Which is the most appropriate strategy for conducting multivariate voxel-based group studies on diffusion tensors ?

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Abstract

There is a real need in the neuroscience community for efficient tools to compare Diffusion Tensor Magnetic Resonance Imaging across cohorts of subjects. Most studies focus on the comparison of scalar images such as fractional anisotropy or mean diffusivity. Although different statistical frameworks have been proposed to compare the whole diffusion tensor information, they are still seldom used in neuroimaging studies. In this paper, we investigate on both simulated and real data whether there is a real added value of considering the whole tensor information for conducting voxel-based group studies. Then, we compare two statistical tests dedicated to tensor, namely the Cramér test and a tensor-based extension of the General Linear Model (GLM), the latter presenting the advantage to account for covariates. We also evaluate the impact of different metrics (Euclidean, Log-Euclidean and affine-invariant Riemannian metrics) for estimating the GLM parameters. Finally, we address the problem of interpreting the change detection maps obtained by tensor-based methods by proposing a way to characterize each of the detected clusters according to several scalar indices. Our study suggests that if there is no prior assumption about the nature of the expected changes, it is really preferable to use tensor-based rather

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than scalar-based statistical analysis. The Cramr test can advantageously be used when no confounding variable hampers the group comparison, otherwise the GLM should be considered. Finally, the different metrics show similar performance in the real scenario, with a significant computational overhead for the Riemannian framework.

Keywords: Diffusion tensor imaging, general linear model, group comparison, tensor-based regression, Euclidean, Log-Euclidean and Riemannian manifolds.

1. Introduction

Diffusion Tensor Magnetic Resonance Imaging (DT-MRI) allows clinicians and neuroscientists to investigate the white matter structure by probing water molecule diffusion. Group studies allow to find out brain regions that are statistically different between two populations or that are significantly correlated with some covariates. As a consequence, there is an increasing need for efficient tools to compare DT-MRI across cohorts of subjects according to clinical or cognitive data. This may help to characterize the damages caused by a pathology and to understand the mechanisms underpinning the disease. Group comparisons of DT-MR images are usually performed using either region-of-interest-based analysis, tract-based analysis, or voxel-based analysis [1]. In this paper, we will focus on voxel-based analysis, whose major interest is that it does not make any assumption on the spatial location of the expected changes.

Most voxel-based studies focus on the comparison of scalar images derived from DT-MRI such as Fractional Anisotropy (FA) or Mean Diffusivity (MD) using either the voxel-based statistical analysis framework provided in SPM¹ [2] or the tract-based spatial statistics (TBSS) method provided in the FSL library² [3]. However, these methods do not exploit all the information contained in tensor images and thus cannot detect all kinds of changes. Although different statistical frameworks have been proposed to compare either several scalar

¹<http://www.fil.ion.ucl.ac.uk/spm/>

²<http://fsl.fmrib.ox.ac.uk/fsl/>

indices simultaneously [4], eigenvalues or eigenvectors of diffusion tensors [5], or even the whole diffusion tensor information [6, 7, 8, 9, 10], they remain seldom used in neuroimaging studies.

In this paper, we investigate whether there is a real added value of considering the whole tensor information as compared to a single scalar index or several scalar indices simultaneously for conducting voxel-based group studies. To this end, we consider a tensor-based extension of the General Linear Model (GLM), which provides a convenient way to carry out statistical analysis while taking into account several covariates. We evaluate the impact of considering different manifolds for estimating GLM parameters, namely the Euclidean, Log-Euclidean [11] or the Riemannian framework [12]. We also provide a comparison with an alternative tensor-based test, namely the tensor-based Cramér test, which has already been reported as the best performer among various tensor-based statistical tests [6]. Finally, we deal with the problem of interpreting the change detection map obtained by tensor-based methods by proposing a way to characterize each of the detected clusters according to several scalar indices. To investigate these different points, a simulation framework has been set up, based on DT-MRI acquisitions of healthy subjects in which different kinds of lesions have been introduced. A group study on a cohort of patients suffering from neuromyelitis optica (NMO) is also presented.

The content of the paper is organized as follows. Section 2 depicts the whole framework for DTI group comparison by describing the pre-processing steps, the spatial normalization, the regression, the statistical analysis and the characterization of the detected clusters. The evaluation framework is presented in section 3. Results on both simulated and real data are presented in section 4 and discussed in section 5. Finally, conclusions and perspectives are given.

2. General framework for DTI group comparison

2.1. Overview of the processing pipeline

The goal of voxel-based group comparison is to decide for each voxel $\mathbf{s} \in \mathbb{R}^3$ whether there is a significant difference between two groups of subjects while taking into account some covariates such as age, gender, etc. To this end, all subjects should first be registered into a common space according to a deformable registration method (section 2.2). A prerequisite to this step is to first control the quality of each acquisition to assess whether it can be included in the analysis. This is performed through visual inspection of each DWI image and by using a dedicated tool, DTIPrep³ [13]. Then, each Diffusion-Weighted Image (DWI) are corrected for subject motion and eddy current distortions using FSL’s Diffusion Toolkit. Finally, tensors are estimated from the DWI images according to a weighted least square (WLS) estimation procedure [14].

After the registration step, all tensor images are filtered in the Log-Euclidean space [11] using a Gaussian kernel (FWHM=8mm in all our experiments). This allows to account for the spatial information from the neighboring voxels and also, by the central limit theorem, to render the data more normally distributed [15]. Then, the statistical analysis is conducted.

A convenient way to carry out statistical analysis while taking into account several covariates is to consider the General Linear Model (GLM). It can be done either on a given scalar image such as FA or MD, or on several scalar images simultaneously, or on tensors directly using either an Euclidean, a Log-Euclidean or a Riemannian metric in the regression (section 2.3). A statistical F-test is then used to evaluate whether a given explanatory variable has a significant contribution in the regression model (section 2.4). Finally, the statistical map is thresholded and each detected cluster is characterized by a signature obtained as a combination of several scalar indices (section 2.5). A graphical overview of the pipeline is presented in Fig. 1.

³<https://www.nitrc.org/projects/dtiprep/>

Figure 1: Pipeline overview.

75 2.2. Spatial normalization

Before performing voxel-based statistical analysis, all images are first registered on the same arbitrary chosen reference image belonging to the control group. To this end, all FA images derived from DT-MRI acquisitions are registered through an affine method followed by a non-rigid method [16] using the sum of squared differences metric. Spatial transforms are then applied on tensor images using the Preservation of Principal Direction (PPD) [17] reorientation strategy. This step is required to ensure the orientational consistency of the

warped tensor field. The basic idea is to apply the local affine component F of the deformation field on the three tensor eigenvectors (e_1, e_2, e_3) , and then to
85 estimate the rotation that leads to the reoriented eigenvectors $(\tilde{e}_1, \tilde{e}_2, \tilde{e}_3)$, such that Fe_1 and $\tilde{e}_1$ are aligned, and such that Fe_1 and Fe_2 span the same plane as $\tilde{e}_1$ and $\tilde{e}_2$ [17].

2.3. Multi-linear regression

In this section, we will present several regression schemes on either scalar
90 images or on tensor fields. Let $\mathcal{M}$ be a manifold and $\{y_i\}_{i \in [1..N]} \in \mathcal{M}$ be the observations at a given voxel $\mathbf{s} \in \mathbb{R}^3$ from N individuals, each individual being characterized by K explanatory variables $\{x_{i,j}\}_{j \in [1..K]}$ such as age, gender or group affiliation. These observations can be either scalar indices such as FA or MD ($\mathcal{M} \subset \mathbb{R}$) or full tensors ($\mathcal{M} \subset \mathbb{R}^6$). The regression problem consists in esti-
95 mating a function $f : \mathbb{R}^K \mapsto \mathcal{M}$ that best fits all the couples $(\{x_{i,1} \dots x_{i,K}\}, y_i)$. A simple parametric approach is to consider the multi-linear function:

$$y_i = \alpha + \beta_1 x_{i,1} + \beta_2 x_{i,2} + \dots + \beta_K x_{i,K} + \varepsilon_i \quad (1)$$

where α is the intercept, β_i are the regression coefficients and ε_i are the residuals.

For the scalar case, this corresponds to the standard GLM, which is commonly used in neuroimaging studies [2]. For the tensor case, we investigate
100 the use of different metrics to compute the residuals, namely an Euclidean ($\mathcal{M} \subset \mathbb{R}^6$), a Log-Euclidean ($\mathcal{M} \subset \text{Sym}(3)$) and a Riemannian ($\mathcal{M} \subset \text{Sym}^+(3)$) metric, in order to evaluate their impact in the context of group comparison.

Scalar regression In the scalar case, the General Linear Model (GLM) aims at representing N scalar observations (FA or MD) $Y = [y_1 \dots y_i \dots y_N]^t$
105 as a linear combination of K explanatory variables, whose values for the i^{th} observation are stored in the design matrix $X[i, j] = x_{i,j}$, for $i = 1 \dots N$ and $j = 1 \dots K$. If the residuals ε_i are assumed to be independent and identically distributed (i.i.d.) according to a normal distribution, then the least squares esti-

mate of B is obtained analytically:

$$\hat{B} = \arg \min_{B \in \mathbb{R}^K} \|Y - XB\|^2 = (X^t X)^{-1} X^t Y \quad (2)$$

110 The regression methods on scalar images will hereafter be referred to as General
Linear Model for FA (GLM-FA) or for MD (GLM-MD).

Tensor-based regression: Euclidean framework Scalar regression does
not capture all the information embedded in the diffusion tensor, in particular
the orientation information. Thus, we extended the GLM to take advantage of
115 the full tensor information [10].

A 3×3 diffusion tensor matrix is symmetric ($\in \text{Sym}(3)$) and may be represented by a vector: $D^i = [D_{xx}^i \ D_{xy}^i \ D_{xz}^i \ D_{yy}^i \ D_{yz}^i \ D_{zz}^i]^t \in \mathbb{R}^6$. The previous regression framework can straightforwardly be extended to the multivariate case by assuming the noise on the tensor components to be i.i.d.. We also assume
120 equal noise variance for all components (homoscedasticity assumption⁴). The basic idea is to concatenate all tensor components of the N individuals in a single vector $Y \in \mathbb{R}^{6N}$. For each explanatory variable, six regressors are estimated, one associated with each tensor component. This is done by constructing a new design matrix $X[i, j] = x_{i,j}$, for $i = 1 \dots N \times 6$ and $j = 1 \dots K \times 6$, where each
125 explanatory variable is replicated in six columns: the first column is composed of the values of the explanatory variable for the entries corresponding to the first tensor components D_{xx}^i and of zeros for the others entries, the second column is composed of the values of the explanatory variable for the entries corresponding to the second tensor components D_{xy}^i and of zeros for the others entries, and
130 so on for the four others columns. With that formulation, the least squares estimate of B has also a closed-form solution and leads to the estimation of K regressors of six components [10]. This method will be referred to as General Linear Model for Diffusion Tensors (*GLM-DT*).

⁴In a previous work, we have also investigated the heteroscedasticity assumption (i.e., different noise variances for each tensor component), but our experiments did not enable us to exhibit any improvement [10].

Tensor-based regression: Log-Euclidean framework The previous
135 Euclidean framework does not take into account that diffusion tensors are symmetric positive-definite matrices, *i.e.* $\mathcal{M} = \text{Sym}^+(3)$, which is only a subset of $\text{Sym}(3)$. Consequently, the estimated regression can possibly map some sets of explanatory variables to vectors that do not correspond to positive-definite matrices. A way to circumvent this limitation is to conduct the regression on
140 the logarithm of tensors [11]. Indeed, the logarithmic transformation enables to map the space of symmetric positive-definite matrices $\text{Sym}^+(3)$ to the space of symmetric matrices $\text{Sym}(3)$. Thus, the same previous framework can be used to estimate the regression. The corresponding regression model is then given by:

$$Y = \exp(XB + \varepsilon) \quad (3)$$

145 where $\exp(\cdot)$ stands for the matrix exponential. This method will be referred to as General Linear Model for Diffusion Log-Tensors (*GLM-LOG-DT*).

Tensor-based regression: Riemannian framework Recently, Kim *et al.* have proposed a multivariate General Linear Model on Riemannian manifolds, which naturally accounts for the positive-definite nature of diffusion tensors. The corresponding regression model is given by:
150

$$y_i = \text{Exp}(\text{Exp}(\alpha, \sum_{j=1}^K \beta^j x_{i,j}), \varepsilon_i) \quad (4)$$

where Exp refers to the exponential map⁵. The regressors β and the intercept α are simultaneously estimated using a gradient descent scheme by minimizing the distance between the data y_i and the estimate $\hat{y}_i = \text{Exp}(\alpha, \sum_{j=1}^K \beta^j x_{i,j})$. To this end, the following geodesic distance is used:

$$d(y_i, \hat{y}_i) = \sqrt{\langle \text{Log}(y_i, \hat{y}_i), \text{Log}(y_i, \hat{y}_i) \rangle_{y_i}} \quad (5)$$

⁵The notation Exp , that refers to the exponential map defined in the context of Riemannian manifolds, should not be confused with the previously used notation $\exp$, that refers to the matrix exponential.

155 The implementation of this method has been made available online⁶. This method will be referred to as Manifold General Linear Model for Diffusion Tensors (*MGLM-DT*).

2.4. Statistical test

The objective of the statistical test is to evaluate whether a given explanatory variable has a significant contribution in the regression model. To this end, an F-test is used to compare the Residuals Sum of Squares (RSS) of two nested models: a full model taking into account all the covariates (RSS₂) and a restricted model where the covariate of interest is discarded (RSS₁):

$$F = \frac{\frac{RSS_1 - RSS_2}{p_2 - p_1}}{\frac{RSS_2}{N_{obs} - p_2}} \quad (6)$$

with p_2 and p_1 representing respectively the number of covariates for each model and N_{obs} the total number of data samples⁷. Assuming that the residuals follow a normal distribution, F follows a Fisher distribution with $p_2 - p_1$ and $N_{obs} - p_2$ degrees of freedom under the null hypothesis that the full model does not provide a significantly better fit than the restricted model. The Gaussianity assumption on the residuals is a reasonable hypothesis for the Euclidean and Log-Euclidean frameworks, but it is no longer valid for the Riemannian framework. In the latter case, permutations may be used to estimate corresponding p -values [9], but it was not done in this work because of prohibitive computational time. Notice that even for the Euclidean and Log-Euclidean frameworks, alternative p -value estimation strategies can advantageously be used, such as permutations [18] or wild bootstrapping [19] in order to better control Type I errors.

A two-steps post-processing is used to obtain the final detection maps. First, the obtained p -value maps are corrected for the multiple comparisons problem

⁶https://www.nitrc.org/projects/riem_mglm

⁷In the scalar-based regression, $N_{obs} = N$ (N being the number of subjects), $p_2 = K + 1$ (K explanatory variables and the intercept coefficient) and $p_1 = K$. In tensor-based regressions, $N_{obs} = 6N$, $p_2 = 6(K + 1)$ and $p_1 = 6K$.

using the False Discovery Rate method (FDR) according to a user-defined value (generally $\alpha = 0.05$). Then, only connected components whose volume is greater
180 than a user-defined threshold N_c are kept.

2.5. Characterization of the detected clusters

Since tensor-based methods can detect various kinds of changes without providing information on the nature and the direction (in terms of augmentation or diminution) of the observed changes, there is a need to characterize the
185 detected clusters in order to make them interpretable by a physician. Thus, we propose the following procedure to characterize *a posteriori* the detected clusters in terms of alterations of Axial Diffusion (AD), Radial Diffusion (RD) and Fractional Anisotropy (FA).

It is a three-steps process: first, the spatial means of the three scalar indices
190 (AD, RD and FA) are computed on each detected cluster and for each subject. Then, a GLM followed by a two-tailed Student's test are conducted on these values for each scalar index separately, while introducing the same covariates as for the tensor-based statistical analysis. Finally, the list of all the clusters associated with the outputs of the statistical tests for each scalar index is presented to
195 the physician: +, - and n.s. stand respectively for a significant augmentation, a significant diminution and no significative change at a user-defined p -value threshold. This may help the physician to interpret each cluster as a favorable or a deleterious change and give him some informations about the nature of the alteration. Notice that this step is performed on the unsmoothed tensor images
200 in order to better reflect the region properties. Indeed, Gaussian smoothing is required to conduct voxelwise analysis, but should generally be avoided for region-based analysis.

We chose to consider AD and RD, since they have been shown to be valuable biomarkers to characterize induced white matter changes in mouse models [20].
205 However, using these two indices only is not sufficient to unambiguously interpret all situations, especially when the two indices exhibit significant modifications in the same direction. For instance, an increase (or a decrease) of both

AD and RD can either leave the FA unaltered, or can lead to an augmentation or a diminution of it, depending whether the AD increases (or decreases) in a higher (or a lower) extent than the RD. Depending on the impact on the FA, the biological interpretation can be very different. This is why, we also consider the FA to disambiguate these cases.

Table 1 provides the list of all possible combinations of AD and RD alterations and their corresponding interpretation. The bottom part of the table details the cases requiring the FA to disambiguate. Notice that clusters that do not present significant alteration of both AD and RD are labeled as uncategorisable since it can be explained by either a modification of diffusion orientation or because these clusters present heterogeneous modifications that are averaged out when computing the mean of the scalar indices.

3. Validation framework

The evaluation was conducted on both simulated and real data. All DT-MRI images were acquired on a 1.5T Siemens scanner with 30 encoding gradients (b -value of 1000 s/mm^2) and two baseline images (*i.e.*, b -value of 0 s/mm^2). The image dimensions are $128 \times 128 \times 41$ and the spatial resolution is $1.8 \times 1.8 \times 3.5 \text{ mm}^3$.

3.1. Synthetic data

The simulated data are built from a group of 22 healthy subjects (23 subjects were initially enrolled, but one examination did not pass the quality control step). A set of 11 images with simulated lesions in the corpus callosum (CC) are generated from the DT-MRI acquisitions of 11 healthy subjects. We focused on the CC since it consists of a single direction white matter tract, where the second-order tensor assumption holds. These simulated images, considered in the experiments as the patient group, are compared with a group of 11 images of healthy subjects, while introducing age and group affiliation as covariates. For the statistical test, the group affiliation is discarded in the restricted model. Four

AD	RD	Interpretation of changes		Type of changes
n.s.	+	radial diffusion augmentation		deleterious
−	n.s.	longitudinal diffusion diminution		deleterious
−	+	longitudinal diffusion diminution AND radial diffusion augmentation		deleterious
n.s.	−	radial diffusion diminution		favorable
+	n.s.	longitudinal diffusion augmentation		favorable
+	−	longitudinal diffusion augmentation AND radial diffusion diminution		favorable
n.s.	n.s.	diffusion orientation modification OR cluster with heterogeneous changes		uncategorisable
Cases requiring the FA to disambiguate				
AD	RD	FA	Interpretation of changes	Type of changes
+	+	n.s.	mean diffusion augmentation	deleterious
+	+	−	radial diffusion augmentation	deleterious
+	+	+	longitudinal diffusion augmentation	favorable
−	−	−	longitudinal diffusion diminution	deleterious
−	−	n.s.	mean diffusion diminution	favorable
−	−	+	radial diffusion diminution	favorable

Table 1: List of possible changes of AD and RD (and FA if there is an ambiguity) and corresponding interpretation (Legend: + = significant augmentation, − = significant diminution, n. s. = not significant).

Kind of change	Corresponding tensor modification
Mean diffusion augmentation	$\lambda'_i = (1 + \alpha)\lambda_i$, with $i = 1, 2, 3$
Radial diffusion augmentation	$\lambda'_i = \lambda_i + \alpha \frac{\lambda_1 - \lambda_i}{2}$, with $i = 2, 3$
Longitudinal diffusion diminution	$\lambda'_1 = \lambda_1 - \alpha(\lambda_1 - \lambda_2)$
Orientation modification	$D' = RDR^t$, with R a rotation matrix

Table 2: Equations to simulate the four kinds of lesions (see [21] for details). λ_i is the i^{th} eigenvalue of the tensor matrix sorted in descending order (λ_1 represents the eigenvalue associated to the principal direction)

kinds of lesions are simulated: mean and radial diffusion augmentation, longitudinal diffusion diminution and diffusion orientation modification (Table 2).

A parameter α varying from 0 to 0.9 by steps of 0.05 controls the amplitude of the simulated lesions (Fig. 2). An image is generated for each α and each
240 kind of lesions, leading to $4 \times 19 = 76$ groups of 11 patients images. This allows us to investigate the statistical power of the tests by testing different size effects (through the coefficient α that controls the amount of simulated modification) for a given number of subjects.

Notice that the three first kinds of lesions are consistent with real case sce-
245 narios [20]. For instance, a decrease of longitudinal diffusion can be linked to axonal modifications including reduced axonal caliber, while an increase of radial diffusion can be linked to a dysmyelination process. On the other hand, the change of diffusion orientation is rather a toy example, since a realistic diffusion orientation modification would imply the deflection of the whole trajectory of a
250 fiber bundle.

In order to make a fair comparison between all the methods while not intro-
ducing a bias by arbitrarily choosing a given p-value estimation procedure, we
conducted ROC analysis [22] directly on the computed statistics. This allows
us to compare the statistical maps with the ground truth for various statistical
255 thresholds. The Area Under the ROC Curve (AUC) is computed for each ex-
periment. An AUC of 50% corresponds to a random detection and 100% to a

Figure 2: Representation of the four kinds of lesions. The green and the red tensors represent the initial and the modified tensors, respectively.

perfect detection. AUCs are plotted with respect to the modification amplitude α for each kind of simulated lesion (Fig. 3 and 5). By this way, it is possible to assess the performance of each method for major changes as well as smaller ones and for different types of lesions.

3.2. Neuromyelitis Optica cohort

The Neuromyelitis Optica (NMO) is an inflammatory disease that mainly affects the spinal cord and the optic nerves. Alterations of the normal appearing white matter have already been demonstrated in several brain areas such as the corpus callosum, the occipital lobe and the cortico spinal tract [23]. These alterations may be associated with clinical disorders such as cognitive, visual (blindness) and motor disorders. Thirty seven NMO patients were initially enrolled. After visual inspection of DWI images, three patients were excluded due to the presence of strong image artifacts. The remaining data successfully passed the quality control performed by the DTIPrep software. Finally, a group of 34 patients suffering from NMO is compared to a group of 22 healthy subjects by considering age and group affiliation as covariates. For the statistical test, the group affiliation is discarded in the restricted model.

4. Results

275 In our experiments, we have investigated three crucial questions that arise
when conducting group comparison in DT-MRI, which are: (i) is there a real
added value of considering the whole tensor information as compared to a single
scalar index or several scalar indices simultaneously ? (ii) is the GLM tensor-
based method more effective than alternative tensor-based tests such as the
280 tensor-based Cramér test, which has already been reported as the best performer
among various tensor-based statistical tests [6] ? and (iii) what is the most
relevant manifold to estimate the GLM parameters ?

For conducting statistical analysis on several scalar indices simultaneously,
we used the same framework as for the Euclidean tensor-based regression (sec-
285 tion 2.3) by concatenating all scalar indices into a single vector. To meet the
homoscedasticity assumption, each scalar index is firstly normalized to zero-
mean and unit variance for each voxel and accross the whole population. Notice
also that the tensor-based Cramér test is a nonparametric test that relies on
Euclidean interpoint distances between tensors [6] and that does not allow to
290 take into account covariates.

Hereafter, the results of these investigations obtained on both simulated and
real data are presented. The usefulness of characterizing the detected changes
is also highlighted on the NMO database.

4.1. Results on synthetic data

295 4.1.1. Scalar-based vs tensor-based regression

Fig. 3 shows the results of the comparison between the two univariate
scalar-based methods ($GLM-FA$ and $GLM-MD$), the multivariate scalar-based
method ($GLM-FA+MD$) and the Euclidean tensor-based method ($GLM-DT$).
It highlights that only the tensor-based $GLM-DT$ method is able to detect the
300 four kinds of lesions, since the scalar methods $GLM-FA$, $GLM-MD$ and $GLM-FA+MD$
fail to detect the modification of diffusion orientation. We can note
that $GLM-MD$ and $GLM-DT$ exhibit very close performance for the three first

Figure 3: Comparison between the scalar-based methods ($\blacksquare$ = GLM-FA, $\blacktriangle$ = GLM-MD), the multivariate scalar-based method ($\star$ = GLM-FA+MD) and the Euclidean tensor-based method ($\bullet$ = GLM-DT).

kinds of lesions and that *GLM-FA* and *GLM-FA+MD* outperform the two other methods for detecting radial diffusion augmentation. For the modification of diffusion orientation, one would have expected that the three scalar-based methods lead to almost 50% AUC (*i.e.*, random detection) for all lesion amplitudes, since the change of orientation does not alter the tensor eigenvalues. The observed detections are explained by the Gaussian filtering, which is performed as a pre-processing step: averaging rotated tensors with neighboring non-rotated tensor produces tensors with different shapes, yielding changes in FA and MD. To conclude, the *GLM-DT* method seems to be the one that offers the best compromise for detecting all changes, although it does not clearly outperform the three other methods for all kinds of lesions.

Figure 4: Comparison between the tensor-based GLM methods (● = GLM-DT with covariates, ▲ = GLM-DT without covariate) and the tensor-based Cramér test (★ = Cramér).

4.1.2. GLM tensor-based regression vs tensor-based Cramér test

Fig. 4 shows the results of the comparison between the GLM-DT and the Cramér test. Results of the GLM-DT without covariate are also presented in order to investigate the influence of considering the age as a covariate (remind that the Cramér test does not account for covariates). GLM-DT with and without covariate lead to very close results, while the Cramér test outperforms these two methods for the four kinds of simulated lesions, especially for small lesion amplitudes. Notice that the two groups of subjects used for the simulation study are very homogenous in age (29 ± 5 year old *vs* 27.1 ± 3.8 year old), explaining why there are little differences between GLM-DT with and without covariate. The Cramér test clearly exhibits the best statistical power, but its performance could have seriously been deteriorated if the populations were more heterogeneous in age.

Figure 5: Influence of the manifold ($\bullet$ = GLM-DT, $\blacktriangle$ = GLM-LOG-DT, $\blacksquare$ = MGLM-DT).

4.1.3. Manifold influence

Fig. 5 sums up the results of the comparison between the Euclidean, the Log-Euclidean and the Riemannian manifolds. It highlights that the performance of the methods varies with the kind of simulated changes. *GLM-DT* outperforms the two other methods for detecting a longitudinal diffusion diminution. On the other hand, the *GLM-LOG-DT* and the *MGLM-DT* exhibit slightly better results for detecting an augmentation of the radial diffusion. Notice that all the three methods show similar performance for detecting either modifications of orientation or mean diffusion augmentation. Finally, it has to be pointed out that the Log-Euclidean and Riemannian manifold frameworks lead to close results.

4.1.4. Characterization

Table 3 presents the results of the characterization procedure applied to three of the simulated data sets ($\alpha = 0.2$, $\alpha = 0.5$, $\alpha = 0.9$). The statistical variations of AD, RD and if required FA (only for the ambiguous cases) are reported for

the whole ground truth area (i.e., the corpus callosum). The results show that the characterization procedure performs well for most cases. Two cases deserve a bit more explanation, namely the radial diffusion augmentation for $\alpha = 0.9$ and the longitudinal diffusion diminution for $\alpha = 0.5$ and 0.9 . Concerning the radial diffusion augmentation at $\alpha = 0.9$, one would not have expected to observe a significant change for the AD. It has to be pointed out that the p-value associated with the AD modification is high ($p = 0.023$) as compared to the one associated to the RD index ($p = 9.74 \cdot 10^{-11}$), thus still objectifying that this is mainly a change of radial diffusion. In the same way, concerning the longitudinal diffusion diminution ($\alpha = 0.5$ and 0.9), one would not have expected to observe a significant change for the RD. It has to be pointed out that the p-value associated with the RD modification is also high ($p = 0.016$ for $\alpha = 0.5$ and $p = 0.019$ for $\alpha = 0.9$) as compared to the one associated to the AD index ($p = 1.3 \cdot 10^{-11}$ for $\alpha = 0.5$ and $p = 3.3 \cdot 10^{-13}$ for $\alpha = 0.9$). The fact that the AD is decreasing in a larger extent than the RD is also confirmed by the significant decrease of the FA. Consequently, according to Table 1, this modification will still be well categorised as a longitudinal diffusion diminution.

This phenomenon is in fact a side effect of the registration step. Indeed, if the registrations are estimated on the lesion-free images ($\alpha = 0$) and the corresponding transformations are applied on the images with simulated lesions, then the AD (resp. the RD) become unaltered for the radial diffusion augmentation (resp. the longitudinal diminution). The reason why the registration causes these changes of AD (resp. RD) is related to the large modification on the FA induced by the simulated lesion, the FA being precisely used to drive the registration process. Note that we do not observe in the real scenario such a modification of FA on such a large spatial extent, thus limiting the chance of getting such distortions in the estimated deformation fields.

4.2. Results on NMO patients

In order to obtain comparable detection maps for all statistical analysis, p-value maps should first be computed. Unfortunately, this step can only be

Simulated lesion	Amplitude of the simulated lesion								
	0.2			0.5			0.9		
	AD	RD	FA	AD	RD	FA	AD	RD	FA
Mean diffusion augmentation	+	+	n.s.	+	+	n.s.	+	+	n.s.
Radial diffusion augmentation	n.s.	+		n.s.	+		−	+	
Longitudinal diffusion diminution	−	n.s.		−	−	−	−	−	−
Diffusion orientation modification	n.s.	n.s.		n.s.	n.s.		n.s.	n.s.	

Table 3: Results of the characterization procedure for the *GLM-DT* method (Legend: + = significant augmentation ($p < 0.05$), − = significant diminution ($p < 0.05$), n.s. = not significant)

done through permutations for the MGLM and Cramér test, which would have been computationnaly prohibitive, especially for the MGLM method. In order to make a fair comparison, we chose to adjust the threshold for each method
375 so that the same number of voxels are detected within the white matter mask. In all experiments presented in the sequel, statistical maps were thresholded in order to keep the 5% most significant voxels within the white matter mask; a cluster-based threshold of $N_c = 10$ was then applied.

4.2.1. Scalar-based vs tensor-based regression

380 Fig. 6 shows the results obtained by the two univariate scalar-based methods (*GLM-FA* and *GLM-MD*), the multivariate scalar-based method (*GLM-FA+MD*) and the Euclidean tensor-based method (*GLM-DT*) for the comparison between 34 NMO patients and 22 healthy subjects.

Similarly as for the experiments on synthetic data (see section 4.1.1), the

Figure 6: Comparison between the scalar-based methods (*GLM-FA*, *GLM-MD* and *GLM-FA+MD*) and the Euclidean tensor-based method (*GLM-DT*). Statistical maps were thresholded in order to keep the 5% most significant voxels within the white matter mask; a cluster-based threshold of $N_c = 10$ was then applied.

385 methods *GLM-MD* and *GLM-DT* present very similar results. To strengthen
this claim, the Dice coefficient between the detection maps obtained for these
two methods is plotted in Fig. 9 for several statistical thresholds. It shows
a Dice coefficient always superior to 0.7 for a wide range of thresholds. The
main difference between the two methods concerns the putamen, which is a
390 structure that has already been reported as involved in NMO [24] and which is
only detected by the *GLM-DT* (Fig. 6).

In the same way and in accordance with the results obtained on synthetic
data, the *GLM-FA* and *GLM-FA+MD* also share similar behavior (Fig. 6). This
is confirmed by Fig. 9, which shows a dice coefficients superior to 0.6 for a wide
395 range of thresholds. The most prominent difference between these two methods
and the *GLM-MD* and *GLM-DT* is that they do not detect alterations in the
body of the corpus callosum and that the *GLM-FA* cannot detect alteration in
the occipital lobe, which are both structures that have already been reported
as involved in NMO [23, 25, 24].

400 Finally, the major difference between all these methods concerns the statis-
tical threshold requires to detect the 5% of the most significant voxels within
the white matter. The corresponding p -value thresholds are $p_{GLM-FA} = 0.02$,
 $p_{GLM-MD} = 0.04$, $p_{GLM-FA+MD} = 0.03$ and $p_{GLM-DT} = 0.002$. Conse-
quently, *GLM-DT* clearly outperforms the two other methods in terms of sta-
405 tistical power. Notice that for a p -value threshold of 0.002, neither *GLM-FA*
nor *GLM-MD* can detect any change, while *GLM-FA+MD* can still detect very
small clusters in relevant regions such as the putamen, the occipital lobe and
the internal capsule. This gain in statistical power is explained by the fact that
GLM-DT relies on six times more data samples than the univariate scalar-based
410 methods and three times more than the *GLM-FA+MD*.

4.2.2. *GLM tensor-based regressions vs tensor-based Cramér test*

Fig. 7 shows the results of the comparison between the *GLM-DT* and the
Cramér test. Results of the *GLM-DT* without covariate are also presented as
well as the test evaluating the influence of the age using the *GLM-DT* with

Figure 7: Comparison between the GLM tensor-based methods (*GLM-DT* with and without covariates) and the dedicated tensor-based test (Interpoints). Statistical maps were thresholded in order to keep the 5% most significant voxels within the white matter mask; a cluster-based threshold of $N_c = 10$ was then applied.

415 covariates. In contrary to the conclusions obtained on synthetic data, *GLM-DT* with and without covariate lead to significantly different results, which is explained by the fact that the two populations under study are in that case not homogeneous in age (NMO: 44.9 ± 12.2 *vs* Controls: 28 ± 4.4). Testing the effect of age using the *GLM-DT* with covariates (Fig. 7, bottom part) 420 exhibit detections in regions around the ventricles and in several cortical areas. These detections are in fact the consequence of brain atrophy related to aging, which induces enlargement of brain ventricles and cortical sulci. Although the *GLM-DT* without covariate and the tensor-based Cramér test both succeed to detect keys regions of the NMO such as the occipital lobe, they also detect many 425 regions around the ventricles related to age effect. Consequently, these results emphasize the importance of taking into account covariates in group study in order to bring out only the influence of a given effect.

4.2.3. Manifold influence

Fig. 8 sums up the results from the comparison between the Euclidean, 430 the Log-Euclidean and the Riemannian manifolds. Visually, all three methods lead to very close results, which does not allow us to assert that one method outperforms the others. To strengthen this claim, the Dice coefficient between the detection maps obtained for each pair of methods is plotted in Fig. 9 for several statistical thresholds. This objectifies the good agreement between the 435 tensor-based methods, with a Dice coefficient always greater than 0.7. The best agreement is obtained between the *GLM-LOG-DT* and *MGLM-DT* frameworks (Dice coefficient greater than 0.9), which is in accordance with the conclusion drawn from simulated data.

4.2.4. Characterization of detected regions

440 The characterization procedure is applied on the detection map obtained with the *GLM-DT* method by considering a statistical threshold $p_{FDR} = 0.05$ and cluster threshold $N_c = 10$. It leads to the detection of nineteen significant clusters located in eighth different anatomical regions. The sign and the statistical

Figure 8: Influence of the manifold for conducting tensor-based comparison between NMO patients and healthy controls. Statistical maps were thresholded in order to keep the 5% most significant voxels within the white matter mask; a cluster-based threshold of $N_c = 10$ was then applied.

Figure 9: Dice coefficient between the detection maps obtained for every couples of methods *vs* percentage of detected voxels in logarithmic scale. Only the couples of methods which have a Dice coefficient superior to 0.5 are displayed.

significance ($p < 0.05$) of the change for each scalar index (AD, RD and FA) are reported for each cluster in Table 4.

Among theses clusters, eight are classified as deleterious changes, six as favorable changes and five as uncategorisable changes. Four clusters in the occipital lobe are characterized as an augmentation of the mean diffusivity in the patient group as compared to the control group, which may reflect a demyelination process that is probably related to the visual disorders induced by the pathology. Similar signature is observed for the cluster located in the corpus callosum. One cluster located in the parietal lobe presents a radial diffusion augmentation. Two other clusters located respectively in the frontal lobe and in the cerebellum present an axial diffusion diminution. All these changes can also be linked to a demyelination process.

The six clusters that are categorized as favorable changes might be the consequences of compensation phenomena or therapeutic drugs effects. The remaining clusters belong to the uncategorisable group, which can be explained by either a modification of diffusion orientation or because these clusters present

Brain location		Impacted fiber tracts	AD	RD	FA
Occipital lobe	r. & l.	optic radiation			
		inf. long. fasciculus	+	+	<i>n.s.</i>
		corpus callosum (splenium)			
	l.	optic radiation	+	+	<i>n.s.</i>
		corpus callosum (splenium)			
	r.	inf. fronto-occipital fasciculus	+	+	<i>n.s.</i>
	r.	<i>undefined</i>	+	<i>n.s.</i>	
Hippocampus	l.	<i>undefined</i>	+	<i>n.s.</i>	
Corpus callosum	r.	corpus callosum (body)	+	+	<i>n.s.</i>
Parietal lobe	r.	sup. long. fasciculus	+	+	–
Frontal lobe	r.	corpus callosum (genu)	<i>n.s.</i>	<i>n.s.</i>	
		inf. fronto-occipital			
	l.	inf. fronto-occipital	–	–	<i>n.s.</i>
	l.	corpus callosum (genu)	–	<i>n.s.</i>	
Internal capsule	r.	inf. fronto-occipital	<i>n.s.</i>	<i>n.s.</i>	
		dentate-rubro-thalamo cortical			
	r.	cortico-spinal	–	–	<i>n.s.</i>
Temporal lobe	r.	arcuate fasciculus	<i>n.s.</i>	<i>n.s.</i>	
	r.	inf. long. fasciculus	–	–	<i>n.s.</i>
Cerebellum	l.	<i>undefined</i>	–	<i>n.s.</i>	
	r.	<i>undefined</i>	–	–	<i>n.s.</i>
	l.	<i>undefined</i>	<i>n.s.</i>	<i>n.s.</i>	
	r.	<i>undefined</i>	<i>n.s.</i>	<i>n.s.</i>	
	r.	<i>undefined</i>	<i>n.s.</i>	<i>n.s.</i>	

Table 4: Results ($p_{corrected} < 0.05$) of the characterization procedure for the *GLM-DT* method (statistical threshold $p_{FDR} = 0.05$ and cluster threshold $N_c = 10$). (Legend: + = significant augmentation, – = significant diminution, *n.s.* = not significant, r. = right, l; = left, inf. = anterior, sup. = superior, long. = longitudinal)

460 heterogeneous modifications that are averaged out when computing the mean
of the scalar indices.

We are well aware that there are multiple other options to perform such a
classification. We chose this straightforward and computationally efficient way
in order to keep the same statistical framework as for the detection method
465 using GLM with the same covariates.

5. Discussion

5.1. *Scalar-based vs tensor-based regression*

A previous study has already compared scalar-based *vs* several tensor-based
methods for group comparison in DT-MRI [6]. They have considered both Eu-
clidean and Log-Euclidean metrics. One of the main difference with our study
470 is that the authors did not consider any covariates such as age or gender in their
statistical analysis. They also did not have access to a Riemannian Manifold
regression method such as [9]. The comparison between FA-based and tensor-
based methods was also conducted on both simulated and real data. The evalu-
475 ation on simulated data highlights unsurprisingly that tensor-based methods are
the only ones that are able to detect modification of diffusion orientation. The
conclusion concerning the detection of FA alterations is less obvious, since the
FA-based approach slightly outperforms the tensor-based method relying on the
Hotelling’s T^2 test, but exhibits a lower statistical power than the tensor-based
480 method relying on multivariate permutation test. Our results are consistent
with this paper since we also conclude that the tensor-based method is the only
one that can efficiently detect every kinds of changes, although it can perform
slightly worse than scalar-based methods for some particular changes (*e.g.* FA-
based method best detects an augmentation of radial diffusion while MD-based
485 method best detects an augmentation of mean diffusion). Their conclusions on
a cohort of patients with a history of migraine is also not clear-cut since both
FA-based and tensor-based methods can detect a cluster into the bank of the
postcentral gyrus, but with a slightly greater spatial extent for the tensor-based

method. This may be probably explained by a gain in statistical power caused
490 by the permutation test.

In the sight of our conclusions and the ones obtained by Whitcher *et al* [6],
we can give the following recommendation to help the reader to choose between
conducting a group study using either a scalar-based or a tensor-based method.
If one has a strong *a priori* about the kind of changes to detect (*e.g.* a mod-
495 ification of the mean diffusivity), it is preferable to resort to the scalar-based
approach on the appropriate scalar images (*e.g.* MD). This would be easier to
implement and may lead to better performance. Moreover, this would avoid
to resort to tensor-based dedicated methods for interpolation, smoothing and
warping, which are not necessarily provided in standard neuroimaging libraries
500 such as SPM or FSL. If one has no prior assumption on the expected changes,
it would be preferable to use the tensor-based approach rather than performing
several scalar-based analysis on different indices. This avoids the problem of
multiple comparison (as compared to perform several tests on different indices)
and leads to a unique detection map. Nonetheless, using a tensor-based method
505 would necessarily require a characterization step (section 2.5) in order to help
physicians or neuroscientists in their interpretation. Finally, one of the main
added value of the tensor-based method is its ability to detect the modifications
of diffusion orientation. However, this may be of limited interest in the context
of voxelwise group comparison since most pathologies do not cause modifications
510 of diffusion orientation in a consistent area across a population. Modifications
of orientation are generally observed in the vicinity of multiple sclerosis lesions
or glioma and are generally related to the effect of oedema. Consequently, this
property may be more interesting for the follow-up of a given patient [26] than
for group studies.

515 5.2. GLM tensor-based regression vs tensor-based Cramér test

The tensor-based Cramér test has been previously reported as the best per-
former among various tensor-based statistical tests [6]. It has to be noticed that
none of the methods compared in [6] allows to take into account explanatory

variables such as age. This was not a crucial point for their experiment on real
520 data since it involved populations of young adults with little age differences.
Our experiments on simulated data also highlight the superiority in term of sta-
tistical power of the Cramér test over the GLM tensor-based regression. This is
explained by the fact that these experiments also involve young adults of sim-
ilar age. The conclusion obtained on the real database is drastically different,
525 showing the superiority of the GLM tensor-based regression as compared to the
Cramér test. This is explained by the age heterogeneity of the two populations
under study. Taking into account covariates in neuroimaging studies appears
to be a crucial point, especially for studies involving elderly subjects, since ag-
ing induces several brain modifications in terms of both atrophy and diffusion
530 property alteration [27]. Consequently, if one has a strong *a priori* that there is
no confounding variable that can hamper a group comparison, then a nonpara-
metric statistical test such as the Cramér test should be considered. Otherwise,
a GLM tensor-based regression should be preferred.

5.3. Manifold influence

535 In the literature, a few works have already evaluated the impact of the
Euclidean, Log-Euclidean and affine invariant-Riemannian metrics for various
images processing problems [11, 28] but there is still no consensus on the most
appropriate manifold for handling diffusion tensors, especially in the context of
group comparison. Some papers advocate the use of Log-Euclidean or Rieman-
540 nian metrics for conducting DT-MRI group comparison [7, 5, 8, 9] while other
papers claim that these metrics are not superior [6] or even are inferior [28] to
the Euclidean one. In their comparison between Euclidean and Log-Euclidean
metrics, Whitcher *et al* [6] conclude that there is no reason to prefer the Log-
Euclidean distance and that applying matrix logarithms to diffusion tensors
545 tends to reduce the group difference observed in Euclidean space. Moreover,
both theoretic analysis and experimental results reported in [28] support the
claim that the Euclidean metric is more appropriate than an affine-invariant
metric for the analysis of diffusion coefficients and tensors.

Methods	Computation time (s)
GLM-FA	135
GLM-MD	135
GLM-DT	135
GLM-LOG-DT	148
MGLM-DT	253392

Table 5: Computing time for conducting the statistical analysis on the NMO database.

Our experimental results on simulated lesions highlight that all metrics can
550 efficiently detect every kind of lesions, with performance varying for each frame-
work according to the kind of simulated change. The results on the real database
confirm the good ability of the three metrics to detect the regions involved
in NMO, without exhibiting any significant difference between the detection
maps. Regarding the computing time (Table 5), the statistical analysis of the
555 NMO database on a standard workstation is about 2 min for the Euclidean
and Log-Euclidean approaches as compared to about 80 hours for the Riemannian
framework. This time gap may probably be reduced by optimizing the
implementation of the Riemannian framework⁸, for instance by rewriting the
MATLAB code in C++ language. But in any case, the Riemannian framework
560 would still be much more computationally intensive than the Euclidean and
Log-Euclidean approaches.

In conclusion, this study suggests that, despite the mathematical elegance
offered by the Riemannian framework, its superiority on both simulated and
real clinical data could not be demonstrated compared to the Euclidean and
565 Log-Euclidean frameworks. For a similar performance, these two latter methods
present the advantage to be easily implementable and computationally effective.
This conclusion is of course limited to the scope of the present application.

Finally, we want to discuss the fact that the Euclidean framework is gen-

⁸https://www.nitrc.org/projects/riem_mglm

erally considered as a mathematically incorrect metric for handling diffusion
570 tensors, since positive definite matrices do not belong to a vector space (*i.e.*,
the difference between two positive definite matrices does not necessarily yield
a positive definite matrix). However, positive definite matrices lie on a convex
space. This means that a linear combination of positive definite matrices with
positive coefficients will yield to a positive definite matrix. Consequently, com-
575 puting the mean in the Euclidean space of a set of positive definite matrices will
also produce a valid positive definite matrix. Besides, computing the Euclidean
distance between two positive definite matrices D_1 and D_2 amounts to measure
the length of the straight line that link these two matrices. This makes sense
since all matrices D that belong to this line ($D = \lambda D_1 + (1 - \lambda) D_2$, $\lambda \in [0, 1]$)
580 are also positive definite matrices. Consequently, the Euclidean space is *not so*
inappropriate to handle diffusion tensor, thanks to the convexity property.

One problem that can arise when conducting statistical analysis on ten-
sors in the Euclidean space, is related to the use of the Gaussian distribution
assumption. Indeed, it may lead to associate nonzero probabilities to invalid
585 tensors. This can be an issue if the data lie close to the boundary of admissible
space. Nonetheless, this side effect can be neglected if the data are far from
this boundary, which is generally the case in the context of our application,
in particular thanks to the gaussian smoothing of the data which is performed
before conducting the statistical analysis. To illustrate this discussion, we can
590 make a somewhat simplistic analogy with the positive real space $\mathbb{R}^+$, which is
also a convex space but not a vector space. Although using an Euclidean met-
ric on this space can be considered as mathematically incorrect, many people
are still conducting student t-test to compare e.g. age, size or weight between
populations.

595 5.4. Limitations of the study

Although this study was carefully prepared, our work still suffers from some
limitations that are discussed in this section.

First, we have to point out that group study should ideally be conducted

on isotropic data. Unfortunately, this was not the case for the experiments pre-
600 sented in this paper since we used data that came from a clinical scanner using
standard sequence parameters optimised for the clinical routine. We acknowl-
edge that this is a limitation of our study and that the results obtained on real
data should be interpreted with caution. In fact, we do not really expect that
resolution anisotropy will induce spurious false detection, but rather that it will
605 introduce more variability in the data that might prevent detecting some rele-
vant change. Spurious false detections might appear for instance if one group is
more prone to head motion than the other, which is not the case in the context
of this study.

Secondly, one can wonder whether the conclusions drawn from the simula-
610 tion study are really relevant in the sight of the small number of subjects in each
group, which would be considered too small in most neuroimaging studies. In
real neuroimaging studies, the size of the population should generally be larger
for two reasons: (i) the effect to be detected is generally small as compared to
the population variability, thus requiring a large number of subjects to make it
615 statistically significant; (ii) the statistical tests generally require a large number
of subjects (generally $N > 30$) to make the assumption on the statistics distri-
bution valid. In our simulation study, we tried to get around these two points
by (i) controlling the effect size to make it sufficiently high as compared to the
population variability and by (ii) conducting the ROC curve analysis directly
620 on the computed statistics and not on the corresponding p-values, which could
have been wrongly estimated for such a small sample size.

Finally, it has to be noticed that we have conducted our investigation on the
second-order tensor model, whose limitation to properly model fiber crossing is
well known. Being aware of this limitation, we chose to focus our simulation
625 experiment on the corpus callosum, which consists of strongly transverse white
matter fibers tracts connecting the two hemispheres characterized by a single
left-right orientation. Nevertheless, the conclusion drawn from the real data
should be interpreted cautiously given the numerous fiber crossing areas in the
brain. As a perspective, we plan to investigate more complex diffusion models,

630 such as for instance high order tensor models [29].

6. Conclusions and perspectives

In this paper, we have investigated on both simulated and real data whether there is a real added value of considering the whole tensor information for conducting voxel-based group studies. To this end, we compared two statistical
635 tests dedicated to tensor, namely the Cramér test and a tensor-based extension of the General Linear Model, the latter presenting the advantage to account for confounding variables. We have also evaluated the impact of different manifold for estimating the GLM parameters.

First, we concluded that if there is no prior assumption about the nature of
640 the expected changes, it would be preferable to use the tensor-based approach rather than performing several scalar-based analyses on different indices. Conversely, if one has a strong *a priori* about the kind of expected change, it is preferable to resort to the scalar-based approach on the corresponding scalar image. We also want to point out that the tensor-based approach is relevant
645 only if it is followed by a characterization step in order to help the physician or the neuroscientist to interpret the detected changes. Secondly, we concluded about the importance of including covariates in the statistical tests, especially for studies involving elderly subjects, since aging induces several brain modifications in terms of atrophy and diffusion property alteration. Nonetheless, if
650 one has a strong *a priori* that there is no confounding variable that can hamper a group comparison, then a nonparametric statistical test such as the Cramér test should be considered. Finally, the evaluation of the impact of different manifolds (Euclidean, Log-Euclidean and affine-invariant Riemannian metrics) on group comparisons on tensor shows that all the methods perform well and
655 lead to almost the same performance, with a significant computational overhead for the Riemannian framework.

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