

Patient Centered Registration and Analysis of Diffusion MRI for Robust Detection of Spatially Varying Microstructural Changes

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Purpose

In order to detect spatially heterogeneous pathology, such as that due to traumatic brain injury, abnormalities must be identified by comparison of individual subjects to a control group (1 vs. many analysis). The typical approach to this problem entails coregistration of the subject and all of the control volumes to a canonical brain atlas, so that comparisons can be made on a voxelwise basis. Although appropriately registered brains more closely resemble the template, morphological variation can still be readily verified by visual inspection of registered subject brains. Thus, a voxelwise comparison of a set of co-registered brains for the purpose of identifying salient differences will incorporate a systematic limitation of the registration process as a confounding factor. In addition to this systematic error, an additional error is introduced due to differences between the template, the *target* of the registration process, and the subject's registered brain, the *target* of interest. In this study, we propose the subject of interest as the template for the analysis. With this approach, systematic registration errors, though present, will be distributed across controls and therefore less problematic. Most importantly, however, we entirely eliminate the registration error for the subject of interest.

Methods

3T DTI (2mm³, 32 directions, b=800) was performed on 7 TBI patients and 48 normal individuals using a Philips Achieva scanner and 32 channel head coil. FA images were derived and registration procedures applied as described previously (1). A voxelwise ANCOVA was then performed comparing the white matter of the patient to the control group ($p<0.01$; cluster size 100), while adjusting for age, gender and years of education. Three distinct analyses were performed: (1) all subjects and controls were transformed to the JHU atlas, (2) all subjects and controls were transformed to the MNI atlas, (3) all controls were transformed to the patient's T1-weighted volume. The total number of abnormally low FA voxels associated with clusters was evaluated in each study.

Results

We found a significant reduction in the total volume of abnormally low FA values in analyses carried out in the patient's anatomical space compared to either atlas-based analysis. Four of the seven patients demonstrated no abnormally low FA clusters in the patient space analysis, while abnormal clusters were present when these same four patients were registered to either brain atlas. The remaining three patients demonstrated increases of 140% to 1300% in total number of abnormally low FA voxels detected using atlas-based analyses compared to the patient-based analysis. Furthermore, atlas-based analysis demonstrated between 9% to 14% overlap of gray matter/CSF voxels of the coregistered patient volume and either atlas, which may contribute to the excess number of low FA voxels detected in atlas-based analyses. Without careful evaluation, these misregistrations could be misinterpreted as pathology. Since patient based registrations does not involve any manipulation of patient data, these misregistrations cannot occur. We also note that low FA clusters identified by patient-based analysis is typically detected in at least one atlas-based analysis. However, if a cluster is identified in one of the atlas-based analyses but is not detected in the patient based analysis, is inconsistently seen in the alternate atlas-based analysis. When overlap of abnormalities occurs between atlas-based registrations, it is typically evident that these are due to misregistration errors.

Conclusion

Brain templates are employed to facilitate comparison across subjects and can be used as a basis for delineating regions of abnormal diffusion in individual subjects. However, systematic limitations of the registration process and the additional error of inaccuracy introduced due to morphological differences between the template and the subject's brain can introduce error in the identification of diffusion abnormalities. Through a simple, but computationally intensive, change in the registration protocol, using the subject as the template rather than a brain atlas, inaccuracy caused by differences between a brain template and the subject's anatomy is eliminated. Thus, although the systematic error caused by limits in the registration still persist, this error is distributed across controls and does not impact the subject's brain at all. We have demonstrated that atlas-based analyses lead to the detection of more voxels with abnormally low FA voxels as compared to the patient-based analysis; these differences are attributable to registration errors. Patient-based analysis can thus provide more accurate identification of diffusion abnormalities due to pathology. An additional benefit to subject based registration is that diffusion abnormalities can now be visualized directly in the patients anatomic space rather than interpolating results from a brain atlas registrations and thereby enhancing clinical correlation between anatomic location and clinical findings, assist in surgical planning and help refine localization of abnormalities that can aid MRS studies and biopsy procedures. In addition, MR tractography can be performed employing regions of diffusion abnormality as regions of interest (ROI).

References

1. Kim, N., C. A. Branch, et al. (2013). "Whole brain approaches for identification of microstructural abnormalities in individual patients: comparison of techniques applied to mild traumatic brain injury." *PLoS One* **8**(3): e59382.