A model based approach for voxelwise analysis of multi-subject diffusion tensor data

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Introduction and Purpose

Several studies have reported maturational changes in fractional anisotropy (FA) in the white matter (WM), using voxel-based analysis of diffusion tensor data [1-4]. However, such studies have used a linear model for the correlation analysis, which has the potential to obscure maturational 'milestones', in which there are non-linear changes or 'spurts' in maturation (for example, as might occur around the time of puberty). By considering a nested model strategy and combining voxel based morphometry (VBM) with a robust model fitting framework, we aimed to determine whether the change in FA with age during development into young adulthood is a gradual (linear) change, or whether there are any maturational (non-linear) milestones and whether these milestones are different in girls and boys. Our initial results suggest that there are indeed such milestones, such as the predominant FA change in the thalamus and the cingulum which tends to occur at a later stage for boys (~17 year) compared to girls (~12 year).

Methods

Acquisition: DTI data were obtained from 189 healthy young volunteers aged 5.6 – 27.8 years (95M, 94F) on a 1.5 T system, a dual spin-echo EPI sequence (b = 1000 s/mm^2; 6 directions) with native resolution of 2.3 x 1.7 x 3 mm^3 and acquisition time = 6:06 minutes (TR=6400 ms, TE=88 ms, FOV = 220 x 220 mm^2).

Coregistration: Details on the applied coregistration methods to normalize the data (both the affine and non-affine procedure) can be found in Refs. [5] and [6].

General concept: Conventional DTI-related VBM studies are mainly confined to provide information, such as, "in part 'X' of the brain, the FA is correlated with age", without giving any insight in the regional variation of the degree of FA change with age (e.g., Fig. 1 (a) for a single voxel and Fig. 2 (a) for an entire coronal slice) [7]. In the following 'single-voxel' example, however, we modelled the FA change with age by a sigmoid function [Fig. 1 (b)] allowing one to extract more detailed information that is otherwise disregarded. For instance, parameter 't', which defines the sigmoid's point of inflection, corresponds to the age that exhibits the largest degree of FA change, i.e., a maturational milestone. From the results in Fig. 1 (a→c), one could make the following statement: "For this specific voxel, the most rapid FA change of boys occurs at a later age (t_m = 17 y) and during a shorter period (Δt_m = 0.53 y) than compared to girls (t_f = 13 y and Δt_f = 2.8 y). The objective is now to extend this procedure to determine where and when these milestones in FA change occur and whether they differ between sexes.

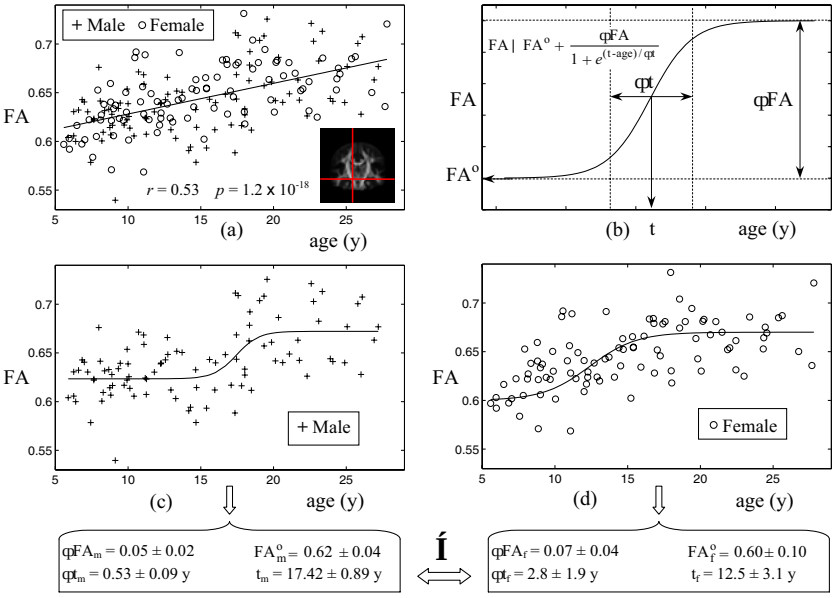

Fig. 1 ***(a)*** *Correlation of age vs. FA for a single voxel;* ***(b)*** *the sigmoid model;* ***(c)*** *and* ***(d)*** *the data fitted to the sigmoid model for males and females, respectively, with precision estimates of the model parameters obtained from the wild-bootstrap procedure.*

Model selection: An important aspect of the proposed group analysis framework is the choice of the applied model to fit the data. After visual inspection, three models with varying degrees of complexity are proposed to model the FA change with age, i.e., a sigmoid (FA_s), relaxation (FA_r), and linear (FA_l) function. Since prior information on the age-FA dependency is generally unknown, an objective selection procedure for determining the optimal model is indispensable. To this end, the calculation of the Akaike Information Criterion (AIC) has been incorporated to examine the complexity of the applied model together with the goodness of its fit to the sample data [8]. In Fig. 2 (b), we applied this model selection procedure for the significantly correlated voxels (with Benjamini-Hochberg false discovery rate for multiple comparisons correction) of Fig. 2 (a), clearly indicating the non-linearity of the FA change with age in several regions of the brain. Note that no denoising has been applied prior to the calculation of the statistics.

Statistical inference: After the appropriate model has been determined for describing the FA change with age, a wild-bootstrap procedure is applied to infer the precision of the derived model parameters (alternatively, randomization - permutation testing could also be considered for this purpose) [9]. Subsequently, further statistical analyses can be performed, such as the single-voxel example presented in Fig. 1 (c, d) which demonstrates a significantly different FA change with age between boys and girls, as indicated by the parameters 't' and 'Δt' of the sigmoid model. In Fig. 2 (c), the VBM-style approach of this concept is presented for each parameter of the sigmoid model. Here, it is demonstrated that the FA maturational milestone (parameter 't') in the thalamus and the cingulum occurs at a later age for males than for females.

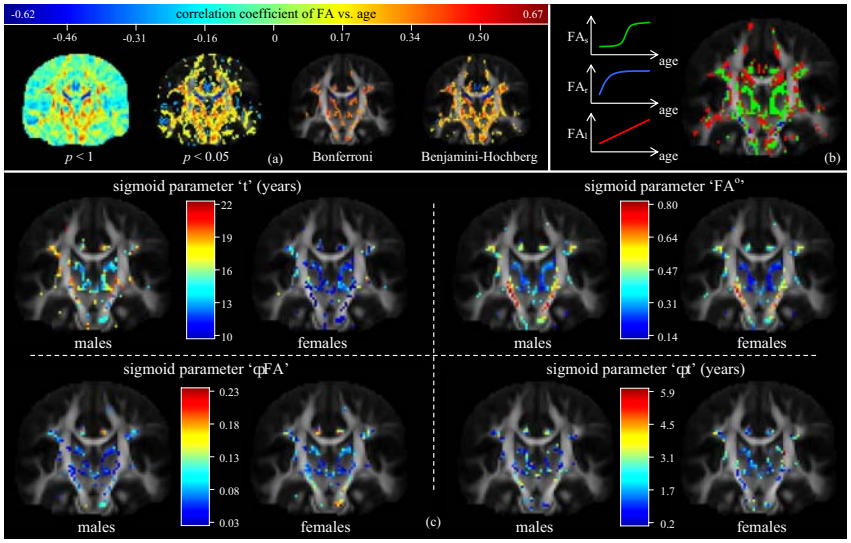

Fig. 2 **(a)** Spearman correlation maps of a coronal human brain slice, i.e., from left to right: all voxels, only voxels with $p < 0.05$, with Bonferroni multiple comparisons correction, and the Benjamini-Hochberg false discovery rate procedure; **(b)** model selection procedure for FA_s, FA_r, and FA_l using the AIC method; **(c)** difference of the FA change with age between boys and girls of the 'sigmoidally labeled' voxels, i.e., the green voxels of **(b)**, for the different sigmoid parameters. Statistical significance is determined by the Mann-Whitney U-test. Note that only 'sigmoidally labeled' voxels exhibiting a significant difference are color-encoded.

Conclusion

In this paper, we presented a new methodology that allows one to study specific properties of the FA change with age. Our results suggest that with this new model based multi-subject analysis, non-linear changes in maturation of the FA change with age (i.e., 'milestones') can be determined which otherwise would be disregarded in conventional voxel-based analyses.

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References

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