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Multivariate statistical analysis of diffusion imaging parameters using partial least squares: Application to white matter variations in Alzheimer's disease

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ABSTRACT

Diffusion magnetic resonance imaging (dMRI) is a unique technology that allows the noninvasive quantification of microstructural tissue properties of the human brain in healthy subjects as well as the probing of disease-induced variations. Population studies of dMRI data have been essential in identifying pathological structural changes in various conditions, such as Alzheimer's and Huntington's diseases (Salat et al., 2010; Rosas et al., 2006). The most common form of dMRI involves fitting a tensor to the underlying imaging data (known as diffusion tensor imaging, or DTI), then deriving parametric maps, each quantifying a different aspect of the underlying microstructure, e.g. fractional anisotropy and mean diffusivity. To date, the statistical methods utilized in most DTI population studies either analyzed only one such map or analyzed several of them, each in isolation. However, it is most likely that variations in the microstructure due to pathology or normal variability would affect several parameters simultaneously, with differing variations modulating the various parameters to differing degrees. Therefore, joint analysis of the available diffusion maps can be more powerful in characterizing histopathology and distinguishing between conditions than the widely used univariate analysis. In this article, we propose a multivariate approach for statistical analysis of diffusion parameters that uses partial least squares correlation (PLSC) analysis and permutation testing as building blocks in a voxel-wise fashion. Stemming from the common formulation, we present three different multivariate procedures for group analysis, regressing-out nuisance parameters and comparing effects of different conditions. We used the proposed procedures to study the effects of non-demented aging, Alzheimer's disease and mild cognitive impairment on the white matter. Here, we present results demonstrating that the proposed PLSC-based approach can differentiate between effects of different conditions in the same region as well as uncover spatial variations of effects across the white matter. The proposed procedures were able to answer questions on structural variations such as: "are there regions in the white matter where Alzheimer's disease has a different effect than aging or similar effect as aging?" and "are there regions in the white matter that are affected by both mild cognitive impairment and Alzheimer's disease but with differing multivariate effects?"

1. Introduction

Diffusion-weighted magnetic resonance imaging (dMRI) has been used in a wide range of studies to understand basic tissue properties in healthy individuals as well as developmental and degenerative changes that occur across the lifespan (e.g. Pfefferbaum et al., 2000; Salat et al., 2005). Through modeling water diffusivity in tissue microstructure, several different voxel-wise parameter maps can be extracted from dMRI data, which have been shown to be sensitive measures for identifying structural variations across individuals and tissue changes resulting from disease (Salat et al., 2010; Rosas et al., 2006; Bozzali

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et al., 2002; Rose et al., 2000). To date, the great majority of research studying dMRI-based maps have used the diffusion tensor imaging (DTI) model and either focused on a single parameter of interest (e.g. typically the fractional anisotropy (FA) or the mean diffusivity (MD)), or analyzed multiple parameters using univariate methods (Salat et al., 2010; Bozzali et al., 2002; Rose et al., 2000; Amlien and Fjell, 2014; Sachdev et al., 2013; Villain et al., 2008; Lu et al., 2014; Bartzokis et al., 2004; Damoiseaux et al., 2009; Takahashi et al., 2002; Douaud et al., 2011). Animal and postmortem studies have loosely linked these different diffusion markers to histological properties and/or specific pathologies, for example, ischemia, cell death and edema have been linked to mean diffusivity (Chenevert et al., 2000; Sotak, 2002), myelinated fiber organization and dispersion to fractional anisotropy (Beaulieu, 2002; Moseley, 2002), and axonal injury (Song et al., 2003) and demyelination (Song et al., 2005; Song et al., 2002; Klawiter et al., 2011) to axial and radial diffusivity respectively. These studies were critical in providing fundamental evidence that the multiple contrasts obtained through diffusion modeling could be used in the differentiation of dynamic processes in brain tissue such as tissue degeneration across different conditions.

One detail that has been frequently neglected in previous research is that different diffusion parameters at the same location quantify different aspects of the same underlying tissue structure. Consequently, a complex phenomenon that alters tissue structure, such as aging or Alzheimer's disease, often affects all the parameters. The proportions of the effects across parameters naturally might differ depending on the type of alteration and the relationships between the parameters extracted from dMRI data. Therefore, it is plausible that differing histopathology may result in different proportional changes to the various dMRI-derived parameters. Joint analysis of the diffusion parameters with a multivariate method may be able to detect such differences, and disentangle similar appearing effects to better characterize conditions, reveal complex spatial variations and yield higher power to differentiate between conditions.

Coutu et al. in (Coutu et al., 2014) recently focused on the utility of a multivariate approach across several diffusion parameters for examining tissue changes associated with aging. In their study, the authors focused on spatial variations in the effects of aging on the white matter. They used seven diffusion parameters available through a diffusion kurtosis-imaging model and identified three distinct classes of aging effects across the white matter. This initial result suggests that joint analysis of diffusion parameters with a multivariate approach may indeed provide important information about disease processes not available through examination of any parameter in isolation. The multivariate approach Coutu et al. took was to compute the Pearson's correlation coefficient between each diffusion parameter and subjects' age at each location in the white matter, and for each point separately define the set of coefficients as the "diffusion footprint", a voxel-wise multivariate representation. In this work, motivated by the results in (Coutu et al., 2014), we focus on the joint analysis of diffusion parameters and extend Coutu et al.'s initial method.

We introduce a novel approach for multivariate statistical analysis of diffusion parameters. Our approach is a new interpretation of the diffusion footprint through partial least squares correlation (PLSC) (Abdi and Williams, 2013) analysis. This interpretation combined with non-parametric permutation testing (Good, 2005), yields a powerful methodological basis with which a new set of hypotheses regarding changes in tissue microstructure can be tested. We first present the PLSC-based group analysis of diffusion parameters and the associated statistical test. Then we define procedures for regressing out variables and comparing conditions in the multivariate setting. These procedures allow comparing conditions based on the *type* of effect they have on the diffusion parameters, i.e. relative proportions of effects on parameters, in addition to effect-size and location. The technical novelties introduced in this article are in the way PLSC is applied on the diffusion data and the two procedures that are defined using the PLSC interpretation of diffusion footprint.

We apply the proposed procedures to examine group differences in diffusion parameters in the white matter among non-demented elderly adults (CN), individuals with mild cognitive impairment (MCI) and individuals with Alzheimer's disease (AD). We provide three different experiments to demonstrate the use of the proposed procedures. In the first set, we use our approach for detecting and visualizing spatial variations in the effects of aging, AD and MCI. These maps provide a more refined visualization of the spatial variation of condition effects compared to the work of Coutu et al. in (Coutu et al., 2014). In the second experiment, we apply the proposed procedures to identify areas where AD's effects are structurally different than the cross-sectional effects of aging in a cognitively healthy population, as quantified through diffusion parameters. Lastly, we examine whether MCI and AD have different multivariate diffusion profiles suggesting possible differing histopathology (either in the pathological process or in the stage of pathology) between these conditions. In this work, we used the diffusion tensor-imaging model as a proof of concept to demonstrate the benefits of the proposed multivariate method given the availability of substantial data provided by the Alzheimer's Disease Neuroimaging Initiative. However, the approach is not specific to diffusion tensor imaging and is applicable to any dMRI model and any set of parameters extracted from such models. More broadly the method can also be extended to any multi-parametric spatial dataset.

2. Methods

2.1. Diffusion footprint

Coutu et al. defined their voxel-wise multivariate representation, diffusion footprint, as the set of Pearson's correlation coefficients between different diffusion parameters and the condition of interest. The underlying idea in using correlation coefficients was to "normalize" different parameters whose absolute values might not be comparable, e.g. mean diffusivity and fractional anisotropy. The set of correlation coefficients captures both the absolute effect size in each parameter, i.e. the value of each correlation coefficient, and how much the condition affects each diffusion parameter relative to each other, i.e. the proportions. Based on this representation one can construct multivariate voxel-wise maps and differentiate between condition effects at different voxels in the image, as the authors did for effect of aging (Coutu et al., 2014).

In the next section we introduce the interpretation that the diffusion footprint is actually the result of a partial least squares correlation analysis performed on the set of diffusion parameters and the condition, which will lead to various extensions in the type of statistical analysis one can do in the multivariate setting. In this article we construct two such extensions: regressing out variables and comparing effects of different conditions.

2.2. Multivariate group analysis through partial least squares

The proposed approach uses the principles of partial least squares correlation analysis (PLSC) (Abdi and Williams, 2013; Tucker, 1958). PLSC has been previously used in neuroimaging to jointly analyze all the voxels in the brain simultaneously (McIntosh et al., 1996; McIntosh and Lobaugh, 2004; Krishnan et al., 2011). Here we apply the PLSC principles in a voxel-wise fashion to jointly analyze the different diffusion parameters at each voxel independent from the others. In a sense this voxel-wise multivariate work is a straightforward extension of univariate analysis to multi-parametric data. For the sake of completeness we present the proposed approach starting from basics without assuming any knowledge of PLSC.

Let us assume we have N subjects and for each subject there are d diffusion parameter maps and a condition-related variable, which can