SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (Ph.D.)

Characterization of normal and pathological patterns of diffusion anisotropy with diffusion tensor imaging

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1. Introduction

Water is a fundamental constituent of living creatures and tissue water is structured according to the characteristic features of any given tissue type. A unique property of brain tissues is that the propagation of water molecules is hindered by microscopic obstacles like the axonal membranes, myelin sheath or the extracellular matrix, resulting in *anisotropic diffusion*. A new family of imaging technologies was built upon this phenomenon, namely diffusion magnetic resonance imaging (dMRI). The date of this work – 2012 – hallmarks the 25th anniversary of diffusion MRI. Since the first depiction of the diffusion process in the human brain significant conceptual and methodological developments have been applied to dMRI. While the spatial resolution of MR images is typically on the range of a millimeter, a strikingly unique feature of dMRI is that it probes the motion of water molecules on the micrometer scale. This theoretically means a way to sample the microarchitecture of tissue or subcellular water compartments

A significant part the thesis focuses on the application of magnetic resonance imaging and related image processing techniques to characterize normal diffusion anisotropy patterns in the human brain. First, we explore the topography of diffusion anisotropy and structural connections of the insula, then similar dissections for the mediodorsal thalamic nucleus are provided. The second part of our investigations focuses on the anisotropy patterns of diffusion in pathological

conditions, more specifically, to portray the diffusion characteristics in brain neoplasms of glial origin.

1.1. Basics of diffusion-weighted and diffusion tensor imaging

Diffusion-weighted imaging (DWI) provides non-invasive description of in vivo diffusion of water molecules within elementary image units, voxels. In living systems the tissue structure determines the movement of the same molecule, i.e., the diffusion properties and its magnitude as well. The result of this phenomenon is called anisotropic diffusion where the diffusion profile (i.e. the profile of propagation of water molecules) can be described by amorphous 3D or ellipsoid geometric solids. To formalize this direction-dependence of the diffusion process, Basser and Pierpaoli used tensors and suggested the use of quantitative diffusion tensor MRI to characterize microstructural and physiological features of tissues. Therefore diffusion tensor imaging (DTI) has increased sophistication over diffusion-weighted MRI since DTI data have information on the magnitude and orientation of anisotropic diffusion as well. This is achieved by probing the diffusion by repeatedly applying diffusion sensitizing gradients in at least six different spatial orientations. The tensor dataset is used to calculate parametric images such as the fractional anisotropy (FA), mean diffusivity (MD), (average) apparent diffusion coefficient (ADC) or the eigenvalue (λ_1, λ_2, λ_3) maps.

1.2. In vivo mapping of structural brain connections with diffusion tractography

From the perspective of neuroanatomy research, mapping the structural (i.e. anatomical) connections is interesting as the inflow or output of information available to a certain brain territory hallmarks its putative function and determines the influence it can has over other areas. Given that in brain tissue the densely packed axons are the main sources of the diffusion anisotropy, the tensors readily describe the orientation of the dominant fiber population in each voxel. This data can be used to initiate virtual tracking of structural connections along the dominant or nondominant directions of hypothesized fiber directions. Fiber tractography was enthusiastically considered as a tool for *in vivo* virtual dissections of white matter anatomy using DTI data, but this was followed by validation studies and the development of newer computational methods like probabilistic diffusion tractography. This technique allows tracing the structural connections emerging from the cortex or thalamus along trajectories that are defined by the diffusion modeling. This is the rationale for a large number of recent studies that parcellate gray matter *in vivo* by identifying regions that receive or send out similar connections, this is referred to as connectivity-based segmentation of the cortex or the thalamus.

1.3. Using diffusion tensor imaging to describe the connectional anatomy of the insula

The insula of Reil, located deeply within the lateral sulcus, is known to have a multifaceted sensory, motor, visceral and cognitive role and is also considered as a vestibular association area and known to act

as the anatomical representation of interoceptive awareness. Its functional and anatomical diversity has been described in humans and non-human primates, with changes in cytoarchitecture that follow a rostroventral to dorsal and posterior gradient, from agranular to dysgranular and granular cortex. Human functional neuroimaging studies explored the insula by resting-state functional MRI (fMRI); one such work revealed two major complementary networks involving the ventral-anterior and dorsal-posterior insula. DTI revealed a rostrocaudal variation of connectivity-based segments dividing the insula into two clusters, while this was later refined by reporting a more gradual change of connectivity patterns along this axis.

1.4. The application of diffusion tensor imaging to describe the connectional anatomy of the mediodorsal thalamic nucleus

Diffusion tensor imaging augmented with a probabilistic framework of fiber tractography allows mapping thalamocortical (or corticothalamic) connections noninvasively. A novel way to picture structural connections of the thalamus is to delineate and define regions based on their primary sources of afferent or efferent connections. This technique potentially depicts groups of thalamic nuclei that are different in terms of interconnections to the cortex or other, pre-defined “target” regions. Endeavors to study the role of the mediodorsal thalamic nucleus (MD) already postulated it as a possible association hub mediating affective and cognitive functions; whereas we refer to the neuroanatomical studies explicating the connectional anatomy of the

MD. We hypothesize that by using connectivity-based segmentation on the MD, we can discover separated corticothalamic (and thalamo-cortical) networks that pass through this region in living human subjects.

1.5. Characterization of pathological anisotropy patterns with diffusion tensor imaging

Diffusion data are often correlated with cellular physiology and tissue microstructure. In case of changing intra- and extracellular structure, for instance the disorganization that accompanies neoplastic transformation, the diffusion characteristics are bound to be altered. Hence dMRI putatively probes the biological microarchitecture and offers hope to correlate such measurements with tissue properties in pathological conditions or even to reveal the peculiar microstructure of neoplastic tissue. Concerning brain gliomas, such correlations were extensively reported in the literature. The final aim of such studies is to characterize the pathological diffusion anisotropy and help to predict the WHO grade of gliomas using preoperative, non-invasive imaging. Various studies on the relationship between imaging parameters and pathology aim to develop new ways of depictions that can help to characterize tumors; it was possible to visualize biologically diverse regions within a tumor based on image analysis and various modeling approaches, either using magnetic resonance spectroscopy or diffusion tensor imaging data. Such techniques are often referred to as “nosologic maps”.

1.6. Study aims

The primary motivation of the study was to employ *in vivo* diffusion tensor imaging to portray individual anisotropy patterns of cerebral water diffusion in physiological and pathological scenarios. Our experiments were designed to elucidate the following topics.

A. To show the applicability of DTI for studying the diffusion anisotropy patterns and connectional anatomy of the human cerebral cortex, focusing on the insula; whereas to use connectivity-based segmentation to reveal and analyze subdomains in the insula that are segregated by their remote connectivity

B. To use DTI to study the connectional anatomy of the human thalamus, with special attention to the mediodorsal nucleus and to compare the neuroanatomy of the connectionist definition of the subdomains with the cytoarchitectural subdivisions.

C. To use DTI to characterize the spatial patterns of diffusion anisotropy within brain gliomas and correlate such findings with histological features that are used to type such tumors;furthermore, to assess the feasibility of using preoperatively acquired DTI images in glioma grading. Furthermore, to develop a graphical representation (i.e. nosologic) of the imaging-based interpretation of glioma grade.

2. Methods

2.1. Study subjects

We report our study methods in accordance with the envisaged study aims A-C. To meet the study goals, three different study cohorts were construed. For specific aim A, DTI and anatomical MR imaging data of 40, right handed healthy volunteers were used (age: 33.8 ± 12.7); aim B required the sampling of a large, open access database, resulting in the images and phenotypical data of 155 subjects (age: 38.8 ± 19.4). Aim C required retrospective data analysis of 40 patients (age: 38.6 ± 16.6) with brain gliomas and the construction of a dataset that was determined by the availability of an adequate pre-operative radiological workup including DTI acquisitions; the distribution of patients according to the WHO grade was the following: Gr. II.: 26, Gr. III: 3, Gr. IV: 11 subjects.

2.2. Imaging protocol and image processing steps

We used DTI datasets originating from 3 sources (aims A, B, C) therefore parameters of the imaging sequences were heterogeneous; we report these in the order of aims. Voxel sizes were 1.5*1.5*3.3 mm, 1.5*1.5*5 mm and 2*2*2 mm.The number of diffusion weighting directions was 12, 64and 25.The field strength of the scanners used was 1.5T except for aim C where a 3.0T MRI was employed).

The acquisition of raw, diffusion weighted images allowed the voxel-wise estimation of the diffusion tensors for each subject. The

calculation of fractional anisotropy (FA), mean diffusivity (MD) and other parametric images was based on the equations described in the relevant literature.

To study the properties of normal connectional anatomy for specific aims A and B, the following processing steps of the DTI data were performed:

(1) Fitting a symmetric tensor to the DWI data and using the tensor's eigenvalues to calculate secondary, parametric maps, such as the fractional anisotropy image.

(2) Spatial standardization of subjects' images to achieve good anatomical overlap across subjects; i.e. by non-linear registration of T1-weighted and DTI data to a standard neuroimaging template space with the FNIRT algorithm in the FSL software package.

(3) Definition of seed regions on template images of digital brain atlases.

(4) Estimation of intra-voxel distribution of fiber populations.

(5) Performing probabilistic tracking of structural connections arising from the investigated region.

DTI processing steps were carried out using the FMRIB Diffusion Toolbox in the FSL software, with the relevant algorithms and macros for standard image processing pipelines.

2.3. Image processing steps to study the connectional anatomy and normal diffusion anisotropy

The mask of the insular cortex was defined on a T1-weighted standard brain template by manual drawing, while for the MD nucleus, we used a 3D representation of Morel's Stereotactic Atlas of the Human Thalamus. For specific aims A and B, we used probabilistic diffusion tractography to map the fiber trajectories emerging from the observed regions (insular cortex mask and mask of the mediodorsal thalamic nucleus), details about this method is provided elsewhere. We stored the fiber trajectories as connection probabilities in ordered matrices on which a k-means algorithm was run to separate the pathways that were different to the maximal degree, similarly to other studies aiming connectivity-based clustering or gray matter or the thalamus. As a result of this step, two areas were revealed in the left- and right insulae and mediodorsal thalamic nucleus which were segregated on the basis of remote connectivity. We provide a description of such connectivity-based subdivisions, the fiber anatomy from the two, newly revealed networks, the interhemispheric variability of such areas and the properties of diffusion measurement in the clusters.

2.4. Glioma grade assessment by using diffusion tensor imaging: image processing steps

Secondarily, we aimed to use DTI to characterize the spatial patterns of diffusion anisotropy in a pathological scenario, namely in patients with gliomas and correlate such findings with histological

features that are used to type these tumors (aim C); more specifically, to perform analysis based on image features of the following DTI derived parametric maps. Preoperative DTI data comprised: unweighted (B_0) images, fractional anisotropy, longitudinal and radial diffusivity maps, directionally averaged diffusion-weighted imaging, and trace images. Extracting imaging features for this step was carried out in the space of the diffusion tensor images, no registration or transformation of DTI parametric maps was performed. A crucial step during each procedure was the definition of tumor borders and the delineation of from the brain adjacent to tumor areas (BAT). The extent of the tumors and areas of tumor-associated edema were visually inspected on postcontrast T1-weighted, T2-weighted and FLAIR images. Regions of interests (ROI) were placed in two aspects: the tumor core and tumor periphery. The peripheral region was defined as the maximum high intensity abnormality seen on the unweighted, B0 images (non-enhancing, T2 abnormality), while the tumor core was outlined inside that region, on the central, low value abnormality seen on fractional anisotropy images. Sampling consisted of generating histograms for gross tumor volumes; 25 histogram bins (=histogram channels) per scalar map were calculated (150 total). We hypothesized that the representation of image features as histogram is plausible for the characterization of the whole, three-dimensional tumor volume. The histogram bins that allowed the most precise determination of low-grade (LG) or high-grade (HG) classification were selected by multivariate discriminant analysis, this resulted in a predictive model that is optimized to use the histogram

features as input to predict that grade of new cases, where the confirmatory histopathology is not available. Accuracy of the model was defined by the success rate of the*leave-one-out cross-validation* compared with the ground truth histopathology.

We aimed to show a method that portrays glioma grade, therefore databases were construed that incorporated preoperative DTI data, tumor delineations and information on tumor grade; this data was used to train an artificial neural network classifier that performs voxel-by-voxel analysis of tumor grade. Results were mapped to grayscale images whereas grade map was defined as a composite, nosologic map that depicts local grade assignments for intratumoral regions.

3. Results

3.1. Description of the connectional anatomy and diffusion anisotropy of the insula

First, we used a representative subject population of 40 people to demonstrate the averaged fibertracking based tract anatomy of the human insula. Such fiber tracts were clustered into two distinct populations, originating from the anterior and posterior insula (study aim A). As a result of the connectivity-based subdividing of the insular cortex, we defined an anterior (AI) and posterior insula (PI), the former extending to approximately one-third of the antero-posterior (AP) axis of the insula, delimited by a curved plane perpendicular to the AP axis. In both hemispheres, the AI comprised the limen of the insula and the anterior short gyri enclosed by the precentral insular sulcus; this

partition also included the antero-ventral part of the long insular gyri. The outlines of the change in connectivity profile did not respect the known cytoarchitectural subdivisions and were shown to be independent from the gyral anatomy. We observed significant interhemispheric asymmetry in the volumes of connectivity-based subdivisions. This putatively marked a leftward functional dominance of the anterior insula and its reciprocally interconnected targets which influences the size of insular area where similar connections are represented. The mean diffusivity (i.e. magnitude of diffusion) was higher in the anterior insula in both hemispheres while the anisotropy (FA value) was not different.

3.2. Description of the connectional anatomy of the mediodorsal thalamic nucleus

Fiber tract anatomy arising from the mediodorsal thalamic nucleus were observed (aim B), which presents a good overlap with the classical descriptions of thalamocortical connections in primates or with other in vivo studies on humans. The separation border of the connectivity-based clusters was observed to be parallel to the midline resulting in a medial (MD_{med}) and lateral (MD_{lat}) subdivision of the mediodorsal nucleus. This investigation revealed only a limited agreement between the borders of the connectivity-based subdivisions and the classical, cytoarchitecturally described areas (e.g.: MD_{med} vs. MDmc). The MD_{med} cluster extended approximately to one half of the latero-lateral diameter of the MD nucleus, and unlike the borders of the MDmc, it proportionally extends superiorly and anteriorly. We

controlled the anatomical connections of this two segregated networks emerging from the MD. Here we report the connections in the order of descending strength or importance, using the nomenclature by common digital brain atlases (Talairach, Harvard-Oxford Atlas). Connections from the MD_{med}: frontal pole (Brodmann 10), frontal orbital cortex, frontal medial cortex, temporal pole, amygdala, parahippocampal gyrus – anterior division, lateral occipital cortex – superior division. Connections from the MD_{lat} clusters were the following: frontal pole (Brodmann 10), superior frontal gyrus, middle frontal gyrus – anterior parts, inferior frontal gyrus pars triangularis, supplementary motor cortex.

3.3. Glioma grade assessment by using diffusion tensor imaging

Constructing histograms of preoperative radiological images over the tumor volume was a feasible technique to extract image features (study aim C). We examined LG and HG group averaged histograms representing the B_0, FA, DWI, longitudinal and radial diffusivity and trace value distributions in low and high grade gliomas. Discriminant analysis revealed that 6 histogram bins are feasible enough for the discrimination: 3 from the DWI images and single bins from the B_0, fractional anisotropy and the longitudinal diffusivity images' histograms. With all cases left in, the model reached 92.5% precision in classifying cases according to their grade (post hoc classification). The "leave-one-out" cross-validation of the same dataset resulted in 87.5% success rate (a priori classification), this model resulted in high

specificity (88.46%) and high sensitivity (85.71%) in identifying HG gliomas. Three LG gliomas were incorrectly classified as HG gliomas. One of these tumors was a Gr. II. oligoastrocytoma according to WHO histopathology criteria. It is noteworthy that 65% of the tumor cells of this lesion carried mutant p53 protein. The latter feature is ominous and may suggest imminent progression to a secondary glioblastoma multiforme. Preoperative classification of two glioblastoma multiforme cases was also incorrect as they were identified as LG tumors. Next, we evaluated the discriminant analysis on a slightly modified database: the cases with oligodendroglial components were omitted. This approach resulted in high specificity (100%) with low sensitivity (72.7%), classification accuracy for both the training and the cross-validation scenario was 87%. Classifying the tumors using the histogram approach, the WHO grade II-III-IV. separation agreed with the grading of the pathologist in 90% of the cases. By means of cross validation, a success rate of 80% was obtained for grouping the cases. Despite the relatively high overall accuracy, we must emphasize that it was not possible to classify the grade III. cases correctly, all the 3 cases were incorrectly categorized either as grade II. or IV.

The color hue on nosologic glioma grade maps allowed the discrimination of low and high grade cases, this method revealed connection between the heterogeneous appearance of tumors and the histopathological findings.

4. Discussion

4.1. Characterization normal patterns of diffusion anisotropy and connectional anatomy

Regarding the insula (aim A) we report that the DTI-based segmentation overlaps with the same depictions of studies using fMRI; and it is noteworthy that connections of the ventral part of the long insular gyri and the anterior short insular gyri are similar, coherence was more pronounced on the structural connectivity segmentations where a larger proportion of the long gyri were included in the area denoted as anterior insula (AI). There is evidence from primates and humans that the anterior insula presents a significantly different cytoarchitecture as well as afferent and efferent connectivity than the posterior division. The AI, as defined by its connections, embodied the agranular and part of dysgranular insula which is known to be interconnected to the frontal, orbitofrontal cortex and the amygdaloid body in macaque monkeys and our probabilistic fiber tracts confirm such observations. Connectivity data of the human insula is sparse and limited to observations from resting state fMRI measurements or depictions of anatomical connectivity by means of diffusion tensor tractography. Our findings imply that connections of the AI have larger leftward representation relative to the total insular gray matter volume. Further support for our results on interhemispheric differences comes from a study by Cao et al. which demonstrated a marked L-R asymmetry of anisotropy (i.e. the “orderliness” of diffusion) of the subinsular white matter, implying a

putative interhemipsheric asymmetry in the trajectory or density of pathways emerging from or projecting to the insula.

A widely accepted neuroanatomical model describes segregated *cortico-striato-pallidal-thalamocortical* networks, two of those relaying in the MDmc and MDpc. The trajectories of two "cognitive" circuits greatly coincide with the results of the present study suggesting that the two revealed subdivisions might be the thalamic representations of the dorsolateral prefrontal cortex (MD_{lat}) and the orbitofrontal (MD_{med}) segregated networks. This is further supported by the fact that in our study, the algorithms were forced to search for two networks that pass through or originate from the mediodorsal thalamic nucleus and differ from each other with the largest possible degree putatively revealing segregated circuits. We provided a description of two MD connectivity-based subdivisions, namely a medial and lateral part, which only partially coincides with the classical, cytoarchitecture based parts of the MD.

4.2. Characterization pathological patterns of diffusion anisotropy in brain gliomas

We aimed the next part of our work at the clarification of the interrelationship between the anisotropy patterns of cerebral water diffusion and various grades of gliomas. It appears that the heterogeneity among high grade tumors results in a more deviated and less kurtotic distribution of DWI values while the low grade cases present relatively less deviation; our observations support the hypothesis

that intratumoral heterogeneity can be depicted by calculating histograms for the tumor volume. Clonal selection within tumors is common and is indicated by locally altered diffusion characteristics which result in the modified distribution of voxels' values as indicated by a new peak on the histogram. Such changes do not necessarily affect the mean or median values of the entire voxel population, but significantly change the value of an individual histogram bin. Arvinda and colleagues presented a method that employed data from perfusion- and diffusion-weighted imaging and defined cut-off values for accurate classification. Our results regarding the differentiation of LG and HG gliomas had similar specificity values (Arvinda et al.: 87.1% vs. our 88.4%) while the sensitivity was lower in our approach (Arvinda et al.: 90-95% vs. our 85.7%), but a significant difference is that we report results after leave-one-out cross-validation. DTI based grading of gliomas was more precise than data from the literature on grading using features on conventional (Gadolinium-enhanced) MR images. Important limitations of the present study are the relatively low number of cases (40) on the one hand and the unequal representation of LG and HG cases on the other (13 vs. 27). There is also an ambiguity about the correctness of the pathology workup due to the fact that tissue sampling is not representative for the entire lesion. Even though the radiological workup was prepared to represent the whole tumor volume, the diagnoses used to "train" the database originated from the histopathological findings. We also point out that the discrimination of WHO grade III. cases was insufficient.

4.3. Glioma grade assessment using DTI – methodological limitations

Despite all the benefits of multimodal imaging, borders of especially low grade gliomas remain ill-defined and therefore ROI placement is a major cornerstone in the statistical analysis of radiological data. We find it important to minimize the involvement of voxels from non-tumorous areas in the statistical analysis and we suggest the exclusion of displaced or infiltrated WM tracts from the histogram construction; however, eventually measurements of various zones within any given tumor seem inevitable. When delineating HG tumors, the contrast enhancing rims engulfing a necrotic center putatively marks the active part of the tumor, however, this distinction is yet impossible for low grade gliomas. We applied fractional anisotropy images to visualize regions within the tumor where white matter integrity is severely disrupted (i.e. this is hallmarked by low FA values). For such tumors, this region was used as a guidance to outline the three-dimensional volume for the statistical analysis. Similarly, defining the BAT in low grades is not possible unambiguously. We note that the displaced, splayed tracts surrounding the main tumor parts on FA images may indicate relatively spared white matter, but the modality to assess the magnitude of tumorous infiltration is not available yet.

5. Conclusions

In vivo probabilistic tracking of structural connections using DTI data provides a novel window on neuroanatomy that was previously unavailable. We provided evidence that the in vivo tract anatomy of the insula and MD is similar to the depiction of trajectories by tract tracing studies in primates. Connectivity-based parcellation of the insular cortex and the mediodorsal thalamic nucleus revealed distinct and separated networks originating from these territories.

The characterization of anisotropy patterns in brain gliomas allowed us to construct a classifier model that is feasible for the non-invasive, imaging based preoperative determination of grade.

Glioma nosologic grade maps are advantageous in the visualization of the heterogeneous nature of intratumoral diffusion parameters and can further contribute to the characterization of tumors by using preoperative diffusion tensor imaging.

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List of publications related to the dissertation

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