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Atlas-based *vs.* individual-based deterministic tractography of corpus callosum in multiple sclerosis

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Abstract - Diffusion tensor (DT) magnetic resonance imaging is able to quantify tissue microstructure properties and to detect pathological changes even in the normal appearing tissues. DT sequence parameters which provide optimal SNR and minimum acquisition time, and an individual-based tractography post-processing allowed corpus callosum tractography even in multiple sclerosis (MS) patients also with no need of a-priori atlas. In this preliminary study, we were able to obtain reliable individual-based tractography in 28/30 MS patients. DT-derived indices computed in tracks obtained with individual-based tractography were able to differentiate healthy volunteers from MS patients better than the same indices computed with the atlas method. This indicates that such an optimized sequence may be a reliable tool to be used in future MS studies.

I. Introduction

Diffusion tensor (DT) magnetic resonance (MR) imaging allows *in vivo* examination of the tissue microstructure, obtained by exploiting the properties of water diffusion. The diffusion tensor computed for each voxel allows us to calculate the magnitude of diffusion, reflected by the mean diffusivity (MD), and the degree of anisotropy, which is a measure of tissue organization, expressed by indices like fractional anisotropy (FA). The pathological elements of MS have the potential to alter the permeability or geometry of structural barriers to water diffusion in the brain. Consistent with this, several in vivo DT MRI studies have reported increased MD and decreased FA values in T2-visible lesions, normal-appearing white matter (NAWM), and grey matter (GM) from MS patients [1]. Tractography based on DT MRI is an effective tool to evaluate the anatomy of white matter (WM) fiber tracts in humans [1]. Since in MS patients FA is reduced inside the lesions and in the NAWM, the tractography might erroneously terminate. For this reason, studies have been conducted using the tractography-based group mapping method [2][3], which superimposes a template of white matter fiber tract probability map, obtained from a cohort of healthy volunteers (HV), to compute DT derived indices also in patients with MS.

In this paper, we compared the reconstructions of corpus callosum (CC) white matter (WM) fiber bundle made using atlas-based and individual-based tractography to investigate the feasibility and the potential advantages of the latter method.

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II. Material and Methods

A. Subjects

From the population followed at the MS clinic of the Scientific Institute Santa Maria Nascente, Don Gnocchi Foundation ONLUS, we recruited 30 patients with MS (male/female= 8/22; mean age=45.0, range= 26-67 years).

Eighteen HV (male/female=10/8, mean age 43.1 years, range: 24-57 years), with no history of neurological disorders and a normal neurological examination, were also studied.

Local Ethical Committee approval and written informed consent from all subjects were obtained before study initiation.

B. MRI acquisition

Brain MRI scans were obtained using a 1.5 T Siemens Magnetom Avanto scanner (Erlangen, Germany).

The following MR sequences were acquired in a single session: a) dual-echo (DE) turbo spin echo (TSE) (repetition time (TR)=2650 ms, echo time (TE)=28/113 ms, echo train length (ETL)=5; flip angle=150°; 50 interleaved, 2.5 mm-thick axial slices, matrix size=256x256 and field of view [FOV]=250 mm^2; b) three dimensional (3D) T1-weighted magnetisation-prepared rapid acquisition gradient echo (MP-RAGE) (TR=1900 ms, TE=3.37 ms, TI=1100 ms, flip angle = 15°, 176 contiguous, axial slices with voxel size=1x1x1 mm3, matrix size=256x256, FOV=256 mm2, slab thickness=187.2 mm). DE and T1-weighted acquisition schemes were chosen based on published guidelines for MS studies [4]. During the same scanning session, the following sequences were acquired for diffusion tensor imaging (DTI): DTI-A) pulsed-gradient spin-echo echo planar (TR=7000 ms, TE=94 ms, 50 axial slices with 2.5 mm slice thickness, matrix size=128x96; FOV=320x240 mm) with diffusion gradients (b-value=900s/mm^2) applied in 12 non-collinear directions; DTI-B) pulsed-gradient spin-echo echo planar pulse sequence without SENSE (TR=6500 ms, TE=95 ms, 40 axial slices with 2.5 mm slice thickness, matrix size=128x128; FOV=240x240 mm) with diffusion gradients

(b-value=1000s/mm^2) applied in 12 non-collinear directions. Two acquisitions for each set of diffusion gradients were performed, in order to improve SNR. The acquisition time was 3'09'' for DTI-A and 2'56'' for DTI-B.

The main differences between the DTI A and B sequences are b-value (900s/mm^2 vs 1000s/mm^2), pixel size (2,5 mm x 2,5 mm vs 1,88 mm x 1,88 mm) and TR (7000 ms vs 6500 ms). As previously demonstrated [6], DTI-B achieves a better trade-off than DTI-A in terms of spatial resolution and SNR, coupling both decreased pixel size and increased b-value.

MS lesions were first identified by agreement of two experienced observers on proton density (PD)-weighted images, using T2-weighted scans to increase the confidence in lesion identification. Total T2-hyperintense lesion loads (LL) were measured using the Jim software (Jim 5.0, Xinapse System, Leicester, UK).

3D T1-weighted images were automatically segmented to GM, WM and cerebrospinal fluid (CSF), using SPM5 (www.fil.ion.ucl.ac.uk/spm) and maximum image in-homogeneity correction. The segmentation protocol used a cluster analysis method to separate pixels based on intensity differences, together with *a priori* knowledge of spatial tissue distribution patterns in normal subjects. Each pixel was then classified as GM, WM or CSF, dependent on which mask had the greatest probability at that location: this generated mutually exclusive masks for each tissue.

C. *Post processing of DTI data*

The following steps were followed for both DT sequences separately.

Diffusion-weighted images were first corrected for distortions induced by eddy currents using an algorithm that minimizes mutual information between the diffusion unweighted (b0-volume) and weighted images, using FSL package (http://www.fmrib.ox.ac.uk/fsl/).

Then, diffusion tensor was calculated for each voxel, assuming a mono-exponential relationship between signal intensity and the product of the b-matrix and DT matrix components, using the freely available Diffusion Toolkit software (version 0.4.2, www.trackvis.org), with multivariate linear regression [5]. After DT estimation, eigenvalues (λ_1, λ_2, λ_3) were computed, and from them MD and FA indexes. MD is the mean value of the eigenvalues; FA is:

$$FA = \sqrt{\frac{3}{2}} \frac{\sqrt{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}}{\sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad (1).$$

For isotropic diffusion, FA=0; on the contrary, the more an eigenvalue prevails to others, the more FA becomes close to 1 and the tissue contained on the corresponding voxel is anisotropic.

FA and MD histograms were computed on tissues apparently not damaged on conventional imaging with the following steps: first, T2-hyperintense lesions were masked out from MD and FA maps, then GM and WM mutual exclusive masks allowed to extract values of indices separately in WM and GM. In order to avoid MD overestimation and FA subestimation due to the contribution of CSF in voxel classified as GM or WM (partial volume effect), the first line outer voxels were eroded and excluded from the index analysis. From these histograms, average MD was computed for GM and NAWM. Average FA was derived only for the NAWM, since no preferential direction of water molecular motion is expected to occur in the GM, due to the absence of a microstructural anisotropic organization of this tissue compartment.

D. *Fiber tracking*

Fiber tracking was performed by Diffusion Toolkit, v0.4.2 [7] with interpolated streamline algorithm and visualized by the freely available software TrackVis v0.4.2 (www.trackvis.org). Tracking was terminated after encountering a voxel with FA lower than 0.200 for healthy volunteers and 0.050 to 0.175 for patients. FA threshold values used in the present study for the tracking termination condition were chosen patient by patient, taking into account the problem of fiber termination with standard FA values due to the lesional load.

The maximum accepted curvature between two successive eigenvectors was 35° [8].

The individual-based tractography was performed with seeds in corpus callosum (CC), identified in three consecutive mid-sagittal slices of the FA map. In order to study the microscopical properties of the three main CC anatomical parts in isolation, three hand-drawn region-of-interests (ROIs) were drawn, corresponding to genu (anterior portion), body (central portion) and splenium (posterior portion). The inferior part of the body was identified on the midsagittal slice, when it is visible on axial slice, analyzing axial slices from down to up. A second ROI (*not* ROI) is necessary only when some bundles are erroneously reconstructed starting by the first ROI in CC.

The individual-based tractography was compared with the atlas-based one: templates of fiber tracts were obtained for the entire CC and for the three parts described above. The tractography atlas was created from the 18 HV. After the registration (SPM5, www.fil.ion.ucl.ac.uk/spm) of the 18 b0-volumes to the standard Montreal Neurological Institute (MNI) stereotaxic space, the related transformations were applied to the 12 diffusion-weighted and eddy current corrected images for every subject, and a mean 4D-DWI was calculated, averaging all the corresponding volumes. From the mean DWI, DT was computed in each voxel and subsequently FA and MD atlas maps.

Atlas CC fiber tracts were obtained with CC ROI positioned with the same method as the previous approach.

Histograms of MD and FA values were computed for every subject on the CC fiber tract, loading into TrackVis the specific tract of interest (TOI) and individual MD or FA maps, and extracting statistics of MD and FA in TOI. The parameters extracted for all the 48 subjects in these specific tracts were obtained with two methods: using the tract of the single subject or the atlas tract, and the values were compared in the following analysis.

E. *Statistical analysis*

The intra-class-correlation-coefficients between the 2 DTI sequences were calculated in the study, using the values of NAWM-FA, NAWM-MD and GM-MD from all the study subjects (HV and MS patients).

The Spearman rank correlation coefficient (SRCC) was used to estimate the correlation between DTI-derived measures in normal-appearing tissues and CC fiber tracts (entire CC, genu, body, splenium) and the subjects' condition (HV *vs*. MS patients). This analysis was repeated four times, because FA and MD values were computed in CC tracked with two methods and with data obtained from two DTI sequences.

III. RESULTS

A. *Micro-structural indices of fiber integrity: statistical comparison of DTI-A and DTI-B results*

We found a high concordance between measures derived from DTI-A and DTI-B (r values ranged from 0.91 to 0.99). Using the Spearman's rank coefficient, the correlation between DTI-B-derived metrics and subjects' condition was higher than the one between DTI-A-derived metrics and the subjects' condition. Consequently, DTI-B seemed to be more sensitive to the differences between HV and MS patients: figure 1 shows 95% confidence intervals calculated according to the standard methodology as mean values ±1.96*standard errors for CC metrics computed with DTI-A and DTI-B.

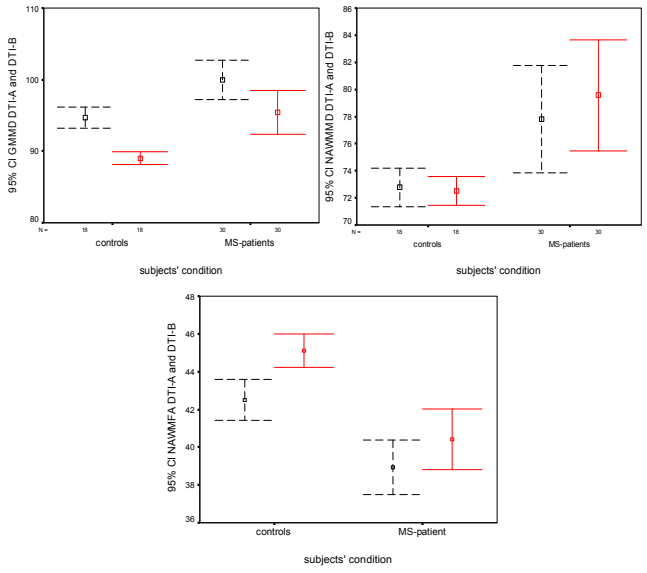

Fig. 1. Mean values ± 1.96*standard errors of GM MD (top left), NAWM MD (top right) and NAWM FA in HV and MS patients, for DTI-A (dotted-black) and DTI-B (red).

This result was also confirmed by comparing the SRCC between all the parameters computed using DTI-A *vs*. DTI-B and the subjects' condition, both for individual- and atlas-based tractography. Again, we found that DTI-B discriminates better HV from MS patients that DTI-A (with the individual-based method, absolute SRCC values ranged from 0.62 to 0.83 for DTI-A and from 0.75 to 0.84 for DTI-B; with the atlas-based method SRCC ranged from 0.57 to 0.68 for DTI-A and from 0.58 to 0.71 for DTI-B).

B. *Statistical comparison of micro-structural indices in the CC derived from individual-based and atlas-based tractography*

For all the HV, tractography was successfully obtained with a FA threshold of 0.200 (see an example in Fig. 2).

The individual-based tractography algorithm with different FA threshold allowed to perform CC fiber tracking for 28/30 patients (see an example in Fig. 3).

Significant differences were found in DT metrics in CC (genu, body and splenium) derived from the two different tractography methods.

The SRCC analysis showed that the individual-based tractography had a better performance than the atlas-based one to describe the micro-structural indices of the CC. Indeed, when we analyzed the SRCC of DTI-derived metrics in CC and in its three regions, obtained with the same sequence but with the two tractography methods, it was found that the discrimination between the two groups was significantly better using individual based- than atlas-based tractography (absolute SRCC of the DTI-B derived metrics ranged from 0.75 to 0.84 for individual-based and from 0.58 to 0.71 for atlas-based tractography).

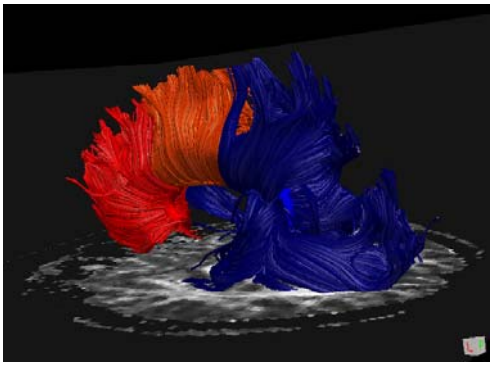

Fig. 2. Corpus callosum tractography for a 50-year old healthy subject.

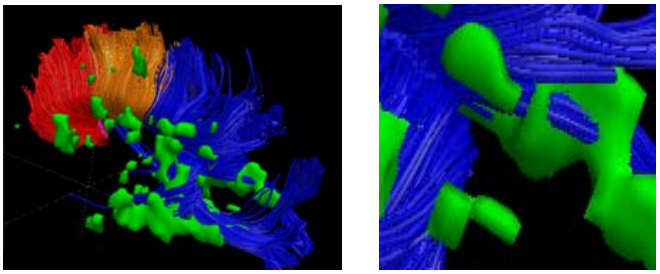

Fig. 3. Corpus callosum tractography of a 47-year old man with RRMS and a lesion load of 8.7 ml (right). Lesions are superimposed on tractography and visualized as green blobs. Below: zoom of tracts which pass through the lesions of the same patient.

IV. DISCUSSION

Both the DTI sequences showed a good correlation with the subjects' condition, i.e. were able to discriminate HV from MS patients, but the sequence (DTI-B) with higher resolution and higher diffusion sensing had the best

performance. This sequence may, therefore, represent a powerful tool for future MS studies aimed at investigating the disease burden and possibly its evolution.

The main aim of the study was to compare the atlas- and individual-based tractography in MS patients. The success of the individual-based approach is to follow the tract passing trough lesions even if the loss of anisotropy could cause termination of fiber tracking, without overestimation of tract damage due to partial volume effect, a problem that seems to affect the atlas-based method. However, the atlas is necessary for patients with a great lesion burden in the tract of interest, which interrupts the tractography algorithm. Figure 4 shows the CC individual tractography of one MS patient in which individual tractography stops near the lesions. We found that atlas-based measures may overestimate the damage in comparison to the individual one, even if it is able to differentiate MS patients from HV.

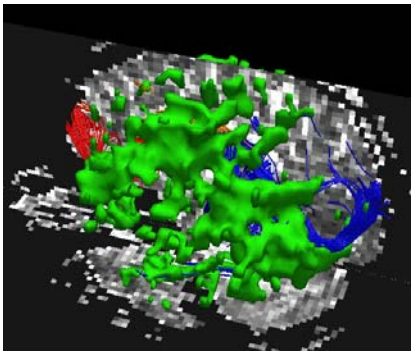

Fig. 4. Corpus callosum tractography of a 38-year old woman with MS and a lesion load of 33.10ml. Lesions are superimposed on tractography and interrupt it due to the great volume.

Fig. 5 shows the results of the tractography of CC body for one MS patient, thus highlighting how the body was obtained: even if with the "classical" approach the tractography algorithm was interrupted due to the lesion, after reducing the FA termination threshold the fiber was tracked through the lesion.

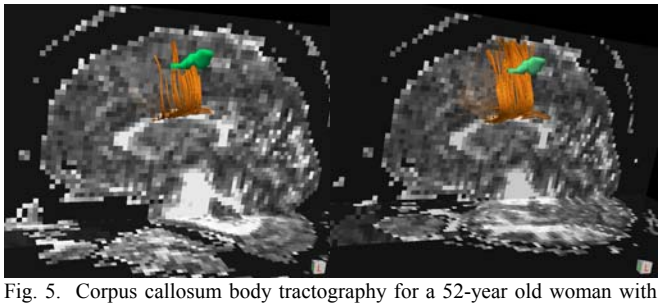

Fig. 5. Corpus callosum body tractography for a 52-year old woman with SPMS and a lesion load of 29.61ml. In the figures only the lesion trough which the tract of interest pass by has been segmented. Left: tract is interrupted by the lesion (FA threshold = 0.200); right: tract is not interrupted by the lesion (FA threshold = 0.075).

DTI-derived parameters in the entire CC and in its three portions were found to be significantly correlated with the presence of the disease, thus confirming that the damage due to MS is not only focused in lesions visible in conventional MRI, but also in "normal-appearing" fibers and that the microscopical damage can be quantified by DT MRI. Using DTI-B and the individual-based tractography we were able to better differentiate patients from controls. This combination of sequence parameters and tractography method might, therefore, be a powerful tool for future studies. However, the individual-based tractography approach remains time consuming, due to several reasons. First , it is necessary the selection of the best FA threshold, second, the elimination of fibers outside the tract of interest is needed. Atlas-based methods require only the time for the co-registration of DTI maps to the atlas (around 3 min).

Further studies are needed to validate the methods and to assess their intra- and inter- observer reproducibility. Furthermore, future studies are warranted to *a priori* define the best FA threshold to be used for individual-based tractography in MS patients.

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