Cluster-Based Statistics Along White Matter Tracts

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Introduction Diffusion tensor imaging (DTI) has become a modality of choice for studying the white matter (WM) pathology due to its unique *in vivo* characterization of WM microstructure. Wide ranges of paradigms have been developed for studying group differences between healthy subjects and a population with pathology using DTI. The voxel-based approach involves the fitting of smoothed and registered diffusion image data such as the fractional anisotropy (FA) map, followed by the extraction of a map of test statistics and p-values which are then corrected for multiple comparisons. While this approach is powerful and has a solid mathematical background, it has two main drawbacks 1) lack of specificity as it does not take into account the underlying structures and 2) its statistical power is fairly low as the number of simultaneous hypotheses (voxels) is very large. The widely used TBSS [3] technique aims to solve these problems by working on a reduced number of voxels representing the whole white matter. However, its white matter extraction protocol also lacks specificity, and technical problems have been shown to affect its results. Recently introduced structure-specific methods that use a single prototype tract to represent a whole bundle enjoy several advantages: 1) Sound and accurate representation of near tubular WM bundles such as the uncinate fasciculus (UF) and the cingulum; 2) Specificity and increased statistical power due to the reduced number of statistical hypotheses; 3) Ease of graphical representation.
We are looking for clusters of points along the bundle in which the statistical difference is significant. The aim of this work is to introduce a cluster-based statistical analysis method to perform statistics along a WM bundle. We formulate the random field analysis presented in [4] for the univariate case and we show that in addition to being a sound and specific approach, it also has increased sensitivity while retaining correctness.
Materials and methods *Data acquisition and preparation.* Diffusion-weighted images (DWI) from 18 chronic SZ patients and 23 HC matched by age, gender, handedness and parental socio-economic status were acquired on a GE Signa HDxt 3.0T scanner using an echo planar imaging sequence with a double echo option, an 8 Channel coil and ASSET with a SENSE-factor of 2. The acquisition consisted in 51 directions with b=900 s/mm2, and 8 images with b=0s/mm2, with scan parameters TR=17000 ms, TE=78 ms, FOV=24 cm, 144 × 144 encoding steps, 1.7 mm slice thickness. 85 axial slices covering the whole brain were acquired. Then, we deformably registered all the DW images to an unbiased template. Then we performed ROI-based tractography to extract the left uncinate fasciculus for each subject.
Data analysis. We extracted the prototype WM tract from the whole population using the method introduced in [1] as shown in fig. 1. We calculated the FA, and the newly introduced curving and dispersion measures [2] along each tract and projected and resampled them over the prototype tract obtaining a set of one-dimensional functions (fig. 2). For each measure, we fitted a one-dimensional t-field (or t-process) to the data by using a GLM approach [3]. This method is not only simple to implement as a weighted least squares problem but also allows the incorporation of covariates in the analyses. After fitting the t-process, we calculated the point-wise p-value to assess the power of usual volume-less techniques for statistical significance. Then, in order to test the power of our approach, we analyzed the t-process plot for each measure in order to search for a cluster-forming threshold. Finally, we calculated the significance of each cluster above the threshold for the FA, curving and dispersion measures [4]. When more than one cluster was found, we corrected for multiple hypotheses using the FDR technique [5].
Results By using the spatial extent of focal differences, our method is able to show dissimilarities between the two populations where point-based methods where not. This is shown in fig. 3 where the p-value function corresponding to a fitted t-process does not exhibit points with p-value smaller than 0.1. Moreover, when significant points were present in the p-value function, they were typically scattered along the tract (data not shown). On the other hand, when we calculated p-values for clusters above a cluster-forming threshold selected by visual inspection of the t-process plots (Fig 4.), we found at least one cluster per analyzed measure which was significant, even after performing multiple hypotheses-corrections with the false discovery rate technique [4]. These results are shown along the tracts in figure 5.
Discussion We present a novel statistical analysis methodology to perform population-based analysis along white matter tract bundles. The method presented takes advantage of the fact that differences along a tract have a spatial extent (i.e., they are grouped into clusters). In applying our method to several measures along the uncinate fasciculus we found an increased sensitivity and power with respect to point-wise methods.
References: [1] Wassermann ISBI 2010. [2] Savadjiev Neuroimage 2010. [3] Smith Neuroimage 2006. [4] Friston HBM 1994 [5] Pacifico J. Am. Stat. Assoc 2004

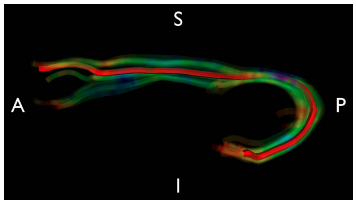

Fig 1. Uncinate fasciculus and its prototype tract in red.

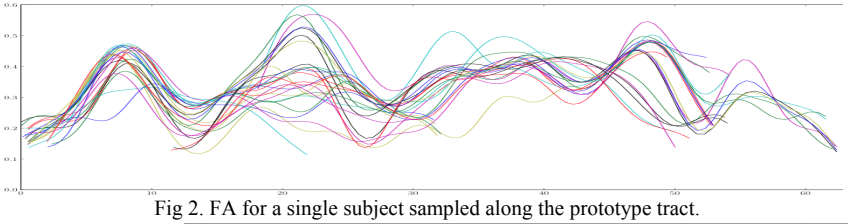
Fig 2. FA for a single subject sampled along the prototype tract.

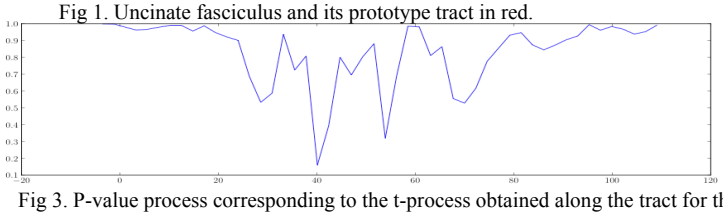
Fig 3. P-value process corresponding to the t-process obtained along the tract for the curving measure. No points, the minimal p-value is above 0.1

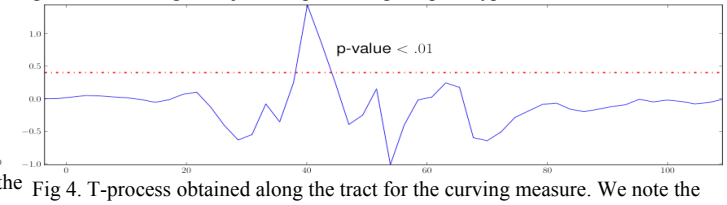

Fig 4. T-process obtained along the tract for the curving measure. We note the existence of a ~10mm cluster above a value of 0.4 with a p-value < 0.01

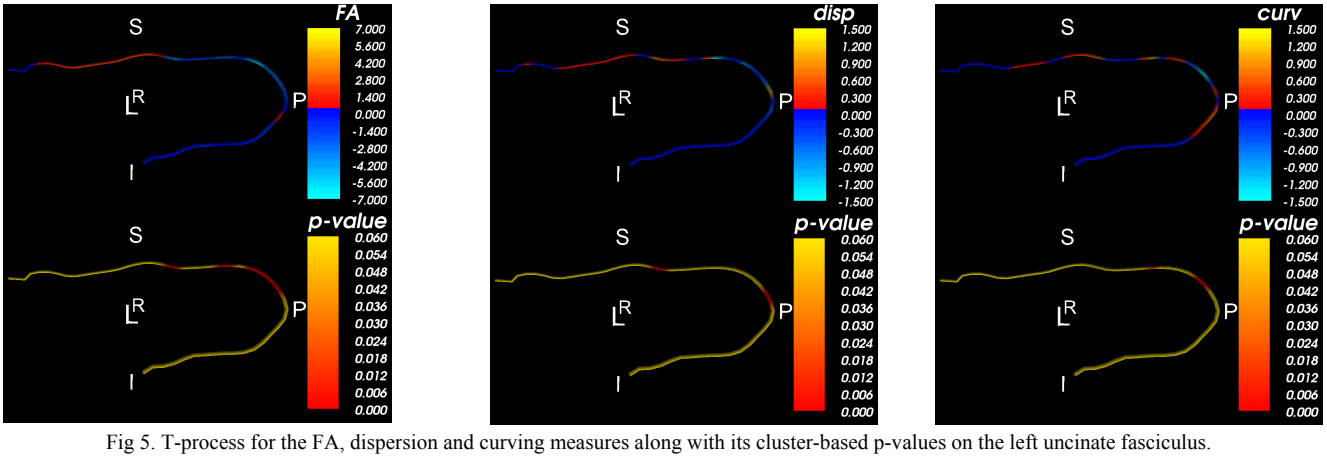

Fig 5. T-process for the FA, dispersion and curving measures along with its cluster-based p-values on the left uncinate fasciculus.