Construction of a population based diffusion tensor image atlas of the Sprague Dawley rat brain

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Introduction/Purpose: The rat is a commonly used animal model for a wide range of human neurological disorders, and innumerable strains, substrains and genetically modified rats are employed to mimic various neuropathologies. Longitudinal investigations of such animal models require sensitive tools for *in vivo* monitoring of brain neuropathology. Magnetic resonance diffusion tensor imaging (DTI) allows *in vivo* and non invasive estimation of the diffusion coefficient of water molecules in brain white matter, and is increasingly employed to evaluate white matter integrity. Sensitive DTI derived measures, such as fractional anisotropy (FA), mean diffusivity (MD) and principle direction of diffusion ($\mathbf{e_1}$) have been suggested as biomarkers of pathologic WM changes. In such studies, control subject groups are quantitatively compared to group of subjects in which pathology is diagnosed or induced. The two most commonly used methods for quantitative DTI analyses are a hypothesis-driven manual region of interest (ROI) analysis and automated voxel based analysis (VBA). ROI approaches are challenging due to time consuming, manual delineations of anatomical boundaries. VBA analyses are typically conducted by co-registration towards a chosen single subject template, which not necessarily is representative for the investigated groups. To allow more consistent and reproducible ROI delineation and VBA analyses, we here propose an accurate *in vivo* population based 3D DTI atlas of the normal adult Sprague Dawley rat brain based on precise, manually delineated anatomical labels. This atlas will provide an average anatomical template for coregistration of DTI images for VBA analyses, and facilitate automated atlas-based segmentation of rat brain structures of interest.

Methods: **(1) *In vivo* scans:** *In vivo* experiments were carried out on 9 normal adult, male, Sprague Dawley rats using a 9.4T Bruker Biospec scanner (Ettlingen, Germany). DWI images were acquired using a fast spin echo sequence with an encoding scheme of 6 DW-gradient directions using b-value = 800 s/mm^2, TR/TE=2200/ 34ms, δ/Δ = 5/ 12ms, acquisition matrix = 256 x128 (zerofilled to 256 x256), FOV= 35 x35mm^2, slice thickness=0.43mm. Additionally, one b_0 image was acquired. For each animal, DWI-datasets were acquired for 7 repetitions (two averages each) which resulted in a total scan time of 4h. **(2) *Ex vivo* scans:** In 4 other Sprague Dawley rats, *ex vivo* DTI scans were acquired at the Center for In Vivo Microscopy at Duke University (Durham, NC) using a 7T Magnex 7.0T/210 mm bore magnet controlled by GE EXCITE consoles. Specimens were imaged in a home-built solenoid radiofrequency coil with long axis of the brain parallel to the coil axis. A diffusion-weighted spin-echo pulse sequence with extended dynamic range was used to acquire 3D volume images (FOV=45x22.5x22.5mm^3, Data matrix = 512x256x256, resolution = 0.0879x0.0879x0.0879mm^3, TR=100 ms, TE=15.6 ms, NEX=2). Diffusion encoding was performed using a pair of half-sine gradient pulses (δ/Δ=3.2/8.3 ms, G=600 mT/m, corresponding to a *b*-value of 800s/mm^2). **(3) Non-rigid coregistration:** In order to minimize global morphological differences, a coarse alignment of multiple datasets was established by applying an automated affine coregistration technique with 12 degrees of freedom (rotation, translation, scaling and shearing). Residual local image misalignments are corrected by performing a non-rigid coregistration technique, in which the images are modeled as a viscous fluid whose deformation is driven by a simplified Navier Stokes equation [1]. The coregistration algorithm takes full advantage of the relevant information that is encoded in DT images, particularly the tensor orientation, thus enabling a better alignment of different WM structures [2]. After applying the non rigid deformation field, tensor reorientation is performed based on the preservation of principal direction (PPD). **(4) Population based atlas construction:** Of all 9 *in vivo* datasets, a population based DTI atlas that preserves the orientational DT information robustly and contains a minimal bias towards any specific individual data set, was created [3]. **(5) Manual segmentation:** A selection of gray matter (the caudate putamen complex, lateral globus pallidus, medial globus pallidus, substantia nigra), white matter (external capsule, corpus callosum, internal capsule and cerebral peduncle, fimbria of the hippocampus, anterior commisure, optic tract and stria terminalis), and other boundaries (lateral ventricle, external brain surface) where manually segmented on basis of high resolution *ex vivo* T_1 and color encoded FA maps, with RGB-colors representing the orientation of the primary eigenvector and intensity values in proportion to the FA value, using the Paxinos and Watson [4] rat brain atlas as a general reference. The parcellation maps were non-linearly warped, conducted by the non-rigid coregistration of DWI datasets, towards the *in vivo* population based atlas in order to correct for spatial differences between *ex vivo* and *in vivo* datasets.

Results: The proposed atlas (illustrated in Fig. 1) allows automatic segmentation of ROIs in rat data and synthesis of different DT results in a standard framework. Our preliminary results indicate that more accurate image alignment is obtained after a non-rigid coregistration towards our population averaged template, as compared to subject based templates.

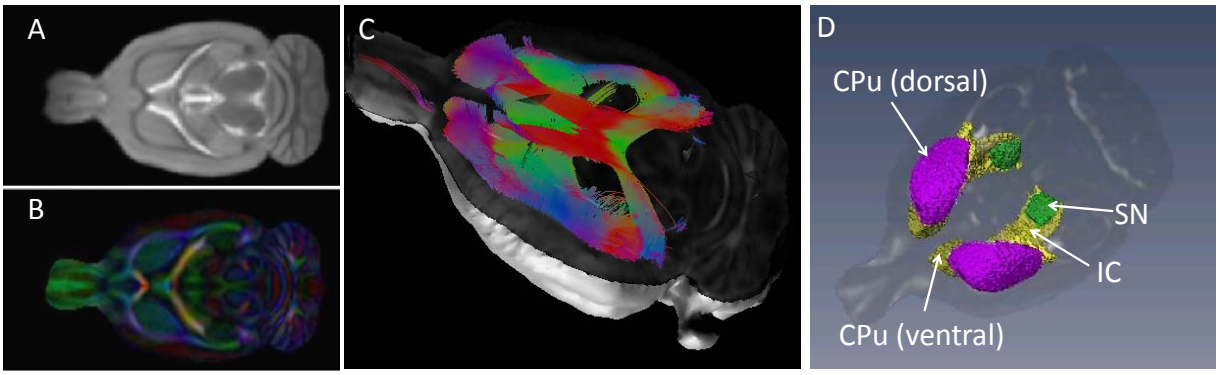

Figure 1: A single horizontal slice of the population based atlas is shown: B_0 map (A) and a color encoded FEFA map for which the colors indicate the main direction of the underlying fibers (B). The sharp resolution of the atlas is particularly evident in the cerebellum where the perpendicular orientations of the different layers are visible. Since the atlas contains all DTI information, continuous DT fibers can be reconstructed using a streamline tractography algorithm. In (C), all DT fibers in the brain are visualized in the exploreDTI software [5]. Additional grey matter structures were manually delineated to enable automated ROI analysis. In (D), the caudate putamen complex (CPu), substantia nigra (SN), and internal capsule (IC) are superimposed on a transparent FA map.

Summary and conclusion: In this study, an anatomically labeled DTI atlas of the adult Sprague Dawley brain is proposed. The atlas was constructed using a population based atlas approach to create a template which represents the unbiased average anatomy. During the construction, a non-rigid coregistration technique was used to avoid local misalignment inaccuracies, and smoothing, due to intersubject morphological differences. The manual delineation of brain structures was performed on high resolution *ex vivo* scans and the resulting parcellation maps were non-linearly warped into the *in vivo* atlas space afterwards. We conclude that the reliability of the results of ROI and VBA analyses can be increased with use of this population based DTI atlas

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