Implications of Heterogeneous Variance of Tensor-Derived Quantities for Group Comparisons

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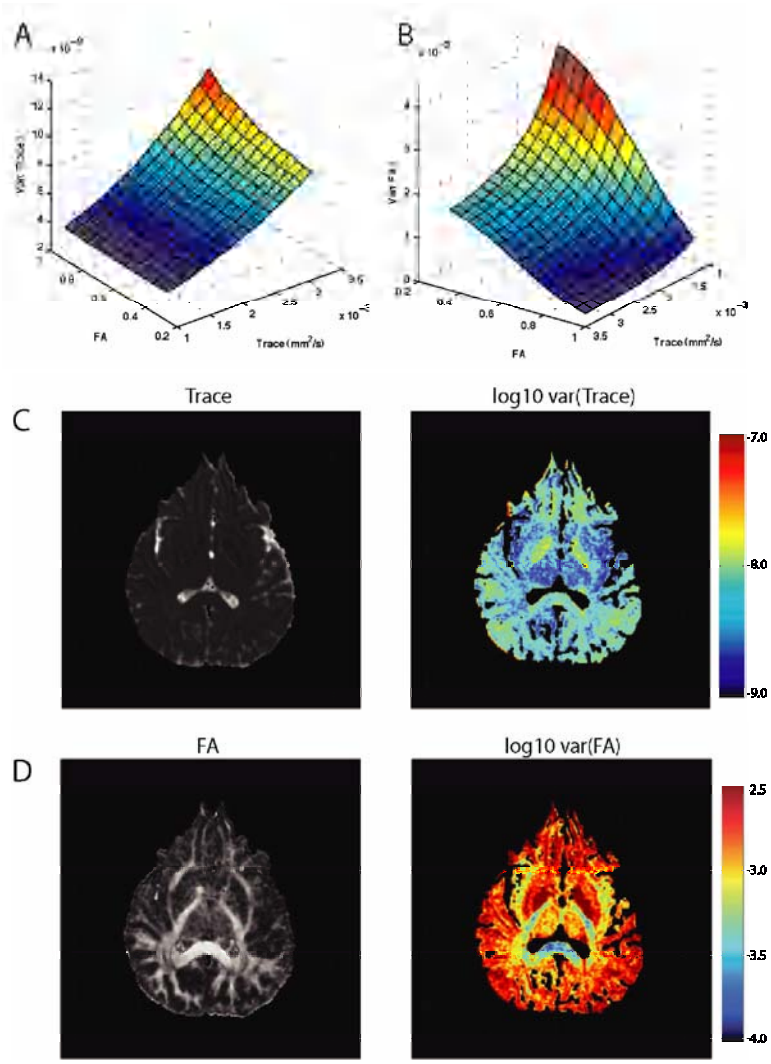
INTRODUCTION

Diffusion tensor imaging (DTI) is a quantitative MRI method that is widely used to study the microstructural properties of white matter in the brain. This sensitivity to microstructure and tissue organization makes DTI an important tool for studying the normal, diseased, and developing brain. DTI is applied to studies in which scans of subjects from a patient group and a control group are compared. In performing group analysis on each voxel (as in voxel-based morphometry (VBM)) or region of interest (ROI) analysis, the mean values of tensor-derived quantities, such as trace and fractional anisotropy (FA), are statistically compared between the groups. Most such studies use a simple t-test of the null hypothesis that the means are equal in the two groups. A key assumption of this test is that the variances of the measurements in each group are equal. The purpose of this study is to examine this assumption and to describe a method for valid inferences when the variances of trace and FA are unequal.

METHODS

SIMULATIONS: A series of Monte Carlo simulations were used to examine the dependence of the variance of trace and FA on their respective values. Prolate, cylindrically-symmetric tensors were specified for equally-spaced values of trace (1.0945×10^{-3} to 3.2835×10^{-3} mm^2/s) and FA (0.30 to 0.95) on a 15x15 grid. For each trace/FA pair, 50000 data sets were generated from a design with 16 icosahedral directions [1] at each b=0, 300, 650, 1000 s/mm^2. The T2 weighted signal was set to 1000 with SNR equal to 20. Data were simulated with Rician noise as described in [2]. The tensors were estimated by nonlinear least squares (NLS) using Newton's method [3]. For each tensor estimate, the trace and FA were calculated. Sample variances of trace and FA were computed and plotted as a function of trace and FA for each trace/FA pair.

REAL DATA: A healthy male volunteer (age 27) gave informed consent in accordance with our institutional review board for human subjects. DWIs were acquired on a 3T scanner with a SE-EPI pulse sequence with cardiac gating. Scan parameters: 10 axial slices, 3 mm thick, 5 mm gap, FOV 24x24 cm, 120x120 matrix interpolated to 256x256, TE 72.3 ms, 16 icosahedral directions at each b=0, 300, 650, 1000 s/mm^2. Tensors were fit with NLS using Newton's method [3]. Trace and FA maps were generated and maps of their variances were created using variance estimators described in [4].



RESULTS

There is a strong dependence of the variance of trace and FA on the values of trace and FA. Figure A shows that as trace increases, the variance of trace increases. Also seen is a slight dependence of var(trace) on FA, with higher FA giving higher var(trace). In Figure B, the effect of trace and FA on var(FA) is more dramatic. As FA increases, var(FA) decreases nonlinearly. As trace increases, var(FA) decreases. The simulations were repeated for oblate tensors. Dependence of variance on trace and FA follows the same trends as seen in Figures A and B. The variances of trace and FA in the human data reflect the same trends as in the simulations. Figure C shows that var(trace) depends on tissue type. The effect is characterized by the FA of the tissue. Regions with high FA (e.g., corpus callosum) have more variable trace estimates than regions with lower FA. Figure D shows that the variance of FA ranges by roughly an order of magnitude in white matter, with a strong dependence of the variance of FA on the value of FA. Consequently, the variance of FA depends strongly on the spatial location in the brain.

DISCUSSION AND CONCLUSION

The main finding of this study is that variances of tensor-derived quantities such as trace and FA are not homogeneous. If the value of the quantity changes, as can happen in disease states, the variance will differ from the variance in healthy subjects. This difference in variance violates an assumption of the t-test that is used in VBM and ROI group studies. More work is needed to examine the impact of this violation. Future work involves examining the effects on type I and type II error rates for group comparisons. One solution to provide valid statistical inference for group studies is to estimate group effects with weighted linear least squares. The weights are selected as the inverse of the variance of the measurement. This requires an estimate of the variance of each trace/FA measurement from each subject. Possible methods for estimating variances are bootstrap analyses [5] and asymptotic variance estimators [4], as were used in this study.

REFERENCES

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