The role of probabilistic tractocraphy in the surgical treatment of deep seated brain tumors

Ph.D Thesis Summary

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The Role of Probabilistic Tractography in the Surgical Treatment of Thalamic Gliomas

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Abbrevations

AC – anterior commissure

ALIC – anterior limb of internal capsule

ARAS – ascending reticular activating system

ASSET – array spatial sensitivity encoding technique

CDR – connectivity-defined region

CoG_{conn} – center of gravity connectivity

CM – connectivity map

CST/CBT – corticospinal and corticobulbar tracts

DES – direct electrical stimulation

DOF – degree of freedom

DTI – diffusion tensor imaging

FA – fractional anisotropy

FDT – FMRIB’s Diffusion Toolbox

FLIRT – FMRIB’s Linear Image Registration Tool

FOV – field of view

FSL – FMRIB Software Library

MNI152 – Montreal Neurological Institute 152

MRI – magnetic resonance imaging

NEX – number of excitation

PDM – probability distribution map

PLIC – posterior limb of internal capsule

rp – Pearson’s coefficient

rs – Spearman’s rho

SNR – signal to noise ratio

TBI – traumatic brain injury

TE – echo time

TI – inversion time

TR – repetition time

1. Introduction

In the treatment of intrinsic brain tumors, the gold standard is surgical resection. Although it is now quite obvious that the efficacy of radiotherapy and survival time can be increased by partial or total resection of these tumors, in many cases only stereotactic biopsy is carried out followed by radio- and/or chemotherapy on the basis of the histological findings.

The goal of brain tumor surgery is maximum removal associated with no functional deficit. Tumors involving eloquent (either cortical or subcortical) areas are at a high risk of postoperative neurological deficit. This is especially true for deep-seated brain tumors due to the following reasons:

1, the tumor is located in important subcortical eloquent areas (e.g. thalamus, brainstem)

2, accessing these tumors has higher risk of injuring important subcortical pathways due to their location and the long surgical trajectory.

Surgical resection of these tumors requires a highly experienced neurosurgeon who must be aware of the cortical and subcortical functional neuroanatomy. However, space occupying lesions distort and dislocate normal anatomy, and it can be extremely challenging to recognize those structures that must be kept intact.

Noninvasive (preoperative) and invasive (intraoperative) brain mapping techniques can help to reduce surgical risk, while maximizing the extent of resection. MRI-based preoperative methods are widely used for cortical and subcortical mapping. Functional MRI is a blood oxygen level-dependent method which can be used to identify functional cortical areas. Diffusion MRI-based tractography techniques can depict subcortical white matter pathways.

Although awake craniotomy and DES have the best sensitivity and specificity, their application in case of deep-seated brain tumors is limited. In case of these tumors, preoperative brain mapping methods have the highest impact to minimize risk and improve the extent of surgical resection. As these tumors are located in deep white matter or in the basal ganglia, fMRI is not suitable to map the surrounding brain around the lesion. Tractography on the other hand can identify white matter tracts and subcortical nuclei.

Conventional diffusion tensor imaging-based deterministic tractography can visualize the major white matter pathways reliably. Therefore, it can be used to identify white matter fibers around the tumor (e.g., corticospinal tract) and help to plan the surgical trajectory to avoid injuring important pathways. In eloquent subcortical regions, such as the thalamus and brainstem, a well-planned trajectory alone is not enough to minimize functional deficit. As the structure itself has important functions, its injury during the tumor removal can lead to severe nerurological deficit and significant impairment of the quality of life. In the past decade, diffusion MRI has been used to improve our knowledge on normal brainstem anatomy and on pathologies that distort it. Most tractography studies of the brainstem have at least in part relied on anatomical landmarks located within the brainstem itself. This may render their applicability limited in case of space-occupying lesions when the identification of brainstem anatomical landmarks becomes difficult and unreliable.

The ball and sticks model-based probabilistic tractography has several advantages. It can track fibers in regions with low anisotropy values and visualize crossing fibers. Moreover, it can provide quantitative measures representing the connectivity properties of the seed region. It can be thresholded to exclude false positive results and provides possibility to investigate connectivity of different brain areas, thus subcortical nuclei and pathways become identifiable based on their connections.

2. Objectives

Our aim was to develop noninvasive, reliable and clinically applicable MRI-based brain mapping methods to improve the surgical resection of deep-seated brain tumors. We examined two distinct subcortical eloquent brain regions by probabilistic tractography: the thalamus and the brainstem.

1. Connectivity based thalamus segmentation by probabilistic tractography has been proven to be reliable and reproducible in healthy subjects. In our study we were the first to apply this technique for thalamic tumor patients to differentiate between normal thalamus and tumor tissue, make preoperative planning possible, optimize the surgical approach and facilitate surgical resection.

2. Part of the brainstem is potentially suitable for tractography studies, as it has relatively simple fiber architecture and its main functional regions maintain connections with supratentorial centers through white matter pathways mainly running in rostrocaudal orientation. We were the first to apply connectivity based segmentation technique in healthy subjects to identify four important brainstem subregions (1, frontopontine pathways; 2, corticospinal and corticobulbar tracts; 3, sensory connections involving the spinothalamic tract and the medial lemniscus; 4, reticular formation and ARAS) based on their connectivity to supratentorial structures, thereby avoiding the need for applying masks that rely on anatomical landmarks within the brainstem. This can be significant help in the preoperative planning of tumor resection, make preoperative planning possible, optimize the surgical approach and

facilitate surgical resection. Two representative cases of brainstem tumor patients are included to this thesis to demonstrate the clinical applicability of the introduced method.

3. Materials and methods

3.1 Thalamus tumor

3.1.1 Study population

Five patients with thalamic gliomas were included in the study. Two of these patients will be presented in details in the thesis as representative cases.

3.1.2 MRI acquisition

Scanning was conducted on 1.5 T GE Signa Excite scanner. High resolution T1 weighted (3D IR-FSPGR, 1 mm^3), FLAIR (1 mm^3) and diffusion-weighted images (3 mm^3, b value = 1000 s/mm^2) in 30 independent directions and one nongradient set (b value = 0 s/mm^2) were made with 2 repetitions.

3.1.3 Data processing

Raw MRI data were processed using tools from the FMRIB Software Library (FSL, version 2.0; Oxford Centre for Functional MRI of the Brain (FMRIB), UK; www.fmrib.ox.ac.uk/fsl) according to the method previously described by Behrens et al. Eddy current correction, skull stripping, reconstruction of diffusion tensors and modeling of diffusion parameters were done.

3.1.4 Data analysis

Seven cortical masks were delineated manually on both hemispheres (prefrontal-, premotor-, primary motor-, primary sensory-, posterior parietal-, occipital and temporal cortex). These masks covered the whole cortical surface of each hemisphere. Masks were prepared based on the MNI Structural and Harvard-Oxford Cortical Structural Atlas. The thalamus and the thalamus-tumor complex were outlined individually according to the gray matter areas between the posterior limb of the internal capsule and the lateral and third ventricles. The following step was segmentation of the thalamus-tumor complex and the normal thalamus with the FDT toolbox PROBTRACKX option using standard settings. After segmentation, seed areas of the tumorous hemispheres were thresholded (lower threshold was 10% or less connection probability) to extract possible cortical connections of the tumor (false positive results). Finally, we performed hard segmentation.

3.1.5 Surgery

Images of thalamic segmentation were uploaded to neuronavigation system (StealthStation®, Medtronic). The surgery of all patients was performed under neuronavigation. Preoperative planning was not carried out in the case of Patient 1, because at that time thalamic segmentation was not applied for this purpose at our department. Surgical approach was planned individually for all the other patients based on preoperative MRI scans and safest access was selected by the help of the results of thalamic segmentation.

3.2 Brainstem

3.2.1 Study population

20 healthy subjects were included in the study (age [mean ± SD]: 31.7 ± 7 years, range: 21.7−43.2 years, 12 females) with no previous history of neurological or psychiatric disorders and without any structural abnormalities on the anatomical scans.

3.2.2 Data acquisition

Scanning was conducted on a 1.5T GE Signa Excite scanner with an eight-channel head coil and maximum gradient strength of 33 mTm^{-1}. High resolution T1-weighted scans (3D IR-FSPGR, 1 mm^3) and diffusion-weighted images (DTI, 2.4x2.4x2.4 mm, two repetitions, b = 1000 s/mm^2) in 60 independent directions and six non-diffusion weighted sets (b = 0 s/mm^2) (later referred as nodif image) were acquired.

3.2.3 Data preprocessing

MRI data were preprocessed using tools from the FMRIB Software Library (FSL, v5.0,; FMRIB's Diffusion Toolbox [FDT], v3.0; Oxford Centre for Functional MRI of the Brain [FMRIB], UK; www.fmrib.ox.ac.uk/fsl) according to the method previously described by Behrens et al. Eddy current and head motion correction, followed by skull stripping, reconstruction of diffusion tensors, and estimation of diffusion parameters were done.

3.2.4 Selection and definition of masks

To reduce the effect of the distance dependence of tractography on the connectivity results, targets were preferably chosen to be located in the relative proximity of the seed mask and at a similar distance to it. According to this, the following six target masks were applied: the left (1) and right (2) ALIC to detect frontopontine connections, the left (3) and right (4) PLIC to trace the CST/CBT, the bilateral sensory (5) and medial (6) thalamus to find the main ascending sensory pathways (medial lemniscus, spinothalamic pathways) and the reticular formation, respectively.

The pontomesencephalic seed mask and all target masks were delineated in the subject's structural T1-weighted image space.

3.2.5 Connectivity-based probabilistic brainstem segmentation

3.2.5.1 Probability distribution maps of the subregions

Probabilistic tractography was performed based on a multifiber model using the seed and target regions described above. The default settings of the FDT were applied. On the individual level, these analyses resulted in a probability distribution map (PDM) for each target mask, in which only voxels within the seed mask contained data. To eliminate low-probability connections (false positive results) from these PDMs, they were thresholded. Eight threshold levels were tested: 1%, 5%, 10%, 15%, 20%, 25%, 35% and 50%, of which the 25% threshold was found to yield the anatomically most plausible results. This threshold level was arbitrarily chosen for further analyses.

3.2.5.2 Brainstem connectivity maps derived by hard segmentation

On the individual level, the six PDMs thresholded at 25% were integrated into a single representation corresponding to the connectivity map (CM) of the brainstem. It was created by assigning each voxel in the seed mask with the identity of the target mask that had the highest number of samples projecting to it. This method is called hard segmentation. As a result, the CM of the brainstem consisted of six connectivity-defined regions (CDR), namely the left and right frontopontine, the left and right motor, the sensory (involving the left and right side as well) and the reticular subregions.

To generate the group CM of the brainstem, all individual unthresholded PDMs were registered to standard space. Then the individual PDMs summed, averaged, thresholded (see 3.2.5.1) and then integrated into a single representation corresponding to the group CM of the brainstem.

3.2.5.3 Comparison of segmentation results with microscopic anatomy and anatomical reference material

To qualitatively assess the correspondence between the results of the connectivity-based brainstem segmentation and microscopic anatomy, horizontal histological sections obtained from a single subject and stained for myelin and for cells were consulted. The results of the connectivity-based brainstem segmentation were visually compared with the underlying anatomical structures.

4. Results

4.1 Thalamus tumor

4.1.1. Representative cases

4.1.1.1 Patient 1

A 65-year-old woman presented with a history of vertigo, gait imbalance and sudden onset urinary incontinence. MRI revealed right thalamic tumor, spreading into the right lateral ventricle. We decided to perform surgery from occipital, transcortical, transventricular access. Postoperative CT scan showed marked diminution of the tumor mass, but unfortunately, the patient became somnolent, she had no verbal response nor cooperation. Histology revealed glioblastoma multiforme. Her condition did not improve and she died in pneumonia related sepsis 2 months after surgery. The retrospectively performed thalamic segmentation showed that the tumor originated from the middle part of the medial thalamus and dislocated thalamic nuclei to the way of the chosen surgical trajectory. We suppose that her postoperative conscious state was due to the injury of important thalamic nuclei.

We present this case to emphasize the usefulness of thalamic segmentation in the selection of the appropriate surgical approach.

4.1.1.2 Patient 2

A 32-year-old man complained of paresthesia on the left side and clumsiness of the left hand. CT scans revealed right thalamic tumor. His left-sided hemiparesis increased progressively, muscle power decreased to 3/5 in three weeks. Thalamic segmentation showed that the tumor originated from the medial part of the thalamus and caused anterolateral and inferior dislocation. We chose occipital, transcortical, transventricular access. Follow up MRI showed subtotal resection of the tumor. His neurological state significantly improved after surgery. Histopathologic examination revealed glioblastoma multiforme

4.2 Brainstem

4.2.1 Segmentation pattern on the individual level

The individual CMs were very similar in 13 out of the 20 healthy subjects (65%) resulted in a highly consistent connectivity pattern. Voxels dominantly connected to the left and right ALIC (frontopontine CDR) were located in the medial portion of the cerebral peduncles. This CDR could be followed downwards until the mid-pons. Voxels dominantly connected to the left and right PLIC (motor CDR) were located in the middle and lateral portion of the cerebral peduncles and on the pontine basis on both sides. Voxels dominantly connected to the sensory thalamus (sensory CDR) were located in the dorsolateral part of the mesencephalon and on the border of the pontine tegmentum and basis. Voxels dominantly connected to the medial thalamus (reticular CDR) were located in the mesencephalic and pontine tegmentum.

In 1 subject (5%) the sensory CDR was not appropriately detected, and in 6 subjects the reticular CDR was not adequately reproduced (30%). The connectivity patterns of the frontopontine and motor CDRs were similar in all subjects. The frontopontine CDR could be followed downwards until the mid-pons in all subjects.

4.2.2 Segmentation pattern on the group level

The group CM was very much resembling to the individual CMs. Location of the CDRs in the group level were similar to the identified CDRs of all subjects (as described above) at the individual level.

In the mesencephalic region, the eight group CMs derived using the eight different threshold levels (1%, 5%, 10%, 15%, 20%, 25%, 35%, 50%) appeared similar with regard to the internal boundaries between the CDRs, while lower thresholds resulted in larger CDRs reaching the outer surface of the brainstem. In the pontine region, with increasing thresholds, both the internal and external borders of the subregions became more congruent with the known anatomical locations, but thresholds above 25% resulted in an excessive reduction of the area of the CDRs.

4.2.3 Comparison of segmentation results with microscopic anatomy and anatomical reference material

The group CM derived by the connectivity-based segmentation of the brainstem with a 25% threshold was in good overall visual concordance, with regard to the spatial distrbution of the identified CDRs, with the pathways determined on the histological sections. In case of the sensory CDR, the medial lemniscus was located on the border of the motor and sensory CDRs in the mesencephalon, whereas in the pontine region, part of it was identified in the motor CDR.

4.2.4 Representative cases

4.2.4.1 Patient 1 – Infiltrative tumor

A 6 years old female patient presented with vertigo. There were no other neurological signs or symptoms. The conventional MRI images showed a seemingly expansive tumor mass in the pons. The connectivity based brainstem segmentation was done and the results revealed that the tumor infiltrates the ventral pons and its pathways. Due to the infiltrative nature of the tumor it was considered as inoperable and oncological treatment was initiated.

4.2.4.2 Patient 2 – Expansive tumor

A 16 years old male patient experienced vertigo, double vision, gait disturbances and difficulty to swallow. The MRI showed an expansive tumor in the left dorsal part of the pons and mesencephalon. A biopsy was done which resulted in a grade II-III astrocytoma. The connectivity based brainstem segmentation was done as described in section 3.2.5. The tumor dislocated the brainstem structures from the left side to the right side. According to this, a subtotal resection was done from the left dorsolateral part of the tumor. The patient experienced a significant improvement.

5. Discussion

In the past few decades preoperative functional MRI and tractography became part of the clinical routine to decrease the surgical risk of brain tumors in eloquent brain areas like motor-, speech- and visual cortex, but it is not true yet for tumors of basal ganglia, brainstem and cerebellar peduncles. Preoperative planning may similarly decrease the surgical risk of tumors affecting these areas, but the thalamus and the brainstem contain important gray matter nuclei, that cannot be identified by fMRI and deterministic tractography.

5.1 Thalamus tumor

Sizable, inhomogenously enhancing tumors with considerable mass effect are not possible to be distinguished from normal thalamus by conventional imaging techniques.

With the technique described above, thalamic nuclei can be visualized separately from the tumor, thus based on the normal anatomy of the opposite side it is possible to reconstruct the origin of the tumor reliably.

Yasargil suggested that brain tumors originate from a core and grow expansively dislocating healthy tissues. Hence the most feasible strategy is to target the core of the tumor and start the resection there to remove it the safest way, thus minimizing the risk of damaging healthy structures.

In the case of Patient 1, ventral thalamic nuclei were more dislocated, presumably because the tumor originated from the anterior third of the medial thalamus, from the area neighboring the anterior, medial and motor thalamic nuclei. In Patient 2, the dislocation of the dorsal nuclei was more pronounced, pointing out that the possible origin of the tumor was the middle-posterior third of the medial thalamus around the area surrounded by the ventrolateral, ventroposterior nuclei and the pulvinar.

Occipital, transcortical approach seemed to be the safest in all patients except for Patient 1. We made our choice based upon the facts that occipital, transcortical approach spares eloquent cortical areas and there are no important functional white matter tracts in the vicinity, which decrease the risk of causing neurological deficit. Transventricular approach was supported by the relatively easy access to the thalamus through the lateral ventricles and the more spacious surgical field provided when using this approach. Moreover, this operative trajectory was favorable in all cases except for Patient 1 to reach the core of the tumor without damaging normal thalamus. In Patient 1, on conventional MRI sequences the tumor seemed to have an exophytic part growing into the occipital horn of the lateral ventricle, suggesting an ideal location to start the resection. The retrospectively performed thalamic segmentation showed that the area previously thought to be the exophytic component of the tumor contained posterodorsal thalamic nuclei dislocated by the tumor. Based on the postoperative neurological state of the patient, injury to these nuclei can be suspected.

Our results demonstrate that surgery performed with the help of our imaging algorithm caused no deterioration in the neurological symptoms of our patients, indeed we noticed neurological improvement in three cases and furthermore by two of them we achieved complaint-free state. The border between the normal thalamus and the tumor was not recognizable on conventional imaging in either case, but with the help of our method not only the location of the normal thalamus, but also thalamic nuclei were identifiable. Based on the results of the segmentation we were able to choose the safest way of surgical access combined with the appropriate surgical technique.

Due to technical limitations (resolution of DTI, thresholding, manual delineation of masks under visual control) the border of thalamic structures cannot be determined by thalamic segmentation with complete consistency with the anatomy, but inaccuracies may not be greater than a few millimeters. This technique is not capable to localize thalamic nuclei with submillimetric accuracy, but for preoperative planning millimetric definition is satisfactory. The accuracy of image guided techniques is anyway hampered by brain shift occurring after incision of the dura mater. Tumor resection is performed under visual control and efficacy is still mostly depending on the experience of the surgeon.

5.2 Brainstem

5.2.1 Correspondence between the connectivity-defined brainstem regions and the known anatomy

In this study we evaluated the frontopontine connections, the corticospinal/corticobulbar tracts (CST/CBT), the main ascending sensory pathways (medial lemniscus, spinothalamic pathways) and the reticular formation, because they represent connections to fundamental functional systems, and their size allows identifying them on the individual level with the imaging parameters used.

To limit low-probability connections (false positive results) between the seed and the applied target areas, we tested eight different threshold levels both on the individual and the group level, and found the anatomically most plausible results with 25% threshold.

The location of the CDRs produced by the brainstem segmentation corresponded with the results of previous diffusion imaging studies, as well as the neuroanatomy on the histological slices.

The frontopontine CDR was located in the medial portion of the cerebral peduncles and, similarly to the findings of other studies, it could be followed downwards until the mid-pons, where these fibers end in the pontine nuclei.

The motor CDR was located in the middle and lateral portion of the cerebral peduncles and in the pontine basis on both sides.

Sensory thalamic regions as defined in the Oxford Thalamic Connectivity Atlas mainly correspond to the ventral posterior nucleus of the thalamus. When comparing the location of the sensory CDR to the course of the main sensory pathways identified on the histological specimen, it is apparent that the medial lemniscus was located on the border of the motor and sensory CDRs in the mesencephalon, whereas in the pontine region, part of it could be identified in the motor CDR. This appearance may be due to several factors, for example the low specificity of the PLIC target mask, as it involves sensory fibers as well (thalamocortical projections). Segmentation of the PLIC and selective inclusion of fibers arising from the motor cortex may be a possible solution to this issue.

The reticular CDR was located in the median and paramedian areas of the mesencephalic and pontine tegmentum surrounded laterally and anterolaterally by the sensory CDR in the mesencephalon and in the pons, respectively. The area identified by the connectivity-based brainstem segmentation as the mesencephalic and pontine reticular formation corresponded well with its known anatomical location.

5.2.2 Reproducibility of the connectivity-based brainstem segmentation

On the individual level, all four subregions were successfully identified by the hard segmentation in 13 out of 20 subjects (65%). The sensory CDR was incompletely identified in 1 subject (5%), and the reticular subregion was not detectable in 6 cases (30%). In these latter subjects, the underlying difference between the sensory and reticular connectivity may be due to individual variations of the thalamic connectivity not accounted for by the standard masks of the FSL's Oxford Thalamic Connectivity Probability Atlas.

5.2.3 Potential clinical applicability

The results of the connectivity-based segmentation of the brainstem in 20 healthy adults may provide reference for the investigation of patient populations. Eliminating the need for using anatomical landmarks within the brainstem to start tractography analysis may be particularly helpful in the preoperative evaluation of space-occupying lesions. Connectivity-based brainstem segmentation may be a helpful tool in the preoperative planning of brainstem gliomas, facilitating the differentiation between infiltrative and expansive tumor growth and the planning of the surgical trajectory.

We have presented two representative cases of brainstem glioma to demonstrate the usefulness of probabilistic tractography-based brainstem segmentation in brain tumor surgery. The presented method was able to detect all the six subregions in both patients.

We believe that the two representative cases demonstrate that the presented tractography method is not only capable of identifying the important subregions in tumorous brainstem but also makes it possible to distinguish between infiltrative and expansive tumors in patients when conventional MRI scans are not obvious.

5.2.4 Limitations

There are well known limitations of diffusion tractography that apply to our study as well.

As it was underlined by the cases of those six subjects in whom the reticular subregion could not be identified, hard segmentation only considers the dominant connection of the given region in the brainstem, therefore, it is insensitive to the extent of differences between connectivity values, and can be driven even by small discrepancies. Verifying the PDMs may help evaluate the connectivity in these cases.

The applied masks included other pathways beyond those of interest, like the thalamocortical fibers in the anterior limb of the internal capsule (ALIC), and the occipitoparietotemporopontine and some of the medial lemniscal fibers in the PLIC. Therefore, the segmentation presented here cannot differentiate the fibers of the occipitoparietotemporopontine pathways.

The small number of investigated structures can be generally considered an important limitation of our study. The identification of further brainstem structures by increasing the complexity and specificity of this connectivity-based brainstem segmentation can potentially be the subject of future studies.

The representative cases showed that in case of brainstem gliomas the presented method could provide greater and safer tumor resection but the same technical limitations are present as in thalamic tumor patients. These limitations and their clinical interpretation has been discussed in details in section 5.1.

6. Conclusions

Our aim was to develop new imaging algorithms that may help to decrease surgical risk of deep seated brain tumors and broaden the range of tumors considered to be operable. We suggest that these methods may be applied successfully and routinely in the surgical treatment of thalamic and brainstem gliomas. By determining individual anatomy and identifying the dislocation of subcortical functional regions, surgery can be planned targeting the core of the tumor, which may be safer and more effective than applying empirical surgical techniques. On the other hand, we were the first to apply connectivity-based segmentation by probabilistic tractography ~~to~~ of the brainstem. It allows separation of four functionally important subregions (the frontopontine, motor, and sensory pathways and the reticular formation) in the brainstem based on connectivity to supratentorial structures, which may be an advantage when pathologies within the brainstem hinder the identification of anatomical landmarks. The detected subregions were in good concordance with microscopic anatomy, furthermore, they were shown to be reproducible in a group of healthy subjects. Nevertheless, the representative cases demonstrate the potential applicability of this technique in case of brainstem tumors.

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