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Assessment of Asymmetry in Pyramidal Tract by Using Fiber Tracking

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Abstract*— Diffusion Tensor Imaging (DTI) and tractography are able to model fiber architecture within the white matter and become a major component of clinical neuroradiology. The challenge is to answer neuro-anatomic questions by using group studies. In some diseases, the asymmetry between involved tracts is expected to be greater than that in controls. If the quantitative detection of asymmetry is sufficiently sensitive, it will be a good marker of clinically relevant tract-specific abnormalities. In this work, we quantify the range of asymmetry between the right and left pyramidal tract (PT) and explore the side and handedness effects on the microstructure of the PT in healthy subjects by using a probabilistic tractography. The volume and seven DTI parameters (fractional anisotropy (FA), mean, perpendicular and parallel diffusity, geometric diffusion measures) were determined. The statistical analysis revealed substantial PT asymmetries and an average correlation between FA, mean diffusity and the laterality quotient.

I. Introduction

White matter tractography is a promising application of DTI [1,2,3,4,5]. It uses the directional information of diffusion tensor maps to estimate connection pathways in white matter. Tractography studies on major white matter tracts in the human brain appear to be in good agreement with the anatomical results obtained with dissection or histological methods. The knowledge of the architectonical organization and connectivity may contribute to a better understanding of brain anatomy, both in physiological and pathological conditions. It may be useful in assessing how brain organization is affected by disorders. Asymmetry in the brain is thought to be important to enable the two hemispheres to specialise and operate more efficiently. Brain asymmetry has been observed in animals and humans structurally, functionally, and behaviorally. This lateralization is thought to originate from evolutionary, hereditary, developmental, experiential and pathological factors [6]. In some diseases, the asymmetry between involved tracts is expected to be greater than that in controls. If the quantitative detection of asymmetry is sufficiently sensitive, it will be a good clinical marker. The aim of the study is to further examine possible macro- and microstructural asymmetries in the PT and their relationship to handedness, to quantify the range of asymmetry between the right and left pyramidal tract's (PT) in 11 healthy subjects by using a probabilistic tractography. Fractional anisotropy (FA), a measure of the orientational variance in water molecular diffusivity, the magnitude of water diffusivity (parallel, perpendicular, and mean diffusivity), the indices of tensor linearity, planarity, and sphericity [7], and volume along the pathways were quantified. FA quantifies the degree to which diffusion is direction-dependent and is expressed as a ratio ranging from 0 to 1. Mean diffusivity provides the overall magnitude of water diffusion and is a sensitive indicator of maturational changes in the brain tissue. In addition, perpendicular diffusivity provides a more specific surrogate of changes associated with myelination, whereas parallel diffusivity is more related to the intrinsic characteristics of the axons or changes in the extraaxonal/extracellular space [8,9,10,11]. By using the geometric diffusion measures (Cl, Cp, Cs) local directionality consistency can be determined. The parameters that we studied here were chosen for the reason that they are abnormal in neurologic diseases and they are comparable across individuals and scans. Examining multiple DTI parameters along tracts reconstructed from DTI data represents an important novel contribution of our work. This approach has clinical utility, because using a variety of parameters increases the chance that we will detect abnormalities in individuals with disease. Study and quantification of asymmetry is also essential in the clinical setting, this is because the absolute value of the asymmetry index is probable to be increased in diseases that present asymmetrically, such as Amyotrophic Lateral Sclerosis, Multiple sclerosis, strokes and tumors. We think that the use of asymmetry measurements in these conditions, will be useful for the quantitative evaluation in clinical trials.

II. Materials and methods

A. Human brain data

Magnetic Resonance Imaging (MRI) data were acquired from 11 healthy volunteers (all male, age range: 25-55 yr, mean age: 28.8 ± 8.3 yr), using a 1.5 T Philips Intera system (Philips Medical System, Best, the Netherlands). All volunteers signed informed consent and the study was approved by the local Ethic Committee. Each exam was composed of DTI acquisitions (32DW gradient directions) followed by an anatomic T1-weighted three-dimensional (T1-3D) acquisition. For DTI, we used a single shot, spin-echo diffusion weighted echo planar imaging (EPI) sequence. A diffusion weighting of 1000 s/mm² (high b value) was used. A reference image with no diffusion weighted (b=0 s/mm^2) was also recorded. Due to clinical time constraints, each sequence had to last less than 10 minutes, with an acceptable Diffusion Noise Ration DNR (>50). For each exam, diffusion tensor and measured DNR

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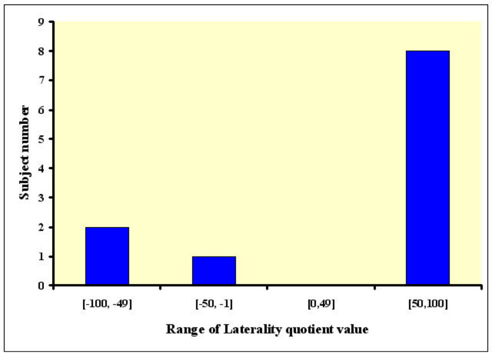

Fig. 1. The distribution of the population according to the range of laterality quotient values

were computed, voxel size varying between 1.5 mm and 3 mm (1.5 mm, 1.9 mm, 2.2 mm, 2,5 mm, 2.8 mm and 3 mm). 2.2 mm was the minimum voxel size which allowed DNR>50 for all acquisition schemes. Then, acquisition parameters were set as followed: echo time (TE) 86 ms, SENSE factor = 2, matrix size 112 $\times$ 112$\times$50, a field of view (FOV) 245 $\times$245 mm^2, slice thickness 2.2 mm (2.2 mm cubic voxel) with no gap, 55 slices parallel to AC-PC line. T1-3D acquisition was also measured (TE=4,6 ms, TR= 25 ms, matrix size 256 $\times$ 256, FOV 240 $\times$240 mm^2, slice thickness 1 mm, slab 180 mm, CLEAR option to have an homogeneous image).

B. *Assessment of Handedness laterality*

Handedness laterality was assessed according to a self-report questionnaire. The assessment was completed by Edinburgh Handedness Inventory [12]. The inventory consists of differents items. Each item was given an answer for hand preference. A laterality quotient (LQ) was assigned to each participant according to the following formula : LQ=(R-L)*100/(R+ L), where R and L are the total scores of the questions answered in 'only right' and 'only left', respectively. The LQ ranges from -100 for extreme left-handedness to + 100 for extreme right-handedness. The handedness degree for both right-handed and left-handed participants therefore can be quantified by the absolute value of the LQ. The population participants contains 8 right-handed and 3 left-handed. The left-handed participants LQ ranges from -50 to -100, mean -77.33, whereas the right-handed participants LQ ranges from 62 to 100, mean 86 (figure 1).

C. *Diffusion Tensor Tractography*

All image MRI and DTI post-processing was done by using Sisyphe, a neuroimaging software developped in the laboratory. The tractography was done by using an algorithm implemented in this software, and based on the method described in [13]. This statistical fiber tracking algorithm is based on two hypotheses :

- Considering a voxel, the probability of a fiber to propagate in a given direction is proportional to the corresponding diffusion coefficient.

- Axonal trajectories or more cautiously trajectories of axonal bundles follow regular curves.

Based on these two postulates a random walk model of a particle diffusing in a nonhomogeneous medium (here a diffusion tensor field, D^α) is constructed, with a curve regularizing constraint emphasizing colinearity :

$$q_{i+1} = q_i + \mu\Omega_i, \tag{1}$$

$$\Omega_i = \left\{ \frac{\lambda d_i + \Omega_{i-1}}{||\lambda d_i + \Omega_{i-1}||} \quad \Omega_i.\Omega_{i-1} > 0, \right. \tag{2}$$

$$d_i = D_i^\alpha r_i, \tag{3}$$

with r_i a random vector uniformly distributed over a unit sphere. The continuous trajectory of a particle in a 3D Euclidean space is given by its time varying position vector q_i, where i is the discrete time step. The curve that the particle propagation generates grows along a unit vector Ω_i, that is a random direction vector modelling the statistical nature of the diffusion process and the curve regularizing constraint. Ω_i is a weighted sum of the random vector d_i, defined on the unit sphere and distributed according to the local diffusive properties and the previous displacement vector Ω_{i-1}, enhancing colinearity. $\Omega_i.\Omega_{i-1} > 0$ is just an additional constraint to avoid backward jumps. μ is the step size , whereas α is an anisotropy enhancing exponent. In order to visualize anatomical connections in the form of separate identifiable tracts or bundles, a virtual dissection in this modelled brain had to be performed. This was done in two main steps; first, a selection by knowledge-based (ROI) placement and second, selection by fibre validity classification. Therefore, trajectories that follow directions of high diffusion should be more likely than those which do not. To select a posteriori the "good" trajectories, a "validity index" (VI) is assigned to each curve. VI is the result of an integration of the tangential diffusion coefficient along the trajectory and normalized to the length :

$$VI = \frac{\sum_{i=1}^{m} \mu\Omega_i^T D_i \Omega_i}{\sum_{i=1}^{m} \mu||\Omega_i||} = \frac{1}{m}\sum_{i=1}^{m} \Omega_i^T D_i \Omega_i, \tag{4}$$

where $\Omega_i^T D_i \Omega_i$ is the double contraction of the DT, D_i, with the unit displacement vector, Ω_i. This contraction is the diffusion coefficient in the displacement direction. For tracts that were selected by one or several Region Of Interest (ROI), the histogram of the fibre population VI could be plotted. It usually followed a bell-shaped distribution. Fibres below a certain quantile (here 20%) were then discarded so that only the most credible fibres with a high VI were retained.

The assessment of the PT is based on the multi-ROI reconstruction (figure 2). For each reconstruction, we examined the right and left tracts for eight parameters : volume (VO), Fractional Anisotropy (FA), Mean Diffusity (MD), Parallel Diffusity (PAD), Perpendicular Diffusity (PED), indices of linearity (Cl), planarity (Cp) and sphericity (Cs). The tract is turned into a ROI by masking the voxels traversed by a tract and an average FA, MD, etc. value were extracted then. For quantifying the differences between the right (R) and left (L)

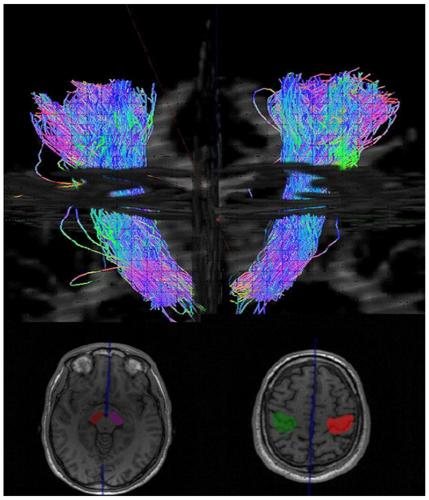

Fig. 2. The left and right pyramidal tract's multi-ROI reconstruction

pyramidal tract's, we define eight asymmetry indices : AIX = $(X_R$-$X_L)$ / $(X_R$+$X_L)$. Where X=FA, VO, MD, PAD, PED, Cl, Cp or Cs. This index is calculated in three cases. In each case we take the fibre density distribution percentile equal to 20%, 50% or 80%. Positive asymmetries indicate that the parameter in question is larger on the right side. Asymmetries can range from -1 to 1.

D. Statistical Analyses

After test of normality, hemispheric differences in the diffusion metrics (measured FA, mean, transverse and axial diffusivities, Cl, Cp and Cs) on both the right and left hemispheres (across all the population and right-handed population) was examined individually using the paired t-test; the rejection level is α=5%. We correlated all the eight indices with the laterality quotient (LQ) to explore their relationship by calculating the correlation coefficient (Pearson and Spearman). All statistical analyses were conducted using the software Statistica (Version 7).

III. Results

A. Anisotropy asymmetry

Across all the population, the higher average absolute value of asymmetry index is given in table 1. Left greater than right asymmetry pattern of anisotopy was found in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, p=0.0006, 0.0003, 0.0044) , see figures (3, 4, 5). We also correlated the asymmetry index with the laterality quotient (LQ) to explore their relationship and we uncover no evidence of correlation in all three cases. In the right-handed population, the higher average absolute value of asymmetry index is given in table 1. Left greater than right asymmetry pattern of anisotropy was found in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, p=0.005, 0.003, 0.008). The correlation between the asymmetry index and the LQ is average (the correlation coefficient value is 0.65, in case of fibre density distribution percentile is equal to 80 %).

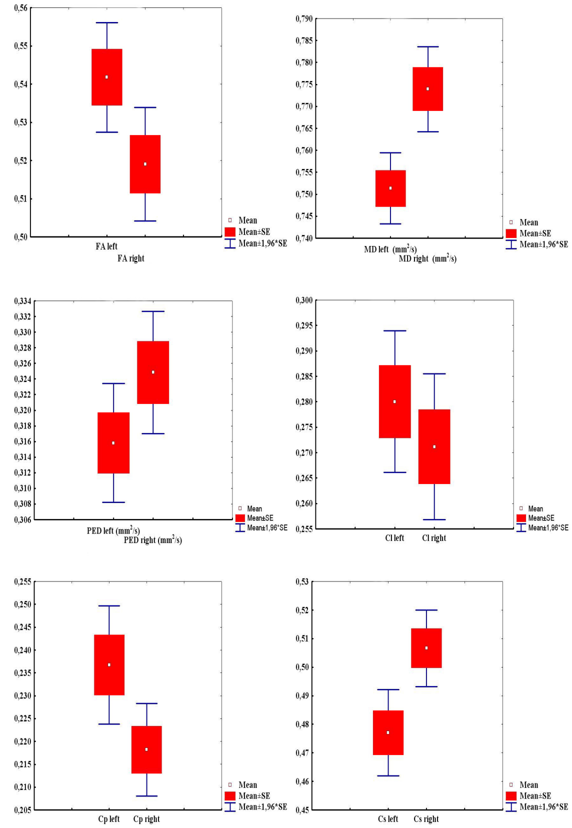

Fig. 3. Significance differences between the left and right side of the pyramidal tract : FA, MD ($\times 10^{-3}$ mm^2/s), PED ($\times 10^{-3}$ mm^2/s), Cl, Cp, Cs. Percentile of fibre density distribution is 80%

B. Mean diffusity asymmetry

The higher average absolute value of asymmetry index for all the population is given in table 1. Higher Mean Diffusity (MD) in the right-side than the left-side was also found along PT in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, p=0.0007, 0.00008, 0.00005), see figures (3, 4, 5). We also correlated the asymmetry index with the laterality quotient (LQ)and we find an average correlation in case of percentile equal 20% (the coefficient correlation value is -0.59). In the right-handed population, the higher average absolute value of asymmetry index is given in table 1. Higher Mean Diffusity (MD) in the right-side than the left-side was also found in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, p=0.0002, 0.0005, 0.00002). The correlation between the asymmetry index and the LQ is weak (the coefficient correlation value is 0.55, the fibre density distribution percentile is equal to 80%).

C. Volume asymmetry

In all the population, the higher average absolute value of asymmetry index is given in table 1, there is no significant difference between right-side and left-side in all three cases. We also correlated the asymmetry index with the laterality quotient

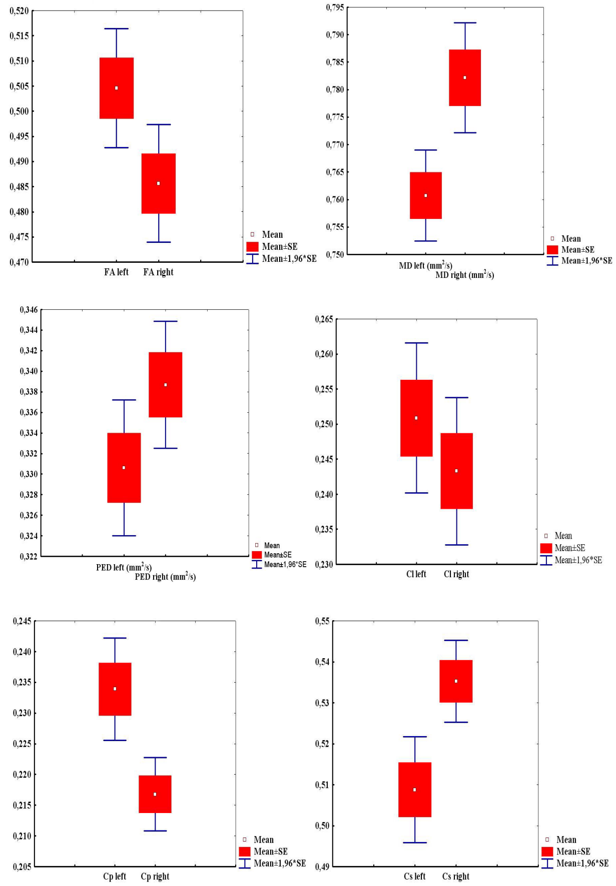

Fig. 4. Significance differences between the left and right side of the pyramidal tract : FA, MD ($\times 10^{-3}$mm^2/s), PED ($\times 10^{-3}$ mm^2/s), Cl, Cp, Cs. Percentile of fibre density distribution is 50%

(LQ), we find a weak correlation (the coefficient correlation value is (-0.54) in case of fibre density distribution percentile is equal to 80%). Across the right-handed population, the higher average absolute value of asymmetry index is given in table 1. No significant difference between right-side and left-side in all three cases. No correlation between the asymmetry index and the laterality quotient.

D. Parallel diffusity asymmetry

Across all the population, the higher average absolute value of asymmetry index is given in table 1. No significant difference between right-side and left-side. We correlated the asymmetry index with the laterality quotient (LQ) and we uncover no evidence of correlation in all three cases. The higher average absolute value of asymmetry index, in right-handed population, is given in table 1. There is no significant difference between right-side and left-side and no correlation between the asymmetry index and the LQ.

E. Perpendicular diffusity asymmetry

In all the population, the higher average absolute value of asymmetry index is given in table 1. Higher perpendicular

index	all the population	right-handed	percentile
AIFA	2.15% ±1.60%	1.9%±1.33%	80%
AIVO	1.60%±3.05%	1.80%±5.26%	80%, 20%
AIMD	1.5%±0.83%	1.30%±0.52%	80%
AIPAD	0.62%±0.80%	0.48%±0.76%	50%
AIPED	1.41%±1.18%	1.03%±0.82%	80%
AICL	1.63%±1.64%	1.26%±1.74%	80%
AICP	3.8%±1.7%	5.01%±2.3%	50%, 80%
AICS	3.02%±1.99%	2.97%±1.76%	80%

Table 1. Higher average absolute value of asymmetry index and the correspondant fibre density distribution percentile in all the population and in the right-handed.

diffusity (PED) in the right-side than the left-side was also found along PT in all three cases (percentiles of fibre density distribution equal 20 %, 50 % or 80 %, p=0.007, 0.0005, 0.0014), see figures (3, 4, 5). We correlated the asymmetry index with the laterality quotient and we find a weak correlation in case of percentile equal 50% (the coefficient correlation value is -0.50). Across the right-handed population, the higher average absolute value of asymmetry index is given in table 1. Higher perpendicular Diffusity (PED) in the right-side than the left-side was also found along PT in the two cases (percentiles of fibre density distribution equal 50%, 80% , p=0.011, 0.009). There is no evidence of correlation between the asymmetry index and the LQ.

F. Linearity asymmetry

Across all the population, the higher average absolute value of asymmetry index is given in table 1. Left greater than right asymmetry pattern of linearity was found in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, p=0.009, 0.005, 0.03), see figures (3, 4, 5). The correlation between the asymmetry index and the laterality quotient (LQ) is weak (the coefficient correlation value is 0.58, in case of percentile is equal 80 %). In the right-handed population, the higher average absolute value of asymmetry index is given in table 1. Left greater than right asymmetry pattern of linearity was found in one case (percentile of fibre density distribution equal 80%, p=0.05). The correlation between the asymmetry index and the LQ is weak (the correlation coefficient values is 0.50, in case of fibre density distribution percentile is equal to 80%).

G. Planarity asymmety

The higher average absolute value of asymmetry index for all the population is given in table 1. Left greater than right asymmetry pattern of planarity was found in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, 0.001, 0.00003, 0.00001), see figures (3, 4, 5). No evidence of correlation between the asymmetry index and the laterality quotient (LQ). Across the right-handed population, the higher average absolute value of asymmetry index is given in table 1. Left greater than right asymmetry pattern of planarity was found in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, 0.0005, 0.0002,

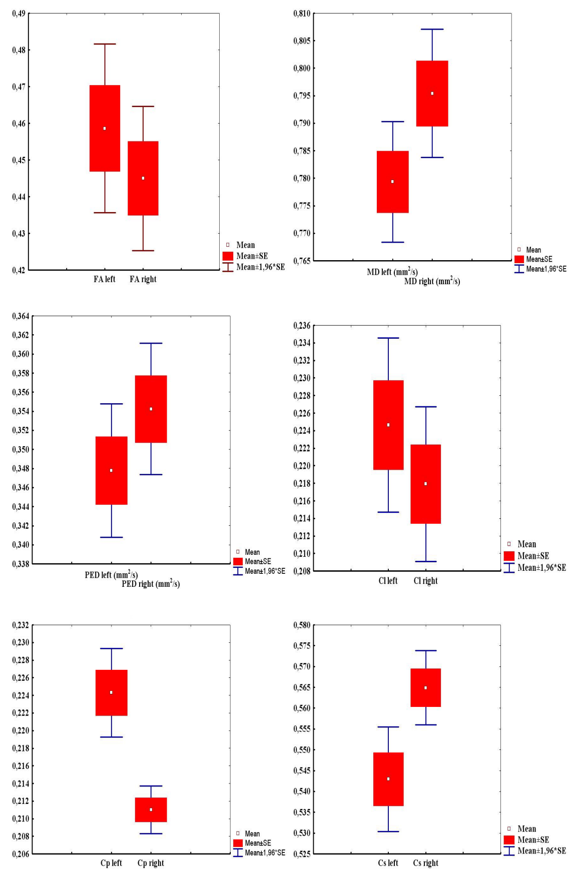

Fig. 5. Significance differences between the left and right side of the pyramidal tract : FA, MD ($\times 10^{-3}$mm^2/s), PED ($\times 10^{-3}$ mm^2/s), Cl, Cp, Cs. Percentile of fibre density distribution is 20 %

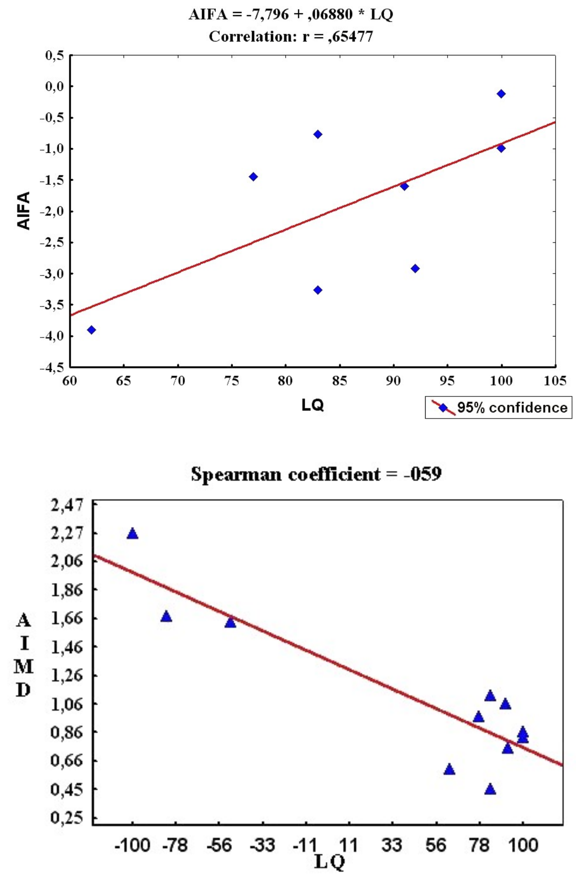

Fig. 6. Study of correlation between different indices and the laterality quotient (LQ) in all there cases (20 %, 50 % and 80 % percentiles), the figures show an average correlation between asymmetry index of mean diffusity (AIMD), asymmetry index of fractional anisotropy (AIFA) and the laterality quotient (LQ).

0.0000). The correlation between the asymmetry index and the LQ is weak (the correlation coefficient value is 0.59, in case of fibre density distribution percentile is equal to 50 %).

H. Sphericity asymmetry

Across all the population, the higher average absolute value of asymmetry index is given in table 1. Higher sphericity (Cs) in the right-side than the left-side was also found along PT in all three cases (percentiles of fibre density distribution equal 20%, 50% or 80%, p=0.0005, 0.0002, 0.0004), see figures (3, 4, 5). We correlated the asymmetry index with the laterality quotient (LQ) to explore their relationship and we uncover no evidence of correlation. In the right-handed population, the higher average absolute value of asymmetry index is given in table 1. Higher sphericity (Cs) in the right-side than the left-side was also found along PT in all three cases (percentiles of fibre density distribution equal 20 %, 50 % or 80 %, p=0.002, 0.002, 0.002). No correlation between the asymmetry index and the LQ.

IV. Discussion

In this article, we present the distributions of various parameters, derived from MR imaging, within the PT reconstructed from 1.5T DTI data obtained from healthy subjects. The parameters we examine are Fractional anisotropy (FA), (parallel, perpendicular, and mean diffusivity) : PED, PAD, MD, the indices of tensor linearity (Cl), planarity (Cp), and sphericity (Cs). For each parameter, we also present the range of asymmetry between the right and left PTs, assessed from summary statistic (mean) derived from the within-tract distributions of the MR imaging parameters. Although we have chosen to focus on the PT because it is one of the major tracts, anatomically well known, the methods we have applied can be used with tracts other than the PT. We find that the average absolute value of asymmetry indices ranges from (0.44 to 3.80 %) across all the population and from (0.23 to 5.01 %) across the right-handed population. Left greater than right asymmetry pattern of FA, Cl and Cp was found and right greater than left asymmetry pattern of MD, PED, Cs was observed across the population in all three cases (20%, 50% and 80%). We correlated all the eight indices with the laterality quotient (LQ) to explore their relationship and we uncover evidence of an average correlation in case of FA (in right handed population, the coefficient correlation value is 0.65) and MD (in all the population, the coefficient correlation value is 0.59) (figure 6). A leftward asymmetry in some parameters agrees well with the results found in a postmortem analysis of ten human brains [14]. Also, higher white matter density in left than right PLIC (different types of fibres arising from anatomically and functionally different cortical and subcortical areas) in a voxel-based morphometry analysis was detected [15]. Extending these findings, a higher FA in the left and higher MD in the right hemisphere was observed. Thus, result obtained in the present work support earlier studies reporting a significant difference (for FA or MD) [16,17,18,19]. Conflicting finding that shows interhemispheric differences in the opposite direction (for specifically, the diffusion-weighted imaging technique seems to be especially sensitive to density variations in axon membrane and myelin material [11, 20]. As a consequence, FA, which indicates the directionality of the diffusion process, is thought to reflect the degree of axonal alignment within the brain tissue. Moreover, the parameter MD, representing the overall diffusion strength, is thought to represent the presence of diffusion barriers. In addition, perpendicular diffusivity provides a more specific surrogate of changes associated with myelination. Thus, the present tract asymmetries in FA, MD, PED, and other parameters is interpreted as evidence of pyramidal tract fibres of the left hemisphere being more numerous or on average more strongly myelinated than those of the right hemisphere. Thus, the PT of the left hemisphere might not only have a relatively greater volume but also seems to exhibit tighter axonal packing [20].

V. Conclusion

The aim of the study was to investigate the asymmetry on the microstructure of the PT. A Left greater than right asymmetry pattern of fractional anisotropy (FA), index of linearity (Cl) and index of planarity (Cp) was observed in PT which supports previous neuroimaging studies. Moreover, higher Mean Diffusity (MD), Perpendicular Diffusity (PED) and index of sphericity (Cs) in the right-side than the left-side was also found along PT, whereas no significant difference between right-side and left-side in term of volume (VO) and parallel Diffusity PAD in all three cases. However, we find a correlation between FA, MD asymmetry index and the laterality quotient in right-handed population and in all the population.

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