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Spatial regression analysis of serial DTI for subject-specific longitudinal changes of neurodegenerative disease★

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ABSTRACT

Quantitative measurement of localized longitudinal changes in brain abnormalities at an individual level may offer critical information for disease diagnosis and treatment. The voxel-wise permutation-based method SPREAD/iSPREAD, which combines resampling and spatial regression of neighboring voxels, provides an effective and robust method for detecting subject-specific longitudinal changes within the whole brain, especially for longitudinal studies with a limited number of scans. As an extension of SPREAD/iSPREAD, we present a general method that facilitates analysis of serial Diffusion Tensor Imaging (DTI) measurements (with more than two time points) for testing localized changes in longitudinal studies. Two types of voxel-level test statistics (model-free test statistics, which measure intra-subject variability across time, and test statistics based on general linear model that incorporate specific lesion evolution models) were estimated and tested against the null hypothesis among groups of DTI data across time. The implementation and utility of the proposed statistical method were demonstrated by both Monte Carlo simulations and applications on clinical DTI data from human brain in vivo. By a design of test statistics based on the disease progression model, it was possible to apportion the true significant voxels attributed to the disease progression and those caused by underlying anatomical differences that cannot be explained by the model, which led to improvement in false positive (FP) control in the results. Extension of the proposed method to include other diseases or drug effect models, as well as the feasibility of global statistics, was discussed. The proposed statistical method can be extended to a broad spectrum of longitudinal studies with carefully designed test statistics, which helps to detect localized changes at the individual level.

1. Introduction

Diffusion Tensor Imaging (DTI) (Le Bihan et al., 2001; Tournier et al., 2011), which measures the random motion of water molecules, provides a non-invasive way to investigate the structural integrity of the brain. It has been widely used in investigating white matter (WM) changes caused by brain development and aging (Westlye et al., 2009), detecting abnormalities in normal-appearing WM due to disease (Weiner et al., 2000), as well as identifying pathologic severity in patients with MS (Werring et al., 1999). In recent years, there has been increasing interest in the investigation of subject-specific changes within the brain without prior information regarding the spatial distribution of the pathology. Consequently, whole brain voxel-based methods (Ashburner and Friston, 2000; Smith et al., 2006; Tustison et al., 2014) have gained much favor during recent years as an important alternative to region of interest (ROI) analysis in detecting localized changes within the brain and are most suitable when changes/effects are diffuse among individual subjects. Both parametric and nonparametric methods have been used to help identify regionally specific changes such as differences due to activation in fMRI (Nichols and Holmes, 2002), neuroanatomical differences in structure MRI data (Bullmore et al., 1999) and pathophysiology in longitudinal studies (Zhu et al., 2013; Chung et al., 2008).

Due to the non-Gaussian nature of DTI data, nonparametric voxel-based methods that do not need any parametric assumptions such as

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bootstrap (Heim et al., 2004; Zhu et al., 2008; Bazarian et al., 2012) and permutation-based methods (Nichols and Holmes, 2002), are more suitable. The nonparametric permutation-based method is able to devise a data-driven null distribution with only minimal assumptions, which gives the user more freedom in devising test statistics of interest. Any sensible test statistic that summarizes the local effect can be used in these hypothesis-testing procedures and the strong control of type I error is guaranteed under very mild assumptions of the null distribution. Such methods have been widely used in the area of fMRI to investigate the regionally specific effect in neuroimaging data (Nichols and Holmes, 2002). However, few of the aforementioned methods have been applied to subject-specific longitudinal studies. This is mainly because the number of available scans in a longitudinal study is often limited by practical factors such as the cost of patient recruitment, and the obtained data lacks sufficient information for a rigorous statistical inference test due to their low degrees of freedom.

The Spatial Regression Analysis of Diffusion tensor imaging (SPREAD) method previously presented (Zhu et al., 2013) combines spatial regression and resampling methods, which provides a novel and efficient whole brain analysis method for detecting localized changes in subject-specific longitudinal study without an a priori hypothesis, for DTI-derived metrics such as fractional anisotropy (FA) and mean diffusivity (MD). SPREAD requires only one scan per time point for a valid statistical inferential test, which greatly reduces the granularity of permutation. The iSPREAD method (Liu et al., in press) further improves the detection sensitivity and accuracy of SPREAD (Zhu et al., 2013) substantially by incorporating a three-dimensional (3D) nonlinear anisotropic diffusion filtering method. Both SPREAD and iSPREAD utilize a novel and effective permutation-based statistical method for whole brain analysis that relies on permuting time/scan labels and spatial kernel regression. They do not require adjustment of signal gains due to different DTI protocols at different time points and are effective for monitoring subject-specific lesion progression in longitudinal studies. However, aside from their many advantages, the following limitations exist for SPREAD/iSPREAD, which are also general to most permutation-based voxel-wise subject-specific methods applied in longitudinal studies:

1) The comparison is often taken pairwise between each time point vs. baseline, which is time consuming in the presence of serial DTI studies with multiple time points.
2) The potential differences caused by registration error or anatomical differences due to atrophic changes may manifest as false-positive voxels in the results. The consequences for such misalignment can either falsely identify positives or neglect true positives, both of which greatly reduce the statistical power and reliability of the results obtained.
3) The apparent and useful prior information of lesion progression models is largely neglected in these existing methods.

Therefore, a general statistical framework that accommodates a serial DTI study with multiple time points while taking into consideration the specific disease progression model is desired.

The main purpose of many longitudinal studies is to identify localized temporal changes within the brain. One crucial step towards detecting localized changes is to choose test statistics that are likely to be the most sensitive and informative in depicting possible departures from the null hypothesis, which assumes that there is no difference between data obtained at different time points. The statistical properties of any given hypothesis-testing procedure depend on both the null hypothesis, which specifies the distributional properties of the measurements without true signal, and the alternative hypothesis, which specifies the possible forms of true signal (temporal changes, in this case). The non-parametric permutation-based methods, such as SPREAD/iSPREAD, permit the use of a wide range of test statistics without the need to derive closed-form distributions of these statistics under the null hypothesis with specific parametric assumptions. This flexibility enables us to focus on choosing the optimum statistics based on different alternative hypotheses.

In this study, we proposed to extend the current SPREAD/iSPREAD method to a general statistical framework that accommodates a wide range of alternative hypotheses used in longitudinal studies. Five test statistics, which were divided into two major types, were implemented in the current statistical framework to help identify several different forms of temporal changes within individual subjects. One type is based on model-free test statistics; another is based on a general linear model that incorporates a certain disease evolution model. Our statistical method is similar in spirit to two well-established methods in statistical parametric maps (SPM) for assessing the regionally specific effects within the brain, namely the subtractive method (Worsley et al., 1992, 1996) and the general linear model (Friston et al., 1994), both of which have been widely used in the fMRI field for detection of brain activation. We use those theories within a nonparametric framework with carefully designed test statistics where the empirical null distribution is generated by permutation.

The aim of the present study was to describe and illustrate a statistical method that enables the investigation of longitudinal changes quantitatively. Simulation data with a predefined region of pathology and disease effects were used to evaluate the effectiveness of the proposed method. A series of DTI scans in three patients suffering from relapsing-remitting multiple sclerosis (RRMS) were used as human brain in vivo examples to demonstrate the implementation and utility of this method. Both simulations and in vivo results show that the proposed method is able to detect temporal changes in serial DTI with high sensitivity and accuracy. Extension of the proposed statistical framework to include other disease evolution/drug effect models as well as different global statistics is discussed. The method is an extension of SPREAD/iSPREAD, as well as an independent statistical framework that can be easily applied to a wide variety of longitudinal studies.

2. Material and methods

2.1. Overview of iSPREAD for serial DTI analysis

Based on the exchangeability of the time and scan labels under the null hypothesis (Zhu et al., 2013), in the first step of iSPREAD analysis, the scan/time labels for FA/MD maps from each subject are randomly permuted at each voxel for $N = 1000$ times to generate a permutation distribution under the null hypothesis at each voxel. The permutated images are then smoothed using the nonlinear anisotropic filtering method for edge-preserving image enhancement, as well as for preserving spatial correlation between neighboring voxels. In the third step, various voxel test statistics are chosen to depict the temporal changes in a serial DTI analysis and will be discussed in detail in the next section. The Westfall-Young procedure (Nichols and Hayasaka, 2003) is used to control the FWER in the last step. Voxels are identified as significantly changing (i.e. lesion areas) if their p-value is less than a predefined p-value (e.g. 0.05). The flowchart of the proposed framework is shown in Fig. 1.

2.1.1. The anisotropic diffusion filter

Nonlinear anisotropic diffusion filtering provides a general scale-space approach for edge-preserving piecewise smoothing of the original image. The nonlinear scale space generated by nonlinear diffusion filtering is proposed from an analogy to thermal equations that describe the diffusion process. The Perona-Malik (PM) (Perona and Malik, 1990) equation for the process is shown in Eq. (1):

$$\partial_t \mathrm{I}(z,\tilde{t}) = \mathrm{div}\left(\mathrm{g}(z,\tilde{t}) \cdot \nabla \mathrm{I}(z,\tilde{t})\right), \tag{1}$$

where function $\mathrm{I}(z,\tilde{t})$ is taken as the image intensity (e.g. FA or MD map in our study), and $\tilde{t}$ is the discrete cases. The conductance function $\mathrm{g}(z,\tilde{t})$