses, leur application en pratique clinique reste difficile à cause d'un temps machine prolongé, d'un manque de disponibilité des machines et des effets inconnus des champs magnétiques élevés ce qui compromet l'accord des comités d'éthiques. Pour autant, nous travaillons ensemble, avec les équipes françaises et américaines, au développement d'un protocole d'acquisition IRM pour obtenir des images de diffusion à très haute résolution spatiale et angulaire (*upsampling*, **Figure 7.2**) et/ou un meilleur contraste avec multiples valeurs de  $b$ .

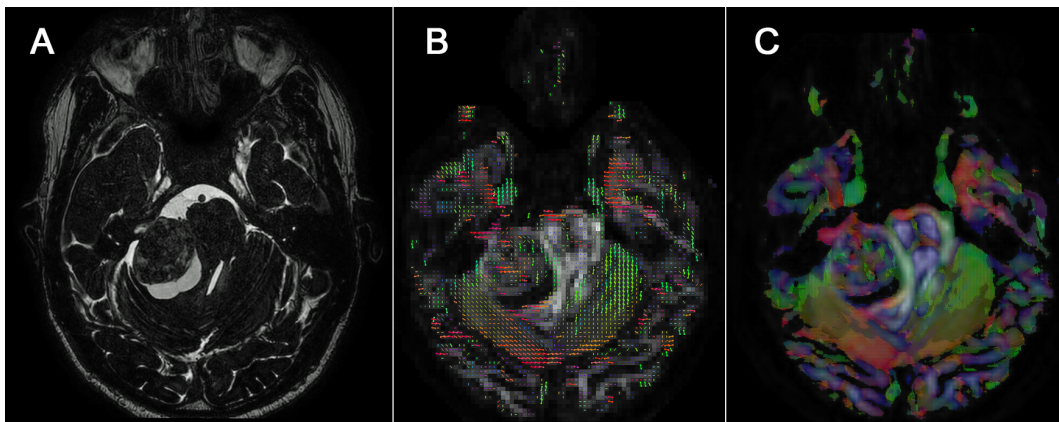


FIGURE 7.2 – **Upsampling.** L'interpolation permet d'augmenter la résolution spatiale de la carte ODF de 2 (B) à 0.5mm (C) et pourrait être une voie de développement pour améliorer la reconstruction des nerfs crâniens surtout lorsqu'ils sont invisibles en IRM classique (A). - *personal data*-

#### 7.2.4 Transfert en routine clinique

Un quatrième enjeu de la tractographie est celui de son transfert en pratique clinique quotidienne. En effet, l'utilisation de cet outil est confrontée à la complexité et la multiplicité des étapes de post-traitement, au placement crucial des ROIs, à l'utilisation de nouveaux algorithmes exigeants en terme de temps ou de puissance de calcul informatique. Pour autant, le dynamisme des communautés web et des développeurs eux-mêmes, grâce à une philosophie d'*open access*, permettent une prise en main du *pipeline* et une résolution des difficultés plus rapide et aisée. FSL, DSIstudio, Mrtrix3, 3Dslicer, ExploreDTI sont tous nés des mains de passionnés qui partagent leur expertise gratuitement sur internet. De même, dans ce travail, j'ai détaillé chaque étape du *pipeline* de tractographie depuis la séquence IRM d'acquisition jusqu'aux paramètres optimisés de tracking en passant par le dessin des ROIs, et j'en ai fourni le script complet.

Ce modèle d'évolution des logiciels libres supprime alors celui des logiciels sous licence industrielle. L'accès au « code source », les tutoriels et les forums de discussion permettent de « démocratiser » l'utilisation de ce type de technologie et de partager l'expérience de leurs utilisateurs. De plus, il est possible d'envisager l'automatisation quasi-complète du *pipeline* pour une utilisation en pratique clinique. Peut-on imaginer que les techniciens d'IRM, les radiologues ou les chirurgiens puissent utiliser cet outil de manière autonome pour produire un rendu 3D des nerfs crâniens dans leur environnement tumoral et anatomique ?



## CONCLUSION

Ce travail sur la tractographie des nerfs crâniens a permis de comprendre les étapes de tractographie, de réunir dans le détail les différents paramètres utilisés autant dans l'acquisition que le post-traitement, de développer un *pipeline* inédit basé sur un algorithme probabiliste pour l'appliquer dans une série de 62 tumeurs complexes de la base du crâne, et de rechercher de nouvelles voies d'amélioration et d'application clinique avec notamment la *full tractography* (**Figure 8.1**). Mon expérience a soulevé certaines limites et a identifié des causes d'échecs de la technique de tractographie. La création d'un **atlas de placement et de forme des ROIs**, nerf par nerf, avec images à l'appui, pourrait ainsi être utile surtout si il est accompagné de conseils et astuces pour la tractographie en **conditions pathologiques**, par exemple : cas du nerf facial en cas d'envahissement complet du méat acoustique interne par la tumeur, cas du nerf cible non visible à aucun moment de son segment cisternal en IRM classique T2 du fait du volume tumoral important. Ainsi, certaines difficultés de la tractographie pourrait être surpassées par l'utilisation des repères anatomiques spécifiques de la base du crâne comme la cochlée ou le sinus caverneux, l'élargissement de la taille des ROIs ( $n$  voxels  $\times$  mm), l'ajout d'une ROI dans le tronc cérébral soit au noyau soit à la zone d'entrée au tronc cérébral en se référant au trajet du nerf sain controlatéral, etc.

Après cette série de 62 cas et ces 2 vignettes illustratives, je poursuivrai l'inclusion des patients et il paraît nécessaire de prévoir une **étude clinique à plus grande échelle** (plus de 100 patients), avec analyse prospective des résultats en aveugle par 3 observateurs, suivi clinique à long terme supérieur à un an, et évaluation des données

socio-économiques (durée opératoire, durée de séjour hospitalier). L'objectif serait de prouver que la chirurgie est véritablement plus rapide et plus sûre grâce à la tractographie avec des recommandations professionnelles à la clé.

Les avancées actuelles en *computer sciences* promettent des améliorations de la qualité du signal de diffusion (*denoising, gibbs correction, distorsion correction, field inhomogeneity correction*) autant que dans l'automatisation du post traitement (***machine learning, clustering***). C'est pourquoi ce travail doit se poursuivre dans l'émulation et la collaboration interdisciplinaire existante au laboratoire CREATIS avec la création d'une équipe dédiée à la tractographie à la conjonction des compétences en : physique, mathématique, informatique, radiologie et anatomie. Le développement de nouveaux algorithmes paraît important, notamment pour l'interpolation des données de diffusion en très haute résolution - *up-sampling* – (**Figure 7.2**). Le passage à l'échelle sub-millimétrique ouvre la possibilité de tractographie des très petits nerfs et celle d'un **atlas très haute résolution du tronc cérébral**. De tels tractogrammes du tronc cérébral et des nerfs crâniens permettraient de revisiter l'enseignement de la **neuro-anatomie** en décrivant la distribution des fibres blanches des nerfs crâniens depuis leur noyau dans le tronc cérébral jusqu'à leur organe cible, et plus encore, retracer la connexion des voies cortico-nucléaires depuis le nerf crânien jusqu'au cortex - par exemple : le nerf cochléaire depuis la cochlée jusqu'à son noyau cochléaire, puis son relai thalamique et sa terminaison au gyrus de Heschl -.

La tractographie comme nouvelle technologie doit s'intégrer dans le **bloc opératoire de prochaine génération**, avec l'implémentation des données de tractographie dans le système de navigation et dans le microscope opératoire. On pourra ainsi créer un environnement de **réalité virtuelle** et superposer sur les images magnifiées du champ opératoire la position des nerfs crâniens ou les faisceaux de substance blanche. Aussi, les tractogrammes devraient pouvoir être visualisés en 3 dimensions, dans l'environnement anatomique réel avec les vaisseaux, par reconstruction à partir des séquences IRM de type « vasculaire » TOF. J'ai initié des partenariats industriels en ce sens pour permettre le partage des tractogrammes entre les différents constructeurs en s'affranchissant des formats propriétaires.

Enfin, la tractographie appliquée aux nerfs crâniens doit naturellement s'étendre vers d'autres pathologies impliquant les fibres blanches : conflits vasculo-nerveux, neuropathies périphériques, tumeurs de la moelle spinale, sclérose en plaque, etc.

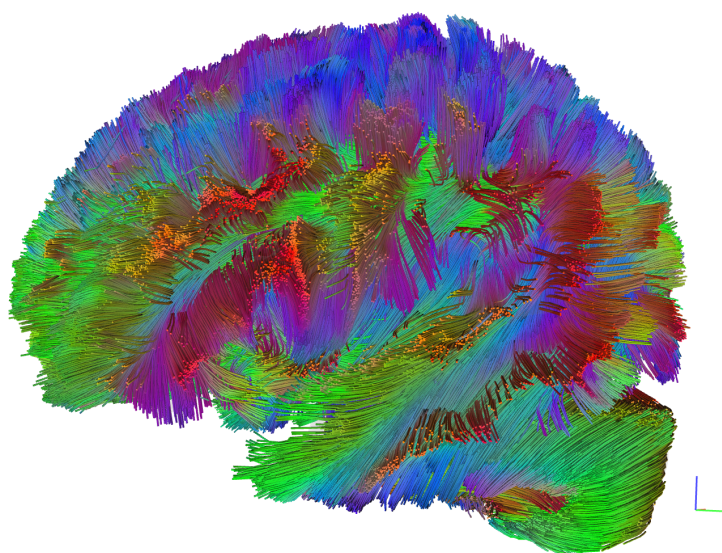


FIGURE 8.1 – **Full-brain tractography** La reconstruction du volume entier suivi de la dissection des faisceaux d'intérêt peut offrir un développement futur en limitant le *design* des ROIs et les erreurs de filtrage.- *personal data* -





## PUBLICATIONS DE L'AUTEUR

### A.1 Revues internationales avec comité de lecture

1. Probabilistic tractography to predict the position of cranial nerves displaced by skull base tumors : value for surgical strategy through a case series of 62 patients. Jacquesson T, Cotton F, Attyé A, Zaouche S, Tringali S, Bosc J, Robinson P, Jouanneau E, Frindel C. Neurosurgery 2018 (epub).
2. Overcoming Challenges of Cranial Nerve Tractography : A Targeted Review. Jacquesson T, Frindel C, Kocavar G, Berhouma M, Jouanneau E, Attyé A, Cotton F. Neurosurgery. 2018 Jul 12.
3. MRI Tractography Detecting Cranial Nerve Displacement in a Cystic Skull Base Tumor. Jacquesson T, Cotton F, Frindel C. World Neurosurg. 2018 Sep ;117 :363-365.
4. Diffusion Tensor Imaging Tractography Detecting Isolated Oculomotor Nerve Damage After Traumatic Brain Injury. Jacquesson T., Frindel C., Cotton F. World Neurosurg 2017 Jan 31
5. A Quantitative Tractography Study Into the Connectivity, Segmentation and Laterality of the Human Inferior Longitudinal Fasciculus. Panesar SS, Yeh FC, Jacquesson T, Hula W, Fernandez-Miranda JC. Front Neuroanat. 2018 Jun 5 ;12 :47

### A.2 Congrès internationaux

1. The challenge of tractography applied to cranial nerves : our experience on the design of the regions of interest, Annual meeting of ISMRM, 2018, Paris, France



2. Synchrotron X-ray phase-contrast imaging to simulate diffusion tensor MRI : application to tracography, (Award) Annual meeting of ISMRM, 2018, Paris, France
3. Tractography applied to cranial nerves, interest in cerebellopontine angle tumors surgery, European Association of Neurological surgery, Venice, Italia

### **A.3 Congrès nationaux**

1. DWI tractography of cranial nerves : Feasibility, development and interest in skull base surgery, 3<sup>e</sup> Congrès de la société française d'IRM, 2017, Bordeaux, France
2. Diffusion weighted tractography applied to cranial nerves : interest in skull base surgery, 65<sup>e</sup> Congres de la Société française de Neurochirurgie (SFNC), mars 2017, Nancy, France
3. Is tractography applicable to cranial nerves : interest in neuroanatomy, 99<sup>e</sup> Congres de L'Association Française des Morphologistes, 2017, Reims, France

# TIMELINE

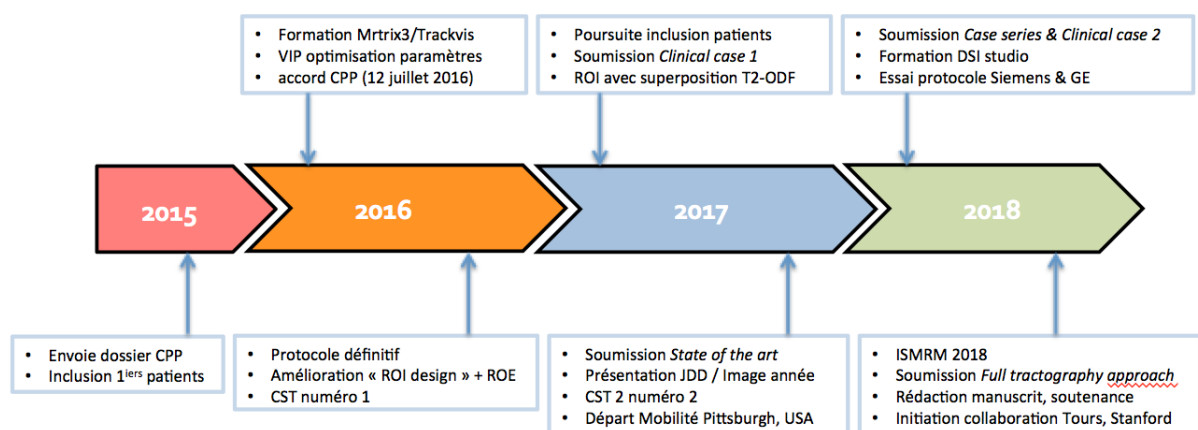


FIGURE B.1 – Déroulé des travaux au cours du temps. Cette ligne du temps présente les différentes étapes qui ont marqué le parcours de ces 3 années de travail, depuis les réflexions éthiques et méthodologiques, jusqu'à la soumission des articles aux journaux à comité de lecture, en passant par l'inclusion des patients, l'apprentissage du code informatique et la mobilité internationale.



FIGURE B.2 – Mobilité internationale

**SCRIPT**

**S**cript of the tractography post-processing steps, using Mrtrix3 and FSL functions. The script automated the following post-processing steps : conversion of acquisition files (Digital imaging and communications in medicine, DICOM), brain mask design, geometric distortion correction, response function generation for the constrained spherical deconvolution, and reconstruction of tracts using regions of interest (ROIs) seeding

**Script Mrtrix3 – Probabilistic cranial nerve tractography**  
**Jacquesson T. – version 8.0**

```

-----
echo "Script cranial nerve tractography 8.0"
echo "1. Choose the anatomic sequence"
mrconvert . T2.mif
echo "2. Choose the diffusion sequence"
mrconvert . dti.mif
mrconvert dti.mif dti.nii -export_grad_fsl bvcs bvls
echo "3. Choose the APA sequence"
mrconvert . APA.mif
echo "4. Choose the APP sequence"
mrconvert . APP.mif
echo "7. Paring APA-APP ..."
mrcat APP.mif APA.mif APP-APA.mif
echo "8. Brain mask generation"
dwi2mask dti.mif mask.mif
echo "Adjust the mask to include the skull base and its CSF cisterns"
mrview dti.mif -overlay.load T2.mif -overlay.opacity 0.5 -roi.load mask.mif
echo "9. Preprocessing / Geometric distortion correction"
dwi2preproc dti.mif dtipreproc.mif -rpe_pair -se_epi APP-APA.mif -pe_dir PA
echo "11. Response function generation choosing harmonic order 6"
dwi2response dtipreproc.mif -lmax 6 response.txt
echo "12. ODF map generation by constrained spherical deconvolution"
dwi2fod csd dtipreproc.mif response.txt fod.mif -lmax 6 -mask mask.mif -cuda
echo "ROI design for cranial nerves II to XII, on both sides L/R"
mrview T2.mif fod.mif -odf.load_sh -overlay.opacity 0.5
echo "Tractography of cranial nerves II to XII"
echo "Chiasma"
tckgen fod.mif -seed_image Chiasma.mif Chiasma.tck -mask mask.mif -select 1000 -trials 10000 -angle 30 -cutoff 0.3 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "IIIG"
tckgen fod.mif -seed_image IIIG.mif IIIG.tck -mask mask.mif -select 500 -trials 5000 -angle 45 -cutoff 0.3 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "IIID"
tckgen fod.mif -seed_image IIIG.mif IIIG.tck -mask mask.mif -select 500 -trials 5000 -angle 45 -cutoff 0.3 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "VG"
tckgen fod.mif -seed_image VG.mif VG.tck -mask mask.mif -select 700 -trials 7000 -angle 45 -cutoff 0.3 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "VD"
tckgen fod.mif -seed_image VD.mif VD.tck -mask mask.mif -select 700 -trials 7000 -angle 45 -cutoff 0.3 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "VIG"
tckgen fod.mif -seed_image VID.mif VID.tck -mask mask.mif -select 100 -trials 1000 -angle 45 -cutoff 0.2 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "VID"
tckgen fod.mif -seed_image VIG.mif VIG.tck -mask mask.mif -select 100 -trials 1000 -angle 45 -cutoff 0.2 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "NFG"
tckgen fod.mif -seed_image NFG.mif NFG.tck -mask mask.mif -select 300 -trials 3000 -angle 45 -cutoff 0.3 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "NFD"
tckgen fod.mif -seed_image NFD.mif NFD.tck -mask mask.mif -select 300 -trials 3000 -angle 45 -cutoff 0.3 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "NMG"
tckgen fod.mif -seed_image NMD.mif NMD.tck -mask mask.mif -select 200 -trials 2000 -angle 45 -cutoff 0.2 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "NMD"
tckgen fod.mif -seed_image NMG.mif NMG.tck -mask mask.mif -select 200 -trials 2000 -angle 45 -cutoff 0.2 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "XIIG"
tckgen fod.mif -seed_image XIIG.mif XIIG.tck -mask mask.mif -select 100 -trials 1000 -angle 45 -cutoff 0.2 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo "XIID"
tckgen fod.mif -seed_image XIID.mif XIID.tck -mask mask.mif -select 100 -trials 1000 -angle 45 -cutoff 0.2 -minlength 10 -exclude cerebellum.mif -exclude tumor.mif
echo
mrview T2.mif -tractography.load {...}

```

**FIGURE C.1 – Script Mrtrix3 – Probabilistic cranial nerve tractography – version 8.0**

## OPTIMIZATION USING THE VIRTUAL IMAGING PLATFORM

Optimization of the tractography parameters has been done through a multi-parametric analysis to assess the best set of tracking parameters for each cranial nerve.<sup>1</sup> For this purpose, we used the Virtual Imaging Platform (VIP) developed at the CREATIS Lab to manage calculations on distributed computing resources of grid infrastructure. Each nerve was tracked following a range of values for each tracking parameter : fractional anisotropy (FA) threshold (0.05 to 0.4), maximum curvature angle (30 to 90), minimum fiber length (1 to 20 mm), estimated number of fibers (100 to 2000). Tractography quality was judged as optimal when leading to the lowest fiber dispersion in a specific nerve. Hence, the best set of tracking parameters was : step size 0.1mm ; minimum fiber length 10mm ; maximal curvature angle 45° ; and FA cut-off of 0.3 (0.2 for cranial nerves VI and IX/X/XI).[37]





# The challenge of tractography applied to cranial nerves : our experience in the design of regions of interest.

**Timothee Jacquesson, Francois Cotton, Justine Bosc, Moncef Berhouma, Emmanuel Jouanneau, Arnaud Attyé, Carole Frindel**

*Abstract ISMRM - Juin 2018 - Paris, France*

## E.1 Introduction

Diffusion tensor imaging (DTI) allow to track white matter fibers in vivo through tractography (Mori et van Zijl 2002; Fernandez-Miranda et al. 2012; Mukherjee et al. 2008). Predicting cranial nerves (CNs) trajectory is important for skull base tumors surgery as well as for neuro-anatomy teaching (Yoshino et al. 2016; Attyé et al. 2015). However, the accuracy of tractography is hampered by the small-scale of CNs regarding the low spatial resolution of DTI (Cauley et Filippi 2013; Hodaie, Quan, et Chen 2010). Tractography of CNs requires also a selective drawing of regions of interest (ROIs) (Yoshino et al. 2015) to initiate the tracking process. ROI design was found to be highly variable in CN tractography studies : single(Taoka et al. 2006; Kabasawa et al. 2007)



versus multiple ROIs;(Gerganov et al. 2011; Zhang et al. 2013; Borkar et al. 2016; Choi et al. 2014; Song et al. 2016) ROI positioned on mid-cisternal segment(Fujiwara et al. 2011; Roundy, Delashaw, et Cetas 2012),brainstem entry zone(Gerganov et al. 2011; Borkar et al. 2016; Song et al. 2016; Zhang et al. 2013; Choi et al. 2014) or cross section orthogonal to the CN trajectory<sup>4</sup>; disk-shape or “single voxel” ROI super selective strategy based on primary tracking map(Hilly et al. 2016; Wei et al. 2015). We therefore propose to report our experience on CNs tractography from data acquisition to tracking parameters and study more specifically the influence of ROI size and placement.

## **E.2 Methods**

### **E.2.1 Participants**

Patients who presented complex skull base tumors were addressed to our neurosurgical department (Lyon, France) and were proposed to participate in this study after information and consent.

### **E.2.2 Acquisition**

A dedicated diffusion sequence was acquired on a 3-T Achieva machine (Philips medical system) using a 32-channel head coil. The parameters of diffusion were : b-value = 1000 s/ mm<sup>2</sup>; 32 directions; voxel size = 2 mm isotropic; slice thickness = 2 mm; no slice gap; field of view = 224x224; scan time = 9’52. A T2 steady state sequence and a T1 post-contrast weighted sequence were added for anatomical reference and tumor morphology reconstruction.

### **E.2.3 Post-processing**

Using FSL®(FMRIB software library, UK), geometric distortions were corrected using acquisition of two images for each diffusion gradient as proposed by Andersson et al. (Andersson, Skare, et Ashburner 2003). Tractography process was performed using Mrtrix3 package software (J-D Tournier, Brain Research Institute, Melbourne, Australia) (Tournier et al. 2008). A constrained spherical deconvolution (6 spherical harmonic terms) was used to create a fiber orientation distribution function (ODF) map (Tournier et al. 2004). ROIs to initiate tractography were selected by superimposing ODF map on T2 in order to identify the CN cisternal trajectory with high accuracy (Figure 1, see chapter 3). For all CNs, probabilistic tractography was applied with the following parameters : step size=0.1 mm, minimum fiber length=10 mm, maximal turning angle=45°, fractional

anisotropy cut-off=0.3. Fibers crossing towards the cerebellum were excluded using a mask. The whole post-processing lasted around 30 minutes using a computer with a multi-core processor (Intel Core® i7, 2.3 GHz, Intel Corporation®, USA / 16 Go 1600 MHz DDR3).

#### **E.2.4 Validation**

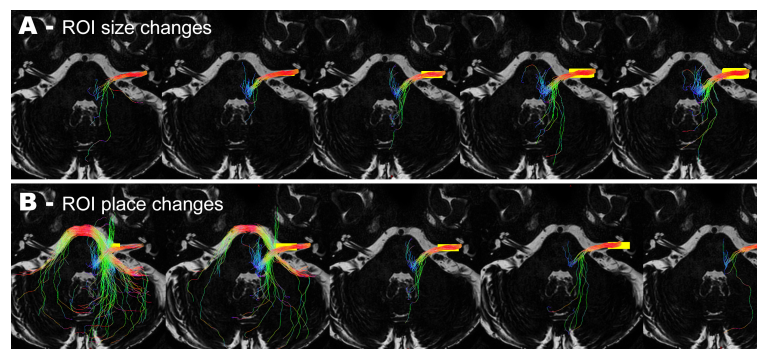
Fiber tracts were assessed by comparison with the previously identified nerves on the T2 anatomical reference or with known anatomical CNs trajectory through skull base cisterns or brainstem (Yagmurlu et al. 2014; Rhoton 1979). The position of displaced nerves was then confirmed intra operatively by direct visualization.

### **E.3 Results and Discussion**

Between 2016-2017, 35 patients were included and thus 700 CNs were tracked. At the healthy side, most CNs were properly tracked according to the T2 anatomic images (Figure 2, see chapter 4) including optic, oculomotor, trigeminal, abducens, acoustic-facial and lower nerves. The trochlear nerve was too thin to be seen on T2 and the hypoglossal nerve was often out of the acquisition box. Around skull base tumors, the tracking was made difficult especially when CNs features were highly modified : stretching, encasement and environment changes. Concerning ROI design, the number of fibers as well as their dispersion slightly increased with the ROI size (Figure 3, A). But, changing the ROI size had in fact little influence as long as tensors that depicted the targeted CN trajectory were still picked and others CNs weren't reached (as shown for the acoustic facial bundle in Figure 3 A). Conversely, even slightly moving the ROI changed significantly the amount of fibers reconstructed. Indeed, a ROI seeded close to the brainstem led to false continuations by recruiting ponto-cerebellar tracts (Figure 3 B left). While a ROI displaced laterally provided less fibers due to a decrease of anisotropy away from the brainstem through skull base foramina (Figure 3 B right).

### **E.4 Conclusion**

In this study, we reported our experience in CNs tractography detailing the influence of ROI design. We demonstrated that understanding in detail the key role of ROI design and its influence helps to provide coherent tracts. We expect this work to enable a more reliable CNs tractography and made it a useful tool for surgical planning of complex skull base tumors.



**FIGURE E.1 – Tractography results on the left acoustic-facial bundle superimposed on T2-cerebral MRI in axial view.** (A) On the basis of the ROI design strategy explained in Figure 2 (central picture, ROI in yellow), the ROI is eroded (to the left) and expanded (to the right). (B) Then the ROI position is displaced medially (to the left) and laterally away from the brainstem (to the right). The number of fibers as well as their dispersion slightly increases with the ROI size. Moving the ROI close to the brainstem induces false continuations by recruiting ponto-cerebellar tracts.

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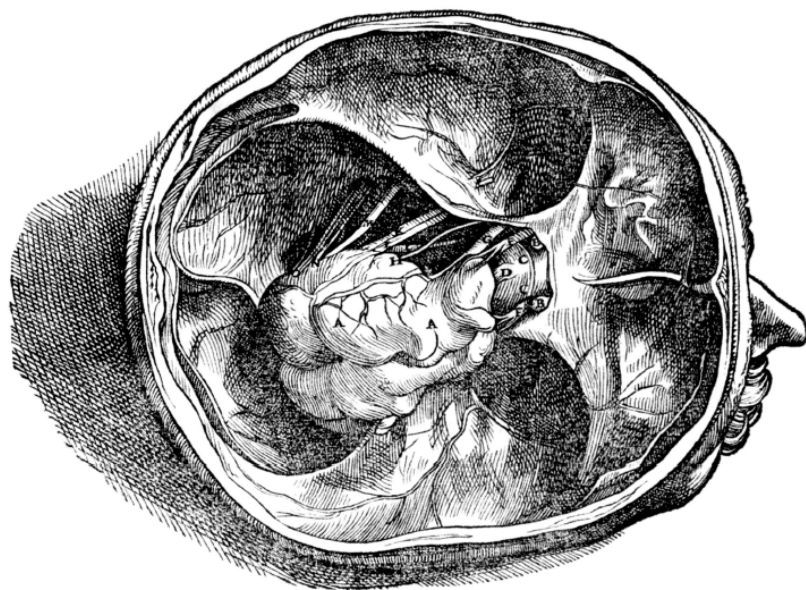


FIGURE 1 – Tumeur de la base du crâne déplaçant les nerfs crâniens, Andreas Vesalius, *De Humani Corporis Fabrica*, 1543