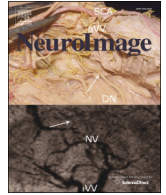




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Full Length Articles

Q1 **Tractography atlas-based spatial statistics: Statistical analysis of diffusion tensor image along fiber pathways**

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ABSTRACT

The quantitative analysis of diffusion tensor image (DTI) data has attracted increasing attention in recent decades for studying white matter (WM) integrity and development. Among the current DTI analysis methods, tract-based spatial statistics (TBSS), as a pioneering approach for the voxelwise analysis of DTI data, has gained a lot of popularity due to its user-friendly framework. However, in recent years, the reliability and interpretability of TBSS have been challenged by several works, and several improvements over the original TBSS pipeline have been suggested. In this paper, we propose a new DTI statistical analysis method, named tractography atlas-based spatial statistics (TABSS). It doesn't rely on the accurate alignment of fractional anisotropy (FA) images for population analysis and gets rid of the skeletonization procedures of TBSS, which have been indicated as the major sources of error. Furthermore, TABSS improves the interpretability of results by directly reporting the resulting statistics on WM tracts, waiving the need of a WM atlas in the interpretation of the results. The feasibility of TABSS was evaluated in an example study to show age-related FA alternation pattern of healthy human brain. Through this preliminary study, it is validated that TABSS can provide detailed statistical results in a comprehensive and easy-to-understand way.

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Introduction

Diffusion tensor imaging (DTI), as a sensitive probe of cellular structure by measuring the diffusion of water molecules, has become a widely used tool for imaging the white matter (WM) of the brain. With its growing popularity, DTI has been applied in a variety of neuroscience studies, such as WM diseases study (Amlien and Fjell, 2014; Barnea-Goraly et al., 2010; Guo et al., 2001; Kubicki et al., 2005), human brain connectome modeling (Hagmann et al., 2007; Tymofiyeva et al., 2013), neurosurgical planning and navigation (Abdullah et al., 2013; Nimsy et al., 2006; Wu et al., 2007) and so on. To perform the quantitative analysis on DTI, several DTI-derived metrics can be calculated to quantify the properties of WM non-invasively. One of the most widely used metrics is fractional anisotropy (FA), which is a useful quantity to measure WM integrity. The voxelwise FA map is usually compared across subjects to reveal diffusion property differences.

There are three mainstream DTI analysis methods: region of interest (ROI) analysis (Schneider et al., 2004; Shimony et al., 1999; Snook et al., 2005; Yoshiura et al., 2005), tract-specific analysis (Colby et al., 2012; Yeatman et al., 2012) and voxel-based analysis (VBA) (Abe et al., 2010; Takao et al., 2010; Tapp et al., 2006).

In ROI-based approaches, ROIs are first specified in each subject image. FA values are extracted and averaged within each ROI. Mean FA values are compared across subjects on a regional basis. However, as FA values are averaged within the ROI, the detailed spatial information is lost through this operation, especially when regions with different diffusion properties are combined.

In the previous tract-based DTI analysis studies, either a mean fiber is used to represent the entire WM tract (Colby et al., 2012; Yeatman et al., 2012), or ad hoc parameterization method is employed to model the shape of the tract (O'Donnell et al., 2009; Verde et al., 2014; Zhang et al., 2010a). This kind of method is limited to some specific WM tracts that either contain fibers with similar diffusion properties so that the diffusion indices of the mean fiber can represent the whole tract, or contain fibers with uniform shape for easy parameterization.

For VBA methods, FA images of different subjects are first registered into a common space. The voxelwise statistical analysis is carried out to study the between-group differences. VBA methods can achieve a more

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detailed spatial statistics, but the results are highly sensitive to registration accuracy and the choice of a smoothing kernel. One alternative to VBA is tract-based spatial statistics (TBSS) (Smith et al., 2006), which was proposed to alleviate the influences of misalignment and the smoothing kernel. TBSS creates a mean FA skeleton image to represent the centers of all fiber bundles, projects each subject's aligned FA image onto the skeleton, and then carries out voxelwise statistical analysis across subjects on the skeleton voxels. TBSS aims to reduce the sensitivity of registration accuracy by introducing the skeletonization and projection steps. After its development and availability within FSL, TBSS has been widely adopted for many DTI analyses (Bodini et al., 2009; Burzynska et al., 2010; Giorgio et al., 2008; Hsu et al., 2008). Nevertheless, in recent years, some studies have emerged to point out the limitations of TBSS. In summary, there are three major points of debate about TBSS: First, the skeleton projection step may break the topological consistency of the transformed brain images (de Groot et al., 2013). Second, any misalignment resulting from the groupwise registration may substantially influence the results. Although some works proposed to use a more advanced registration method to improve alignment accuracy, e.g., ANTS (Schwarz et al., 2014), Elastix (de Groot et al., 2013), DTI-TK (Bach et al., 2014), registration errors inevitably exist to a certain extent, and perfect anatomical alignment is hard to be achieved due to anatomical variability between subjects. Third, as stated in Bach et al. (2014), special care should be taken in interpreting the results of TBSS. TBSS overlays the significant results upon the skeleton voxels, which lack an explicit tract representation. For structures that are in close proximity to each other, it is sometimes hard to differentiate between them. Moreover, it provides limited anatomical specificity with which to interpret the results. Although, these studies have raised awareness of TBSS limitations and suggested improvements to the approach, a consensus has not yet been reached on how to modify the original TBSS scheme.

In order to address the above issues, we proposed an alternative DTI statistical analysis approach, entitled tractography atlas-based spatial statistics (TABSS). It is a whole-brain, fully automated, statistical analysis method. The statistical results are reported upon the WM tracts. In order to validate the feasibility and accuracy of TABSS, we have conducted experiments to compare the FA patterns between a young group and an old group of subjects. The experiment was designed as a verification of TABSS application to a between-group comparison. Age-related FA reduction is widely documented in the literature (Burzynska et al.,

2010; Hsu et al., 2008; Madden et al., 2008; Salat et al., 2005; Teipel et al., 2010). We compared the TABSS results with those previously reported WM regions and found consistency between the findings.

Method

Overview of TABSS

TABSS attempts to inherit the strengths of TBSS to perform automatic whole brain DTI analysis. It does not rely on accurate non-rigid groupwise registration to establish correspondence between subjects for statistical analysis and gets rid of the projection process. This is achieved by establishing a fiber-level correspondence with an existing tractography atlas via feature matching. After correspondence establishment, diffusivity metrics can be sampled along the trajectory of fibers and directly compared between corresponding fiber pairs across subjects. The final statistics are reported in a multi-level way for a comprehensive understanding of any WM alternation patterns. The pipeline of TABSS consists of four steps, as shown in Fig. 1 and summarized as follows.

1. Creation of a tractography atlas: Perform fiber reconstruction on a DTI template to construct the tractography atlas, which serves as the reference space for population analysis.
2. Extraction of WM tracts: Using an automated atlas-guided WM tracts reconstruction method, extract the WM tracts in each subject space.
3. Establish the fiber correspondence: For each subject, and within each WM tract, find the fibers that match with the atlas fibers based on a defined fiber similarity measure. For each fiber with a counterpart in the tractography atlas, extract the diffusivity metrics along the fiber pathway for further analysis.
4. Statistical analysis. Carry out the statistical analysis on the diffusivity metrics within the whole brain space.

Tractography atlas

The tractography atlas was served as the reference tractography for establishing correspondences among populations. In this study, we used the publicly available DTI template – IIT Human Brain Atlas (v.3.1), which contains both anatomical and DTI brain templates in ICBM-152 space (Varentsova et al., 2014). It was constructed by the

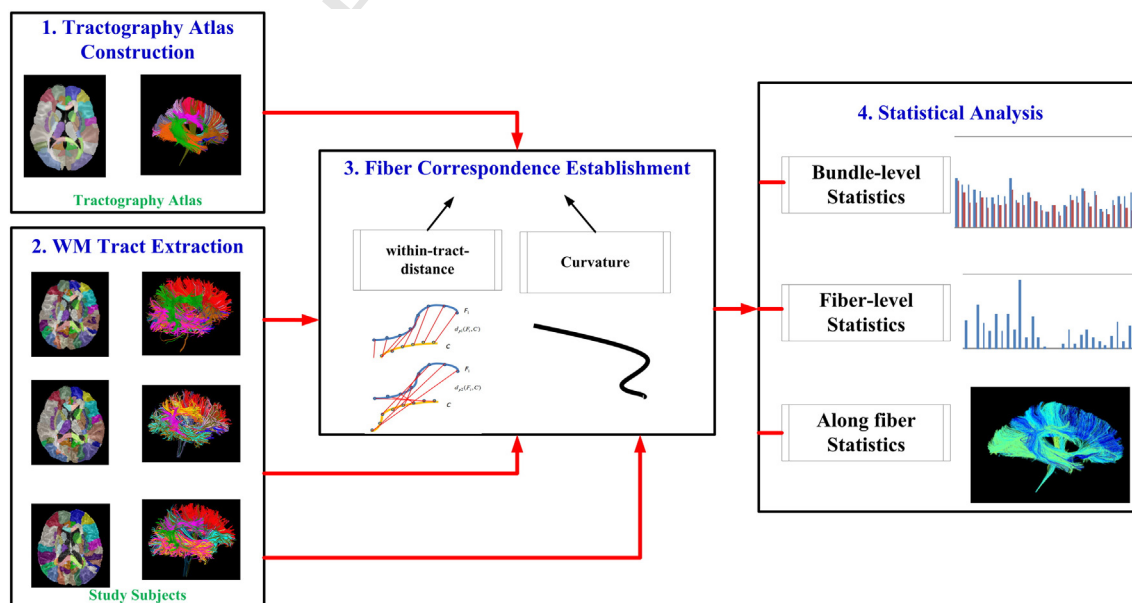


Fig. 1. The pipeline of tractography atlas-based spatial statistics (TABSS) for DTI analysis.

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