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Whole Brain Fiber Based Comparison (FBC) – a Tool for Diffusion Tensor Imaging Based Cohort Studies

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Whole Brain Fiber Based Comparison (FBC) – a Tool for Diffusion Tensor Imaging Based Cohort Studies

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Key words: DTI, ALS, whole brain tractography, tractogram, white matter fibers, mean diffusion, fractional anisotropy, radial diffusion, axial diffusion.

Abstract

We present a novel method for fiber based comparison between Diffusion Tensor Imaging (DTI) scans of groups of subjects. The method entails an initial preprocessing and fiber reconstruction by tractography for each brain in its native coordinate system. Several diffusion parameters are sampled along each fiber and used in subsequent comparisons. Spatial correspondence between subjects is established based on geometric similarity between fibers in a template set (several choices for template are explored), and fibers in all other subjects. Statistical comparison of diffusion parameters between the groups is performed for each template fiber. Results are presented on a single fiber resolution. The method can serve as a first exploratory step in neurologic population studies since it provides pointers to the locations affected by the pathology of interest in the study, without requiring a hypothesis. It is fully automatic and does not make any grouping assumptions on the fibers. The framework is applied to 18 healthy subjects and 23 Amyotrophic Lateral Sclerosis (ALS) patients. Results are compatible with previous findings and with the Tract Based Spatial Statistics (TBSS) method.

1 Introduction

Diffusion Tensor Imaging (DTI) characterizes the diffusion of water in the tissues and is sensitive to the microstructural density, and orientation of tissue membranes (Alexander et al., 2011). This makes it a powerful tool for noninvasive characterization of brain tissues. It is widely used for studying white matter (WM) organization and the microstructural changes that occur with neuropathology and following treatment (Alexander et al., 2007). During the recent 20 years DTI was utilized to study WM architecture and integrity, both in normal and diseased brains. This contribution addresses the application of studying neurological diseases in vivo. This type of research usually aims to identify potential brain targets for therapeutic interventions and to develop diagnostic criteria and outcome measures for clinical trials.

In DTI analysis, a diffusion tensor is computed for each voxel based on a set of Diffusion Weighted Images (DWI). The principal directions of the tensor were shown to generally coincide with the local orientation of WM axon bundles. Tractography algorithms are capable of generating anatomically plausible estimates of WM trajectories ("WM fibers") by tracing these principal directions, creating virtual dissection of major WM tracts for each individual. Diffusion tensors are also used for deriving various diffusivity parameters, such as the Fractional Anisotropy (FA) and the Mean Diffusion (MD). It is noteworthy that DTI-generated fibers may lack the desired integrity in areas of fibers crossings, which is the reason why a plethora of High Angular Resolution Diffusion Imaging (HARDI) models have been introduced in the past 10 years (Prčkovska et al.,2012). However HARDI requires large b-values and at least 60 diffusion orientations, which might not be feasible in clinical application, such as the one here. Therefore this contribution uses DTI, which requires much shorter scan durations that preserve the patient comfort (Prčkovska et al.,2012).

In DTI based research, methods for comparison between groups of subjects can be roughly divided into two categories: comparison of specific predefined brain regions or whole brain comparison. The

advantage of the latter approach is that no prior knowledge of the disease is assumed, and no tedious segmentation of the volumes of interest (VOIs) or fiber tracts is required.

The two most well-known approaches to whole-brain comparison are Voxel Based Morphometry-style analysis, VBM (Ashburner and Friston, 2000) and Tract-Based Spatial Statistics, TBSS (Smith et al., 2006). In VBM-style analysis of WM, FA maps (or maps of other diffusivity indices) are usually used for voxel-wise comparisons between groups of subjects. In TBSS the FA maps of all the individual subjects are projected into a common space and a mean FA skeleton created. Each subject's (aligned) FA map is projected onto the skeleton. Next, voxel-wise statistics of the diffusion parameters are carried out across subjects in this skeleton space (Smith et al., 2006). Both these methods are strongly dependent on registration of all the brains to a single template since the analysis is performed voxel-wise.

Tractography's contribution to population studies became more prominent in recent years. A combination of tractographic and voxel based analysis, tract wise fractional anisotropy statistics (TFAS) was proposed by Mueller et al. (Mueller et al., 2007; Mueller et al., 2009). It is intended to analyze specific WM tracts. Bundles of fibers tracked on an averaged and co-registered brains data are used as a skeleton, which is the basis of voxel-based statistical analysis of the underlying FA maps. TFAS based on different skeletons was used to quantify interconnectivity and to map differences between patients with atrophy of the corpus callosum (CC), where CC is thinned as a result of hereditary spastic paraparesis (cHSP), and age-matched healthy controls. The FA values from the voxels marked by the skeleton were used for t-test comparison between the healthy and the thinned CC groups. Another fiber based analysis scheme was described in a work by Goodlett et al. (Goodlett et al., 2009). First a tensor atlas is constructed from multiple co-registered subjects. Major fiber tracts are reconstructed within this atlas using manually defined seed regions. After creation of the template fiber tracts, diffusion statistics from the individual cases are mapped to the atlas tracts. As a result a fiber bundle is created for each subject using the geometry of the template atlas tract but replacing the diffusion properties with those mapped from the subject. The set of individual tracts with corresponding geometry and varying diffusion

properties is then compared. Yeatman et al. proposed an automated fiber-tract quantification framework that measures tract profiles of MRI parameters for multiple pre-defined WM tracts (Yeatman et al., 2012). The "tract core" is identified as the representative average fiber for each tract. All tract fibers are clipped to include the central part of the tract to equal length and resampled to an equal number of points. Diffusion properties are calculated along the resampled clipped fibers and are summarized at each node by taking a weighted average of the diffusion properties at that node. The resulting profiles are used for inter and intra subject comparison. This approach conserves the along-tract information but averages the measures across the different fibers. A similar approach is described by Colby et al. (Colby et al., 2012), where mean profiles of FA and other metrics are created along a centroid fiber of a pre-defined tract.

In the current work, we propose a novel method for whole brain fiber based comparison between groups of subjects. The preprocessing and tractography of each brain is performed in it brain's own coordinate system. The diffusion parameters sampled along the fibers are used in the subsequent comparison. The spatial correspondence between the subjects is established based on geometric similarities between fibers in a template set and the fibers the other brains. The results are presented for each template fiber. This framework has several advantages over the previously reviewed methods: it does not perform any fiber grouping and does not require manual definition of volumes or tracts of interest. The results are presented in a single fiber resolution, which allows for maximum flexibility in the results' interpretation. Another advantage is that non-linear registration to a common space is not required. As opposed to most of the described fiber based works, our method performs the tractography of each individual brain in its original coordinate space, ensuring an optimal match to the subjects' individual anatomy.

We performed an initial validation of our method using a data set of patients with Amyotrophic Lateral Sclerosis (ALS) and age-matched controls. The results were compared to previously published findings (Ben Bashat et al., 2011; Sato et al., 2010l; Agosta et al., 2010) and to TBSS results.

ALS is a fatal neurodegenerative disease that affects upper motor neurons in the brain and spinal cord, lower motor neurons, as well as sometimes fronto-temporal cortical brain areas. It has a markedly heterogeneous clinical presentation and course (Kiernan et al., 2011). Currently, there is no imaging based diagnostic test for ALS, and confident diagnosis is mainly based on clinical assessments of upper and/or lower motor neuron signs together with a history of progression of symptoms. In many patients with ALS, diagnostic certainty currently entails a delay of about one to one-and-a-half years from onset of symptoms to diagnosis; this delay prevents potentially early treatment with disease-modifying drugs in the future, leads to unnecessary medical interventions and affects negatively patients' quality of life (Paganoni et al., 2014). The greatest contribution of MRI to ALS research so far has been its use in reliably excluding other diagnoses. Extensive search for biomarkers in ALS is now underway and makes use of advances in molecular biology and noninvasive imaging. It was shown (Ben Bashat et al., 2011) that DTI can detect WM impairment in patients with ALS in several brain regions, and might be a sensitive tool for the diagnosis of ALS. Whole brain fiber based analysis approaches hold the promise of discovering useful biomarkers that will advance the formulation of diagnostic criteria.

In the following, we describe the proposed framework for whole brain fiber based comparison. The methodology is described in Section 2; Results are shown in Section 3; Discussion and Conclusions in Section 4.

2 Material and methods

The proposed approach starts with performing streamline tractography for each brain in its native space. The diffusion related parameters, fractional anisotropy (FA), mean diffusion (MD), radial diffusion (Dr) and axial diffusion (Da) are calculated for each brain and sampled along each of its fibers. In a second step the correspondences between the individual fibers in all the brains are found. For that purpose, a template set of whole brain fibers (BT) is selected. For each fiber in BT a set of the closest fibers from each of the other brains in the study is found. Now for each fiber in the template brain we

have a group of parameter values, from the corresponding fibers in the two groups. Typically the groups will be the healthy and the patient group. In a third step a statistical comparison is performed between the sets of values derived from corresponding fibers in the two groups. Each of these steps and the input data is described in detail next.

2.1 Data

Subjects: The data set that is used in this paper consists of two groups of subjects: a control group of 18 healthy subjects and an ALS group of 23 patients. Only patients less than 60 years of age with no more than two cardiovascular risk factors were included. The healthy control group included only individuals with no history of neurological disease and without any abnormalities detected on conventional MR images (T1 and T2 weighted images). These are the same patients which were used in Ben Bashat et al. (Ben Bashat et al., 2011).

MRI protocol: MRI scans were performed on a 3.0T MRI scanner (GE Signa-EXCITE, Milwaukee, WI, USA). The DTI scans were acquired along 15 or 19 gradient directions (b = 0, 1000 s/mm2). Other imaging parameters: field of view = 220mm; acquired matrix 128 x 128; Time to repeat/ echo time (TR/TE) = 11,000/91ms); slice thickness = 3 mm.

2.2 Tractography and Parameter Sampling

The brains in the study were preprocessed using FMRIB Software Library software for eddy current correction and head motion correction (using FSL[1]). For each brain the DTI derived parameters FA, MD, Dr and Da were calculated per voxel. The definitions for the parameters are given in Equations (1-3), where λ_1, λ_2, λ_3 are the eigenvalues of the diffusion tensors. FA measures the fraction of the tensor that can be assigned to anisotropic diffusion while MD provides complementary information. Dr and Da are the apparent diffusivities in the directions perpendicular and parallel to the WM tracts (Alexander et al., 2011).

[1] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki

In each brain the WM fibers are reconstructed with a deterministic tractography algorithm (Fiber Assignment by Continuous Tracking, FACT, DTIStudio[2], (Mori at al., 1999)). All fibers shorter than 50 millimeter are discarded.

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

$$MD=\frac{\lambda_1+\lambda_2+\lambda_3}{3} \quad (2)$$

$$Dr=\frac{\lambda_2+\lambda_3}{2} \quad Da=\lambda_1 \quad (3)$$

Next, all the parameter values are sampled along each fiber. Mean values for each fiber are calculated and recorded ("fiber-mean FA", "fiber-mean MD", etc.). The voxels in which the FA value falls below 0.25 are masked and are not included in the calculation of the mean values.

2.3 Finding Fiber Correspondences

Defining spatial correspondence between the analyzed brains is a major challenge in all works that entail cross-subject comparisons. In voxel based analysis schemes this usually entails mapping all brain volumes onto a common coordinates system usually defined by an atlas or an averaged brain template. In our fiber based framework we need to determine the fiber-to-fiber correspondence for all brains, so that each fiber "knows" to which fibers from the other brains it is to be compared.

Performing tractography for each brain results in a different set of fibers. There are marked variations in the number of fibers per brain as well as shape differences due to misalignment, diverse anatomy and

[2] https://www.mristudio.org/

tractography artifacts. Instead of warping all brains onto a common target we propose to regard them in their native coordinate systems. A fiber-based correspondence between the brains is created using a standard set of fibers – a template. The goal here is to have a set of whole brain typical fibers that can be used to find corresponding fibers across the different brains based on their geometric shape and location. The template will also serve as a reference structure on which the results of the comparison are recorded and presented. A template brain can be an arbitrary chosen typical brain, or a representative set of fibers created specifically for that. For each fiber in the template set we would like to find the corresponding fiber in each of the other brains. For each brain, a two-stage process is performed:

Step 1: The template brain (BT) is affinely registered to the current study brain (B^m, $m=1:M$, where m is the index of a brain and M is the number of brains participating in the study). This is achieved using the Iterative Closest Fiber algorithm, ICF (Mayer et al., 2011). A brief description of the ICF algorithm is presented next: ICF relies on the direct registration between two sets of fibers, without requiring any intensity-based registration as preprocessing. Let BT_i, $i=1..I$ and B_j^m, $j=1..J$, where I is the number of fibers in the template brain BT, and J in B^m, respectively. Here the template brain serves as the model and the current brain B^m serves the target for registration. Each fiber f, $f \in \{ BT_i, i=1..I \}$ or $f \in \{ B_j^m, j=1..J \}$ is a discrete curve defined by a fixed length sequence of N $3D$ points located equidistantly along its trajectory (4). In this work N=20.

$$f = [x_1, y_1, z_1, \ldots, x_N, y_N, z_N] \quad (4)$$

For each model fiber BT_i the matching target fiber B_j^m is found such that:

$$j = \arg\min_n \left(\left\| BT_i - B_n^m \right\|_{L_2} \right) \quad (5)$$

The actual matching of the closest fiber is done by finding an approximate nearest-neighbor using Locality Sensitive Hashing (LSH) framework (Darrell et al., 2006). An affine transform is fitted on the set of matched fibers using a RANSAC scheme (Fischler and Bolles, 1981). The recovered transform is consecutively applied to warp the model fibers towards the matched target fibers. The ICF loop

described above is repeated until convergence of the mean square error measured between the matched model and target fibers.

Step 2: For each template fiber, the *k* closest fibers from B^m are identified and their indices are recorded (again *m* is a serial number of a brain in the study, $1<m<M$ where *M* is the total number of brains analyzed). That is achieved by warping the template fiber set as close as possible to the coordinates of the current study brain using the affine transformation found in the previous step. The distance between each warped template fiber and each target brain fiber is measured in the *L2* sense and the closest fiber is found using LSH approach for approximate nearest neighbors. The use of LSH helps to alleviate the computational burden of finding *k* nearest neighbors for each template fiber from each study brain. The target data is embedded in the bins of several hash tables in a preprocessing step. The LSH hash functions have the property of assigning neighboring feature points to the same bins with an elevated probability (Darrell et al., 2006).

Following the described two-stage process, we now know for each template fiber the indexes of its k closest fibers in each study brain. Any fibers whose distance from the corresponding reference fiber is larger than a selected threshold Td are discarded. The mean parameters values from the k closest fibers are averaged and the resulting value is recorded. Figure 1 illustrates these two steps.

The validity of the fibers matching is assessed by examining a group of fibers in the template and the corresponding matching fibers in each of the brains in the set. Figure 2 (a-c) presents 3 sub-groups of fibers from a template brain. The subgroups are the Corpus Callosum, the midbody of Corpus Callosum and the right Cortico-Spinal tracts that were manually marked on the template brain using the DTIstudio software. The fibers are overlaid on slices of FA in order to provide context to the fibers location and shape. Each subsequent row of the figure shows the matched fibers for one of the brains in the data set. The second and the third rows are brains from a healthy group while the fourth and the fifth row are brains from the patient group. It can be seen that fibers from a certain anatomical tract are indeed correctly matched to the same anatomical tract in each of the brains, even though they differ in shape and

size. Figure 3 depicts for each brain the percentage of template fibers that were successfully matched, with stars denoting the healthy group and dots the patients. Note that a template fiber is defined as successfully matched when its distance from the detected nearest neighbor is smaller than threshold T_d. The behavior remains similar for the two groups, with more than 50% percent of matched fibers for all subjects, most being around 70%-90%.

2.4 Fiber-Wise Comparison

At this point, each fiber in a template brain is related to a collection of k*M (or less) closest fibers. The fiber-mean values of the closest fibers from a particular brain are averaged so that each brain contributes a single FA, MD, Dr and Da value to the comparison for the current template fiber. The number of the compared values for some template fibers may be less than M if nearest fibers from some of the brains were discarded due to the large distance from the warped template fiber. In order to facilitate the explanation, let's assume that we want to compare the fiber-mean FA values of brains from group1 and group2, and that the two groups contain M1 and M2 number of brains. A statistical comparison is made for each template fiber between the M1 (or less) FA values from the group1 brains (e.g. healthy subjects) and the M2 (or less) FA values from the group2 brains (e.g. ALS patients). When the template is one of the regular brains, some of its fibers would be atypical (incomplete or incorrectly connected to another fiber), mostly due to tractography artifacts. Such template fibers would not find their match in most the other brains, and will have a very small number of values for comparison. In this work we require the number of compared values in each group to be larger than M_{min}. Otherwise the fiber is marked as insignificant. Unpaired one-tailed t-tests are used to determine whether for each particular fiber there is a significant difference between the fiber-mean FA values originating from group1 and from group2. The fibers with significantly different values of FA (or MD, Dr, Da) are marked on the template fiber set, providing a clear visual representation of the location and spread of affected fibers.

Several methods of statistical significance testing were considered for this analysis. The issue of multiple comparisons being the main concern as a simultaneous comparison is made over thousands of

fibers. This is the same hurdle that has to be overcome in the field of voxel-wise comparison as well as in microarray analysis and many others. The standard Bonferroni correction controls the Family Wise Error (FEW), that is, it guarantees that there's only a 5% chance (for example) of any false positives appearing in the data (Bland et al., 1995). This is much too conservative for our task since it entails dividing the chosen significance level by the number of fibers. The more modern False Discovery Rate (FDR) correction was thus chosen for this work (Benjamini and Hochberg, 1995). Instead of looking at FEW, it FDR controls the amount of false-positive discoveries in the data. For example, setting the FDR control level to 0.1 guarantees that no more than 10% of the active voxels are false positives. FDR adapts the significance threshold to the data and is less severe than FEW correction when the signal is very small.

The steps of processing required for each template fiber are illustrated in Figure 4. The template brain is shown in (a), with the currently analyzed fiber marked in black. Example brains from the healthy (b) and the ALS groups (c) are shown as well. The currently analyzed fiber from the template is overlaid in black on each of these brains, warped to its coordinates. The k closest fibers found in each of the brains are displayed in red. The data structure used to store the parameters values (e.g. fiber-mean FA) is shown in (d). Each row of this table corresponds to a particular template fiber. Each column corresponds to the mean value from the closest fibers found in a particular brain. Statistical testing is carried out independently for each row in the table on the values found from the healthy brains vs. values originating from the ALS brains. The template fibers for which one group has a significantly different parameter values from the other group, are marked in color (blue: ALS> healthy, red: ALS< healthy), as shown in Figure 5.

3 Results

The results received with our method are described next. First the method is applied using one of the typical brains as the template (Section 3.1). In a second experiment we use the CONNECT/Archi fiber

atlas as a template, where the fibers are pre-segmented into multiple fiber tracts (Section 3.2). Finally analysis with TBSS is performed on the same set of brains for comparison (Section 3.3).

3.1 Single subject template

The proposed method for whole brain fiber-based comparison was applied to the data set described in Section 2.1, containing a group of 23 patients with ALS and a healthy control group with 18 subjects. In this section the template brain was chosen to be one of the typical healthy brains.

The results of our method on the whole brain set of fibers are presented in Figure 5, row 1. These results were produced using the following set of parameters: k=5, T_d=35, M_{min} =4. The issue of multiple comparisons was addressed by using FDR with significance level of 0.1. The first column contains the results of FA analysis, the second column focuses on the MD parameter, and the third shows Dr. Fibers for which the values in the ALS group are smaller than in the control group are shown in red. The blue fibers denote the inverse relation. As expected, we see mostly red fibers in the FA result, meaning there is a significant reduction in FA in the ALS group. The red fibers are concentrated in a few specific regions in the brain. The MD and the Dr results are mostly blue, which is also consistent with our expectation of elevated MD and Dr in ALS patients. The results for Da are omitted here since very small number of significant fibers was found (close to zero), which also conforms to previous findings.

In this contribution we validate the performance of the proposed method by comparison to previous work on DTI analysis in ALS (Ben Bashat et al., 2011). The findings presented in Ben Bashat et al. include reduced WM integrity, as indicated by the reduced FA, increased MD, and increased Dr, mainly in the midbody of the corpus callosum (CC) and the Cortico Spinal tract (CST) in patients with ALS compared to controls. Based on these results, we focus on several sub groups of fibers, manually identified in the template (Figure 5): CC - row 2, CC midbody (Witelson segment 2, 3 (Witelson 1989)) - row 3, right and left CST -rows 4, 5 respectively. It can be seen that the detected fibers are concentrated

in the central part of the CC tract. These fibers have lower FA and higher MD and Dr in the ALS group. A similar relationship can be clearly seen in the CST, which is known to be the main affected fiber tract.

In order to further quantify the results presented in Figure 5, the percentage of significant fibers are summarized in Table 1. We see that elevated Dr was detected in 8.5% of the brain fibers. High percentage of fibers with elevated Dr are present in the CC, and even higher percentage in the CC midbody (26%) and the CST tracts (51%, 79%), with no reduced Dr fibers present. Table I does not include a column for Da since no detections were made for that parameter.

The template for the analysis conducted here was chosen as one of the healthy brains from our study. We tested our method using several different templates. The results using three different templates are presented in Figure 6. Each row corresponds to a particular template. The columns show the results for FA, MD and Dr, respectively. It can be seen that even though the shapes of the individual template fibers vary between the templates, the same effects that were described in Figure 5 are present in each case. In the case of FA this means that we see predominantly red fibers (reduced FA in ALS), and in Md, Dr predominantly blue, which are concentrated mainly in the midbody of CC and in the CST.

3.2 Using a fiber atlas as a template

The use of a population based atlas as a template is shown next. The template used in this experiment is the CONNECT/Archi WM bundle atlas that was developed as part of the FP7 CONNECT project.[3] The atlas was based on twelve subjects of the NMR public database (Guevara et al., 2012) acquired on GE Healthcare Signa 1.5 Tesla Excite II scanner. The diffusion data presents a high angular resolution (HARDI) based on 200 directions and a b-value of 3000 s/mm2 (voxel size of 1.875 x 1.875 x 2 mm). This atlas is a model of the brain white matter organization, made up of a set of generic fiber bundles that can be detected in most of the population. Each of the streamlines comprising the atlas represents a centroid of a fiber bundle (fascicle). The centroids were obtained in a two-step clustering process: first,

[3] http://brainconnect.eu

individual tractograms were clustered in small fascicles yielding one centroid per fascicle (the centroid is in fact the fiber with smaller distance to the others within the fascicle); a second clustering step considers all the individual centroids together and creates fascicles of centroids which actually correspond to the fibers in the CONNECT/Archi atlas used here (Guevara et al., 2012).

The atlas contains 38 known deep white matter bundles: 12 left hemispheric long WM bundles; 5 left thalamic radiations; 12 right hemispheric long WM bundles; 5 right thalamic radiations; 4 inter-hemispheric sub-parts of the CC. It also contains 47 superficial white matter bundles in each hemisphere. Only the deep white matter bundles portion of the atlas was used for this work, as these are the fibers most likely to be reliably reconstructed from our non-HARDI data.

The atlas is presented in Figure 7 where each color signifies a different fiber tract. Results using this atlas are shown in Figure 8. The bar plots show the percentage of the fibers detected per tract. Top row depicts results for FA analysis with the bar plot showing the percentage of fibers with reduced FA in patients. The second and the third row show results for MD and Dr, respectively. The results for Da analysis are not shown since the number of detected fibers there is negligible (less than 1% per tract). The most prominent bars are those corresponding to tracts number 1 (midbody of CC), 11 and 12 (left CST), 28 and 29 (right CST). In MD and Dr we see two additional bars at tracts number 16 and 33, which correspond to right and left uncinate fasciculus.

3.3 Comparison to TBSS

It is interesting to compare the results of our proposed method to results using the current commonly used method, the TBSS (Smith et al., 2006). TBSS, as implemented in the FSL[4] software was applied to our set of brains. The pre-processing steps are the same as used with our method.

For this test, FA, MD, Dr and Da maps were computed using the FSL FDT tool and were aligned into a 1 x 1 x 1mm FMRIB58_FA standard space (Smith et al., 2006). A mean FA skeleton (n = 41) was

[4] http://fsl.fmrib.ox.ac.uk/fsl/fslwiki

created with threshold of FA = 0.2. Diffusivity maps were compared using the FSL randomized tool (patients > controls and controls > patients). The resulting maps was corrected at cluster level (threshold-free cluster enhancement (TFCE)) at a level of p< = 0.05, fully corrected for multiple comparisons across space (TFCE corrected). The maps with most detections (FA, Dr) are presented in Figure 9 in coronal, sagittal and axial views, with the detected regions marked. The red-yellow color range displays regions where the control group FA was higher than the patients FA. The detected regions reside in the CST and in the middle section (the body) of CC, and are therefore in agreement with the results received using our method. The Uncinate tract remains undetected, and almost no detection in MD is seen.

4 Discussion and Conclusion

We presented a novel method for whole brain fiber-based comparison between groups of subjects. The analysis is fully automatic and does not require marking VOIs or defining manual seed regions for tractography. This makes our method especially suitable to serve as an exploratory step in population studies where there is no hypothesis regarding the location of the affected areas. The results are presented at the single fiber resolution level and can be interpreted by examining the entire template fibers set. Once locations of significant differences are identified, the user may choose to further focus on interesting subsets of fibers. Any subsets can be examined, since no prior grouping of fibers was employed throughout the analysis.

An important characteristic of our method is that the majority of the processing is performed in each brains' native space, so that the sampled parameters values as well as the shape of the fibers are not affected by warping the data to different coordinates system. Correspondences between fibers are established using affine transformations and nearest neighbors search, based only on coordinates information. This is a novel way for establishing spatial correspondence. It allows the flexibility of mixing fibers that come from different protocols, as shown by incorporating the HARDI based CONNECT atlas. The fibers reconstructed from HARDI are more reliable than the ones from DTI,

especially in areas of fiber crossings. But the same characteristic fiber shapes and locations are still present, as can be seen in Figure 7.

In sections 3.1 and 3.2 we showed results using two possible templates. We started with a typical brain template, followed by using the CONNECT atlas as a template. The results are qualitatively similar in the two cases. One distinction between the two template options is that in the first scenario we found more matches between the template and the other brains, whereas using the CONNECT atlas less template fibers were matched. The higher quality of fibers of the CONNECT atlas enabled additional detections, such as the detection of significant fibers in the uncinate fasciculus. The role of uncinate fasciculus in ALS was noticed in several published works (Sato et al., 2010; Agosta et al., 2010; and Christidi et al., 2013), who conclude that the subtle involvement of the uncinate fasciculus may precede the appearance of behavioral symptoms in patients with ALS.

It is important to note that an underlying assumption of the presented method is that fiber trajectories can be traced in all subjects of both groups. That means that the method is most suitable when the hypothesis is that the DTI measures may differ between the groups, but the fibers fiber-tracking performance remains mostly unaffected. If, for example, the investigated condition lowers FA in a way that most fibers are not reconstructed in full, the method becomes inapplicable, since very few correspondences would be found between the partial fibers and the template fibers. That situation can be easily identified by looking at the portion of successful matches for each of the brains as shown in Figure 3. Apparently, in the case of ALS the pathologic cases maintain the basic anatomical structure of WM so that the matching works equally well with the patients as it does with the healthy subjects. This is a prerequisite for applicability of our method and has to be verified before applying it to other pathologies.

We are currently continuing the development and investigation of the framework in several directions. These include the transition to simultaneous multi-parametric analysis, incorporating in a single comparison both parameters derived from DTI and structural MRI; Parameter profiles along fibers will be

compared and additional statistical techniques will be incorporated. Further exploration into ALS will be conducted as well as the generalization of the framework to additional pathologies.

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Figure legends

Fig. 1 (a) Warping the template to B^m. blue - template; green – B^m; black - the warped template; (b) Finding closest fibers. green – B^m; black - a fiber from warped template. red - the *k* closest neighbors from B^m.

Fig. 2 (a-c) Several sub groups of fibers manually marked on a model brain; (d-f), (g-i) Matched fibers to each sub group in two arbitrary chosen brains from the healthy control group; (j-l), (m-o) Matched fibers to each sub group in two arbitrary chosen brains from the ALS patient group.

Fig. 3 The percentage of template fibers that were successfully matched in each brain: Healthy brains (stars) and ALS patient brains (circles).

Fig. 4 Illustration of steps performed for each template fiber: (a) template fibers set. One of the fibers marked in black; (b) One of the healthy brains. Shown is the warped template fiber (black) and the 5 closest fibers (red); (c) Same as (b), for one of the ALS patient brains; (d) FA table. Each row corresponds to a template fiber. The fiber-mean FA values from the fibers found for this template fiber are stored in the columns of the corresponding brains.

Fig. 5 Results of whole brain comparison: Fibers in which ALS> control shown in blue; Fibers in which ALS< control shown in red. FA analysis (column a) , MD analysis (b) , Dr analysis (c); Whole brain analysis (1); CC fibers (2); Mid-body of CC (3); Right CST (4); Left CST (5).

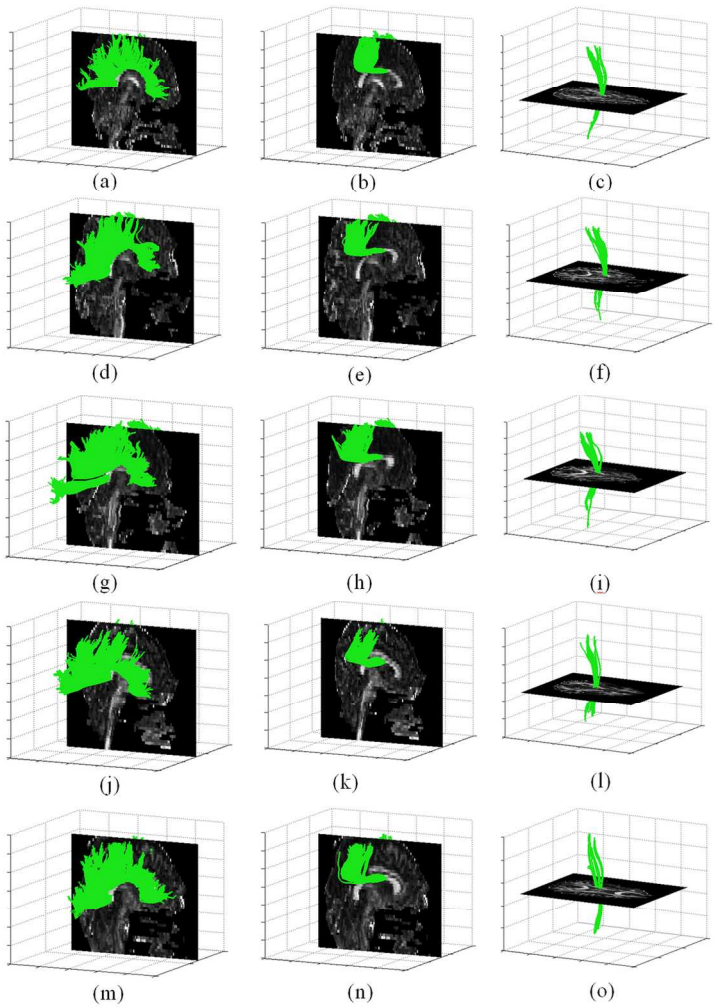
Fig. 6 FA, MD, Dr analysis using different templates, blue: ALS> control ; red: ALS< control; row (1) template1, row (2) template2, row (3) template3; column (a) FA, column (b) MD, column (c) Dr.

Fig. 7 CONNECT fiber atlas, two views. The different colors correspond to the different 38 fiber tracts the atlas contains. For instance the darkest blue in the middle is the body of corpus callosum. The brightest yellow on the right side is inferior right thalamic radiations.

Fig. 8: FA, MD, Dr analysis using the CONNECT atlas. Left column: Atlas fibers with the marked detections (blue: ALS> control; red: ALS< control); Right column: percentage of significant fibers for each tract of the atlas. Relevant tract numbers: 1- corpus callosum body, 11-left cortico spinal tract, 12-left long cortico spinal tract, 16-left uncinate, 28-right cortico spinal tract, 29-right long cortico spinal tract, 33-right uncinated.

Fig. 9: Results of TBSS analysis on FA (top row), Dr (bottom row), where the most prominent detections were made for this data. The colors correspond to the convention of this paper: Control<Patients (blue), Control>Patients (red).

Fig. 1 (a) Warping the template to B_m. blue - template; green – B_m; black - the warped template; (b) Finding closest fibers. green – B_m; black - a fiber from warped template. red - the k closest neighbors from B_m.
69x29mm (300 x 300 DPI)



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169x173mm (300 x 300 DPI)

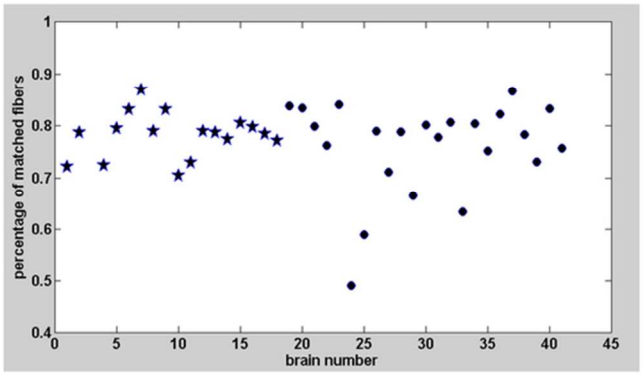


Fig. 3 The percentage of template fibers that were successfully matched in each brain: Healthy brains (stars) and ALS patient brains (circles).
68x28mm (300 x 300 DPI)

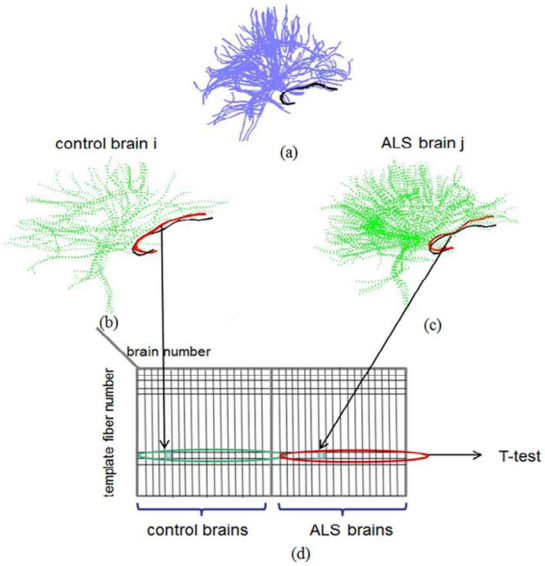
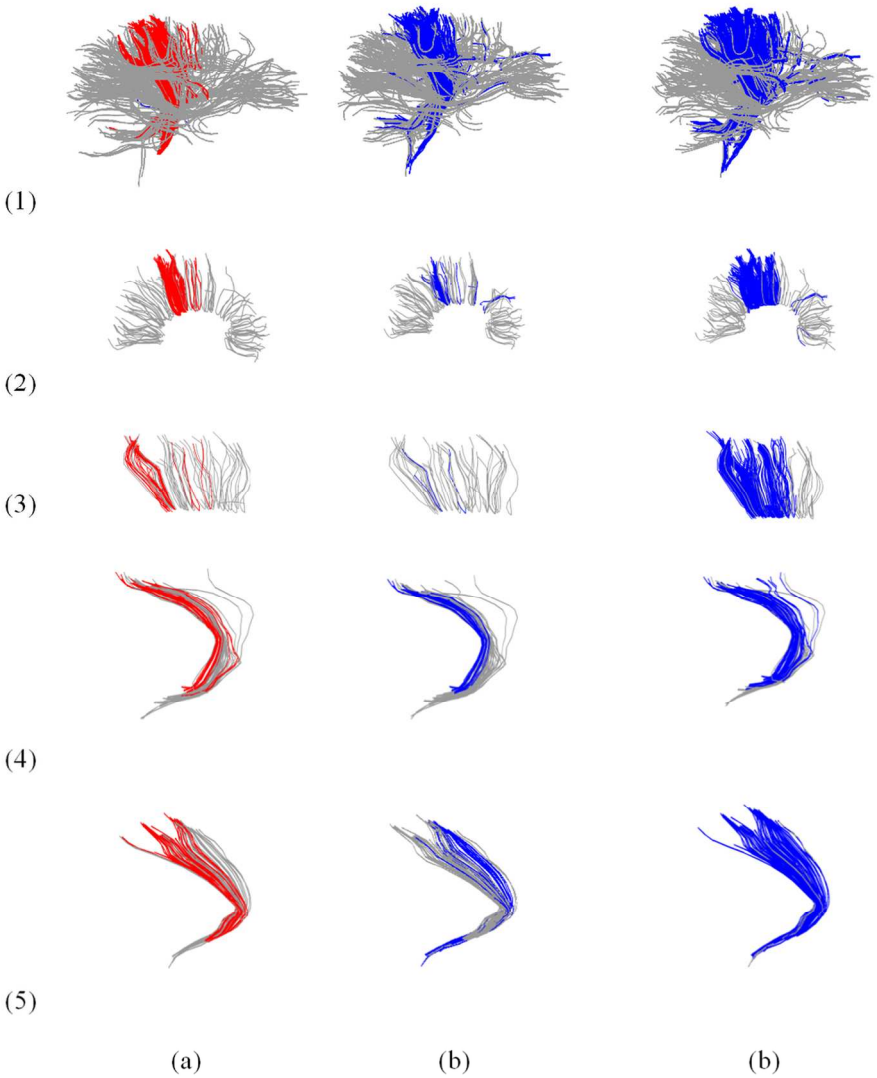


Fig. 4 Illustration of steps performed for each template fiber: (a) template fibers set. One of the fibers marked in black; (b) One of the healthy brains. Shown is the warped template fiber (black) and the 5 closest fibers (red); (c) Same as (b), for one of the ALS patient brains; (d) FA table. Each row corresponds to a template fiber. The fiber-mean FA values from the fibers found for this template fiber are stored in the columns of the corresponding brains.
93x52mm (300 x 300 DPI)



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190x219mm (300 x 300 DPI)

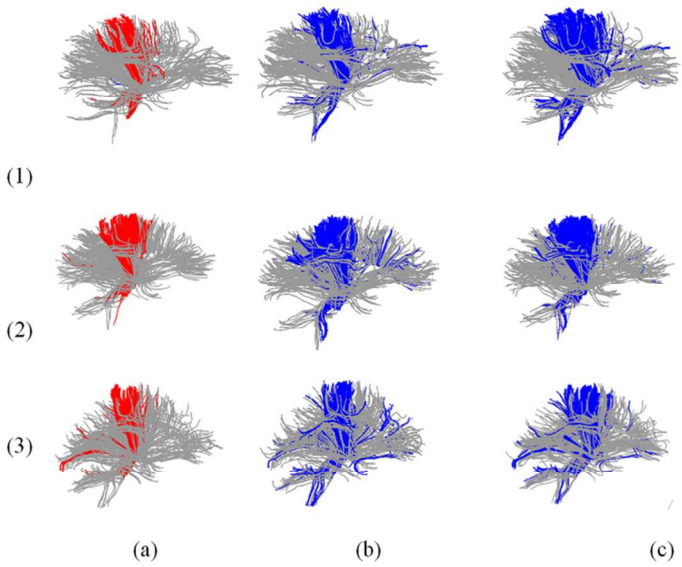
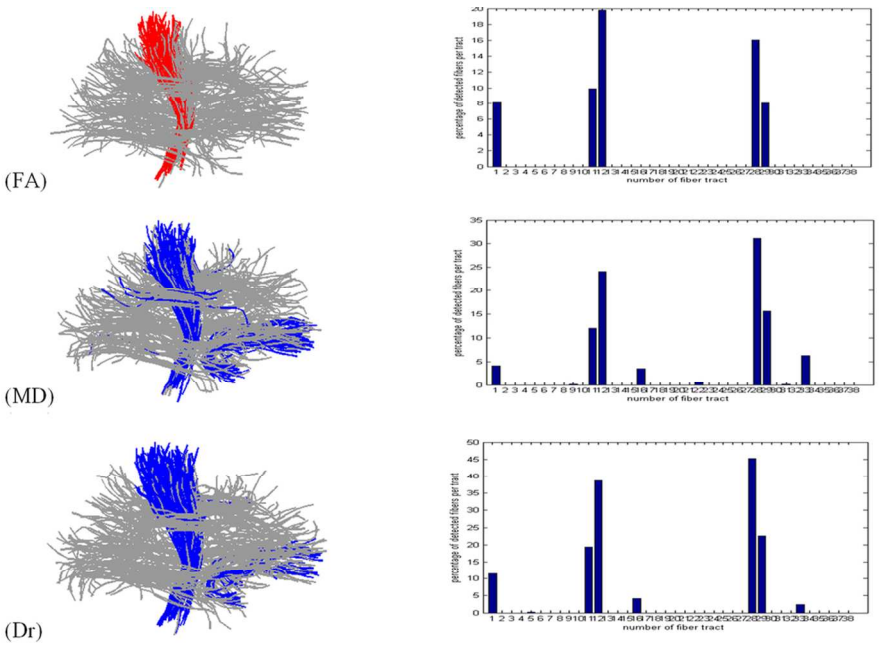


Fig. 6 FA, MD, Dr analysis using different templates, blue: ALS> control ; red: ALS< control; row (1) template1, row (2) template2, row (3) template3; column (a) FA, column (b) MD, column (c) Dr. 92x52mm (300 x 300 DPI)

Fig. 7 CONNECT fiber atlas, two views. The different colors correspond to the different 38 fiber tracts the atlas contains. For instance the darkest blue in the middle is the body of corpus callosum. The brightest yellow on the right side is inferior right thalamic radiations.
48x14mm (300 x 300 DPI)



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107x70mm (300 x 300 DPI)

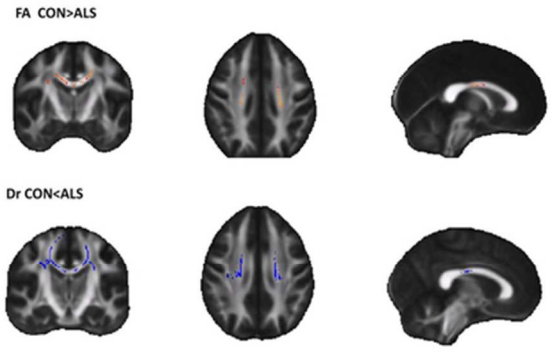

Fig. 9 Results of TBSS analysis on FA (top row), Dr (bottom row), where the most prominent detections were made for this data. The colors correspond to the convention of this paper: Control<Patients (blue), Control>Patients (red).
61x23mm (300 x 300 DPI)

Table I FA, MD, Dr and Da analysis; percentages of significant fibers in the whole brain and different subsets (relative to the size of each sub-set).

	FA ALS< cont	MD ALS >cont	Dr ALS >cont
Whole brain	*2*	*3.6*	*8.5*
CC	*2.2*	*1.1*	*10*
CC Midbody	*2.9*	*0.3*	*26*
CST-r	*22.8*	*20.7*	*51*
CST-l	*36.8*	*29*	*79.3*