Exploratory data analysis of tractographic measures: study of the cingulum in Autism Spectrum Disorders

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Introduction
Autism spectrum disorders (ASDs) are a set of common neurodevelopmental disorders characterized by socio-communication deficits, stereotyped interests and repetitive behavior [1]. Among the several brain regions implicated in the pathogenesis of these disorders, the limbic system represents one of the most studied [2-3]. It comprises several brain structures including the cingulum, the orbitofrontal cortex, the amygdala and the hippocampus and it is involved in emotion, motivation and social behavior. Diffusion tensor imaging (DTI) approach [4] is a powerful tool for non-invasive investigation of microstructure and has been successfully applied to detect different white matter diseases [5]. Measures like fractional anisotropy (FA), mean diffusivity (MD), parallel and perpendicular anisotropy or length, volume and number of streamlines of each fasciculus can be computed and compare for different groups. In order to increase the robustness of statistics it may be convenient to compute the probability distribution of these measures using the techniques of exploratory data analysis (EDA). In this study measures of cingulum length obtained from ASDs and controls were analyzed and powerful statistical methods were used to find a proper fitting distribution and characteristic parameters.

Materials & Methods
Nineteen children with autism (range 3-11 years; mean age 5.29±1.85 years) and nine healthy controls (range 2-11; mean age 5.26±2.61 years) were included in the analysis. Diffusion tensor MRI of the brain was performed on a 1.5 T MR system (Signa Horizon LX, GE Medical System). A multislice echo-planar imaging (EPI) acquisition sequence using 25 directions of diffusion gradients, was realized (pixel resolution= 0.7422mm x 0.7422mm x 3mm, FOV= 190mm x 190mm, TE= 107 ms, TR= 11000 ms, b-value= 1000 s/mm). TrackVis Software (http://www.trackvis.org/) was used for the reconstruction of the cingulum. Measures extracted from the cingulum were analyzed with R Software (http://www.r-project.org/) to evaluate significant differences using Wilcoxon test and to find the probability distribution obtained for both ASDs and controls. The method of Maximum Likelihood was used to estimate the parameters of the distribution obtained for both ASDs and controls.

Results
The statistical analysis by means of the Wilcoxon test on the cingulum measures revealed a significant increase in the length of streamlines bilaterally within the cingulum in ASD group (left cingulum: mean=90.9±3.3, right cingulum: mean=79.8±9.1) than in controls (left cingulum: mean=71.8±16.7; p=0.007, right cingulum: mean=59.7±16.7; p=0.004). Lengths are expressed in pixels. As the difference in the right cingulum was more statistical significant, it was chosen for the density fit. The histogram analysis showed that data had a peak at 80 pixel and an ascending tail faster than the descending one (Figure 2.a). The comparison between empirical and theoretical cumulatives, the Q-Q plot (Figure 2.b) and the survival function showed that the log-normal distribution was the most suitable for fitting the data of length of the cingulum. The empirical cumulative for ASDs and controls were then plotted together to compare the trend of the two set of samples (Figure 2.c). The curve of controls had an earlier increase respect to the curve of ASDs but at the extreme, that means for high values, the two curves overlapped. The distance between the two cumulative was computed using the Kolmogorov-Smirnov test that is of the maximal vertical distance between the curves. The result was p=0.01. Using the method of Maximum Likelihood the parameters of each distribution where finally estimated (mean=4.5, s.d.=0.14 for ASDs and mean=4.25, s.d.=0.21 for controls).

Conclusions
In this study significant increase in the length of streamlines of the cingulum in ASDs in comparison to controls was found. This difference was not related to age as no significant correlation between length and age was found. It is important to underline that the length measure is a mean of all the streamlines so that if the number of short streamlines is higher the mean is lower. Moreover a powerful statistical approach based on EDA was used to fit the measures of length of both ASDs and controls. The distance between the empirical cumulative was found significantly different. EDA technique allows to extract more robust conclusions, to maximize the insights into a data set, to find outliers, to estimate characteristic parameters and to provide a basis for further data collection experiments.

References