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An unbiased longitudinal analysis framework for tracking white matter changes using diffusion tensor imaging with application to Alzheimer's disease

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ABSTRACT

We introduce a novel image-processing framework for tracking longitudinal changes in white matter microstructure using diffusion tensor imaging (DTI). Charting the trajectory of such temporal changes offers new insight into disease progression but to do so accurately faces a number of challenges. Recent developments have highlighted the importance of processing each subject's data at multiple time points in an unbiased way. In this paper, we aim to highlight a different challenge critical to the processing of longitudinal DTI data, namely the approach to image alignment. Standard approaches in the literature align DTI data by registering the corresponding scalar-valued fractional anisotropy (FA) maps. We propose instead a DTI registration algorithm that leverages full tensor information to drive improved alignment. This proposed pipeline is evaluated against the standard FA-based approach using a DTI dataset from an ongoing study of Alzheimer's disease (AD). The dataset consists of subjects scanned at two time points and at each time point the DTI acquisition consists of two back-to-back repeats in the same scanning session. The repeated scans allow us to evaluate the specificity of each pipeline, using a test–retest design, and assess precision, using bootstrap-based method. The results show that the tensor-based pipeline achieves both higher specificity and precision than the standard FA-based approach. Tensor-based registration for longitudinal processing of DTI data in clinical studies may be of particular value in studies assessing disease progression.

Introduction

Diffusion tensor imaging (DTI) is a technique offering sensitivity to tissue microstructure of white matter (WM) (Basser and Pierpaoli, 1996; Pierpaoli et al., 1996). DTI is playing an increasingly important role in assessing white matter abnormalities in a variety of neurodegenerative disorders, including Alzheimer's disease (AD), vascular dementia (Hanyu et al., 1999; Sugihara et al., 2004), and frontotemporal dementia (Borroni et al., 2007; Matsuo et al., 2008). For example, in patients with AD, increased mean diffusivity (MD) and/or reduced fractional anisotropy (FA) compared to healthy controls have been reported for several white matter tracts, including the corpus callosum, cingulum bundle and fornix (Bozzali et al., 2002; Choo et al., 2010; Duan et al., 2006; Fellgiebel et al., 2008; Mielke et al., 2009; Oishi et al., 2011; Rose et al., 2000; Sexton et al., 2010).

Most DTI studies of neurodegenerative disorders have been cross-sectional in nature. Few investigate the changes in DTI measures as a function of disease progression. One notable exception is a longitudinal study of AD by Mielke et al. (2009), which showed that FA in the fornix, cingulum, splenium, and cerebellar peduncle remained stable in AD and healthy elderly subjects over a three-month follow-up. In contrast to many cross-sectional studies, which employ voxel-based analysis, Mielke et al. adopt region-of-interest (ROI) based analysis to provide the sensitivity necessary for detecting subtle temporal changes in white matter over a very short period of time. This suggests that ROI-based analysis, which trades reduced spatial specificity for improved sensitivity, may be an effective approach for measuring DTI changes due to disease progression.

The effectiveness of ROI-based analysis is dictated by the accuracy and consistency of ROI delineation across subjects. To date, most studies of this kind define WM ROIs manually. Manual delineation utilises expert knowledge in anatomy to ensure the accuracy of ROI definition. However, this is labour-intensive and time-consuming. Furthermore, it is also difficult to maintain a high-level of consistency for the entire dataset of a study, especially when placing the ROIs for small and thin tracts, such as the cingulum and the fornix, which are often plagued with partial volume effect with their surrounding anatomy. This becomes even more challenging for studies designed to track longitudinal changes. There is not only a need for between-subject consistency but also for within-subject between-scan consistency. This challenge motivates the present work.

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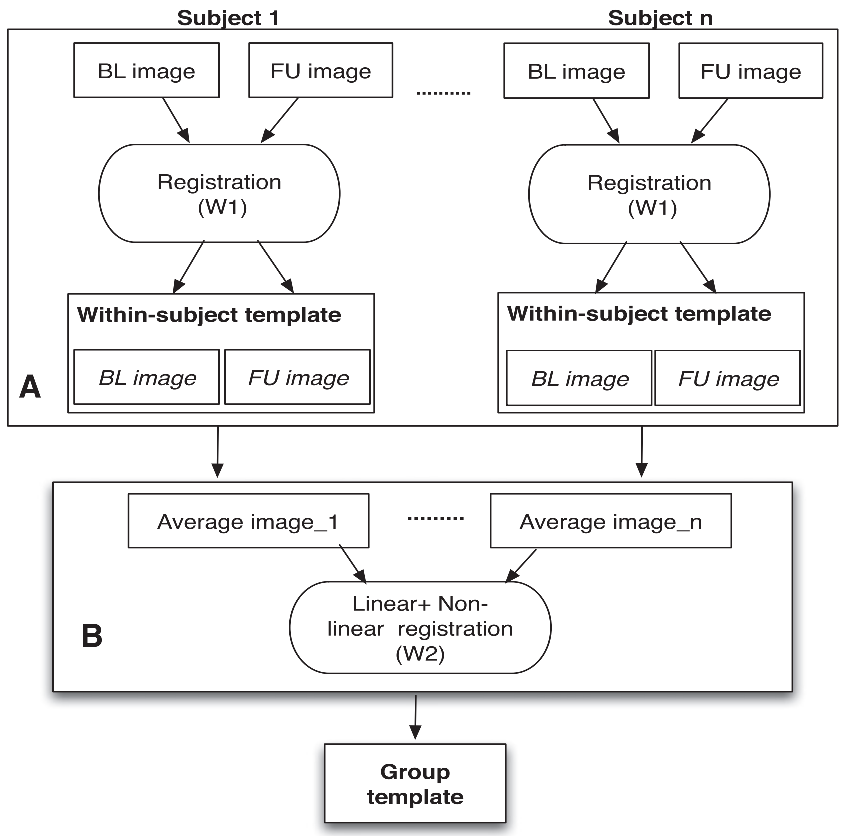

Fig. 1. Unbiased pipeline to study longitudinal changes in DTI parameters. Module A shows the step to create the unbiased within-subject template based on two time point images. Module B shows the step to create the group-wise atlas based on the within-subject templates. Details of registration methods and type of input images for Tensor_GW, FA_GW and FA_HS is shown in Table 1. BL = baseline, FU = follow-up.

In this paper, we propose an automated and unbiased DTI analysis pipeline for tracking longitudinal white matter changes. The pipeline aims to make ROI-based analysis both more accessible and more robust by combining best practices for unbiased longitudinal processing of structural imaging data (Reuter et al., 2012; Yushkevich et al., 2010) with recent advances in tensor-based image registration (Park et al., 2003; Zhang et al., 2006). We evaluate the performance of the proposed pipeline using data from an ongoing longitudinal study of AD and compare it against the more common approach of using FA-based image registration (Ardekani et al., 2007; Jones et al., 2002; Smith et al., 2006).

Materials and methods

Unbiased longitudinal DTI pipeline

Overview of the pipeline

The automated longitudinal processing pipeline is designed to enable a temporally unbiased evaluation of two time points where all time points of a subject are registered together to form a within-subject template. This is created in a mean space in order to avoid any interpolation asymmetry.

Interpolation asymmetries could arise when resampling follow-up images to the baseline scan (Yushkevich et al., 2010), as only the follow-up images are smoothed while the baseline image is unaffected. Module A of Fig. 1 illustrates the generation of an unbiased within-subject template for each subject in the study. The specific choice of registration method is discussed in the subsequent sections. The resulting template is unbiased towards any single time point. The original images, baseline and follow-up, are then transferred to this within-subject space and averaged. Module B of Fig. 1 demonstrates the creation of the group-wise (GW) atlas from the average images using iterative linear and non-linear registration methods. The mapping from the subject native space to its own within-subject template (warp field 1, W1, in Fig. 1) and the mapping from the within-subject template to the GW atlas (warp field 2, W2) were combined to create the deformation field that defines the mapping directly from the native space to the GW atlas.

Choices of registration methods

In this study, we propose that using a registration method that incorporates the entire tensor will provide more accurate and sensitive longitudinal measures than using FA based methods. For the tensor registration, we used a publicly available tool, DTI-TK,[2] for spatial normalisation of DTI data (Zhang et al., 2006). We compared the effectiveness of this method to a widely used FA-based method: all the linear and non-linear registrations were performed using FSL (Smith et al., 2004), FLIRT, FMRIB's linear image registration tool (Jenkinson and Smith, 2001) and FNIRT, FMRIB's Non-Linear Registration Tool (Andersson et al., 2007), with sum-of-squared differences as the cost function. Table 1 shows the detail of the unbiased longitudinal pipeline for each method.

Tensor-based pipeline. In the tensor-based registration pipeline, all linear and non-linear registrations were performed using DTI-TK on tensor images. By computing the image similarity on the basis of full tensor images rather than scalar features, the algorithm incorporates local fibre orientations as features that drive the alignment of individual WM tracts.

For each subject, a within-subject template was generated by computing the initial average template as a Log-Euclidean mean of the input DT images from the two time points. The Log-Euclidean tensor

[2] http://dti-tk.sourceforge.net.