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Insight from uncertainty: Bootstrap-derived diffusion metrics differentially predict memory function among older adults

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Abstract

Diffusion tensor imaging suffers from an intrinsic low signal-to-noise ratio. Bootstrap algorithms have been introduced to provide a non-parametrical method to estimate the uncertainty of the measured diffusion parameters. To quantify the variability of the principal diffusion direction, bootstrap-derived metrics such as the cone of uncertainty have been proposed. However, bootstrap-derived metrics are not independent of the underlying diffusion profile. A higher mean diffusivity causes a smaller signal-to-noise ratio and, thus, increases the measurement uncertainty. Moreover, the goodness of the tensor model, which relies strongly on the complexity of the underlying diffusion profile, influences bootstrap-derived metrics as well. The presented simulations clearly depict the cone of uncertainty as a function of the underlying diffusion profile. Since the relationship of the cone of uncertainty and common diffusion parameters, such as the mean diffusivity and the fractional anisotropy, is not linear, the cone of uncertainty has a different sensitivity. In-vivo analysis of the fornix reveals the cone of uncertainty to be a predictor for memory function among older adults. In the same time no significant correlation occurs with the common diffusion parameters. The present work not only demonstrates the cone of uncertainty as a function of the actual diffusion profile, but also discloses the cone of uncertainty as a sensitive predictor for memory function. Therefore, future studies should incorporate bootstrap-derived metrics to provide more comprehensive analysis.

Keywords

diffusion tensor imaging; bootstrap methods; cone of uncertainty; white matter; memory function

Introduction

Diffusion-weighted magnetic resonance imaging techniques are the only non-invasive methods to derive insight into the fibrous structure of the brain's white matter (WM). Diffusion tensor imaging (DTI) is the most common approach used in clinical research

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settings (Basser et al. 1994a; Basser et al. 1994b; Pierpaoli and Basser 1996). In DTI the spatial distribution of the self-diffusion of water molecules is modeled by a symmetric 3×3 tensor, which renders a diffusion profile that estimates the underlying tissue. Several tensor derived scalar parameters have been introduced to provide a measure of the underlying WM structure, including mean diffusivity (MD) and fractional anisotropy (FA) (Basser and Jones 2002; Basser and Pierpaoli 1996; Mori and Barker 1999). Both parameters have been widely used in normal and clinical populations (Moseley 2002; Sundgren et al. 2004).

As diffusion is measured by means of a diffusion-induced signal attenuation, DTI has an intrinsic low signal to noise ratio (SNR) and is therefore prone to low reliability (Jack et al. 2010). A simple method to reduce the noise is to increase the number of images for image averaging. Unfortunately, this approach requires longer scan acquisition times making it impractical for clinical applications. Moreover, the tensor model, based on the flawed assumption of a Gaussian diffusion distribution in all directions, has limitations especially in resolving more complex tissue structures.

Bootstrap methods (Efron 1979) are non-parametric, statistical algorithms to estimate the distribution of a parameter. The basic idea is to generate an arbitrary number of artificial bootstrap samples by resampling with replacement from the actually acquired data within each subject. Thereafter, any statistic of interest can be derived from the vast number of bootstrap samples. Different bootstrap approaches have been applied successfully to DTI parameters to estimate their measurement uncertainty (Chung et al. 2006; Jones 2003; Pajevic and Basser 2003; Whitcher et al. 2008). The model-based techniques, such as the wild bootstrap (Whitcher et al. 2008), are particularly useful, as they can be applied directly to a common DTI dataset without any further modifications. To provide an uncertainty metric for the principal diffusion direction and thus for the underlying axon orientation, the cone of uncertainty (CU) has been proposed (Basser 1997; Jones 2003).

So far, the estimation of the uncertainty of tensor derived parameters is the only purpose of the bootstrap technique in DTI. The statistics are then used for data quality control (Lauzon et al. 2013) or are included in advanced tractography techniques to assign a probability function to reconstructed virtual fiber paths (Jones 2008; Lazar and Alexander 2005; Vorburger et al. 2012). However, since diffusion induces a signal attenuation and the goodness of the tensor model strongly depends on the underlying tissue structure, the uncertainty of a diffusion parameter is coupled to the diffusion profile itself. That is, bootstrap metrics contain diffusion information and, thus, are diffusion metrics too.

While the relationship between a bootstrap metric and the underlying diffusion profile can basically be investigated using simulations, the functional significance must be examined *in vivo*. A well-known brain-behavior relationship is given for the fornix, a major fiber bundle with efferent and afferent connections to the hippocampus which is the anatomical seat of memory formation. Previous DTI studies (Bennett et al. 2014) showed a relationship between fornix integrity and memory functioning in normal aging. Furthermore, human lesion studies that include patients with fornix damage (Moudgil et al. 2000; Tucker et al. 1988; Valenstein et al. 1987) clearly suggest that damage to the fornix leads to episodic memory dysfunction.

Material & Methods

In-vivo data

Whole brain echo-planar diffusion imaging scans were acquired in 298 non-demented older participants (mean age=75.97±5.36) from an ongoing community-based study of aging and dementia (Brickman et al. 2008) with a 3T Philips Achieva MRI scanner (field-of-view=240×240mm², matrix reconstructed to 112×112, 81 contiguous slices, slice thickness=2mm, parallel imaging reduction factor=2, echo time=68.56ms). Diffusion-weighted scans were performed along 15 directions with a maximum b-factor of 800s/mm², complemented by two scans with b=0s/mm².

Atlas based analysis of the fornix was performed with the FMRIB58_FA standard space FA template (in MNI152 space) and the ICBM-DTI-81 white matter labels atlas using the FSL software package (Jenkinson et al. 2012). In doing so, the FA map was computed for each subject and then registered to the MNI template with FSL's non-linear transformation tool (FNIRT) using a linear initialization (default FSL parameters) and the predefined configuration file for FA registration provided by FSL. By applying the inverse non-linear transformation to the ICBM-DTI-81 atlas, analysis was done in the subject space.

Participants were evaluated clinically with a comprehensive neuropsychological battery. The battery comprises measures of memory, orientation, language, abstract reasoning, and visuospatial functioning (Stern et al. 1992), which have been shown to measure equivalent traits across the two language groups (i.e., English and Spanish) represented in the study population (Siedlecki et al. 2010). Composite scores for the domains of memory, language, speed/executive functioning, and visuospatial functioning were generated based on factor analysis of the battery. These composite scores were averaged z-scores of the individual test scores that loaded on each domain in the factor analysis.

Bootstrapping

In the standard DTI model, the diffusion-weighted signal is given by

$S_i = S_0 \cdot \exp(-b \mathbf{g}_i^T \mathbf{D} \mathbf{g}_i)$, where S_0 is the reference signal, b is the diffusion weighting, $\mathbf{g}_i = [g_{ix} \ g_{iy} \ g_{iz}]^T$ is the diffusion encoding direction for the i -th out of N observations ($i = 1, \dots, N$), and $\mathbf{D}$ is the symmetric 3×3 diffusion tensor. Dividing both sides by S_0 , applying the log transform, and changing the sign on both sides allows for an over-determined ($N > 6$) linear equation system to compute the diffusion tensor:

$$\mathbf{a} = \mathbf{B} \cdot \mathbf{d}$$

In this equation, $\mathbf{a}$ is a $N \times 1$ vector of the log-transformed signal attenuations $a_i = -\log(S_i/S_0) = \log(S_0/S_i)$, $\mathbf{B}$ is a $N \times 6$ matrix

$$\mathbf{B} = \mathbf{b} \cdot \begin{bmatrix} g_{11}^2 & g_{12}^2 & g_{13}^2 & 2g_{11}g_{12} & 2g_{11}g_{13} & 2g_{12}g_{13} \\ g_{21}^2 & g_{22}^2 & g_{23}^2 & 2g_{21}g_{22} & 2g_{21}g_{23} & 2g_{22}g_{23} \\ \vdots & \vdots & \vdots & \vdots & \vdots & \vdots \\ g_{N1}^2 & g_{N2}^2 & g_{N3}^2 & 2g_{N1}g_{N2} & 2g_{N1}g_{N3} & 2g_{N2}g_{N3} \end{bmatrix}$$

and $\mathbf{d} = [D_{xx} \ D_{yy} \ D_{zz} \ D_{xy} \ D_{xz} \ D_{yx}]$ is a 6×1 vector containing the unknown entries of the symmetric diffusion tensor. The ordinary least-square (OLS) solution is then given by

$$\mathbf{d}_{OLS} = (\mathbf{B}^T \mathbf{B})^{-1} \mathbf{B}^T \cdot \mathbf{a}$$

The OLS residuals ($\mathbf{r}$) are defined as the differences between the OLS fit and the measured values:

$$\mathbf{r} = \mathbf{a} - \mathbf{B} \cdot \mathbf{d}_{OLS}$$

Since the wild bootstrap approach directly samples from the residuals of the OLS fit of the tensor model, the residuals have to be modified to justify the assumption of independent and identically distributed errors. According to Whitcher et al. (Whitcher et al. 2008) the residuals were computed as follows:

$$r_i^* = \alpha_i \cdot f_i \cdot r_i$$

where f is drawn from the Rademacher distribution

$$f_i = \begin{cases} 1 & \text{with probability } 0.5 \\ -1 & \text{with probability } 0.5 \end{cases}$$

and α is a weight in order to produce a heteroscedasticity consistent covariance matrix estimator

$$\alpha_i = \sqrt{\frac{1}{1 - h_i}}$$

with h_i being the i -th diagonal element from the hat matrix $\mathbf{H} = \mathbf{B}(\mathbf{B}^T \mathbf{B})^{-1} \mathbf{B}^T$.

The resulting bootstrap sample is then composed by computing the artificial diffusion signal attenuations according to:

$$\mathbf{a}_{\text{sample}} = \mathbf{B} \cdot \mathbf{d}_{OLS} + \mathbf{r}^*$$

The final step is to compute the diffusion tensor from the bootstrap sample

$$\mathbf{d}_{\text{sample}} = (\mathbf{B}^T \mathbf{B})^{-1} \mathbf{B}^T \cdot \mathbf{a}_{\text{sample}}$$

The wild bootstrap was applied to generate 1000 bootstrap samples of the diffusion data per subject. As bootstrap metric of interest the dispersion of the principal eigenvector was chosen. A good measure for this dispersion is given by the apex angle of the CU (aCU) as proposed by Bassar (Bassar 1997; Bassar and Pajevic 2000).

Due to the sign ambiguity of the principal eigenvector, arithmetically averaging the bootstrap derived eigenvector samples ϵ_k is not feasible. Therefore, the dyadic tensors of the principal eigenvector samples $(\epsilon_k \epsilon_k^T, k=1, 2, \dots, M)$ are averaged instead:

$$\langle \epsilon \epsilon^T \rangle = \left\langle \begin{pmatrix} \epsilon_x^2 & \epsilon_x \epsilon_y & \epsilon_x \epsilon_z \\ \epsilon_x \epsilon_y & \epsilon_y^2 & \epsilon_y \epsilon_z \\ \epsilon_x \epsilon_z & \epsilon_y \epsilon_z & \epsilon_z^2 \end{pmatrix} \right\rangle = \frac{1}{M} \sum_{k=1}^M \epsilon_k \epsilon_k^T$$

with M being the number of bootstrap samples. The mean principal eigenvector over all bootstrap samples is then given by the eigenvector of $\langle \epsilon \epsilon^T \rangle$ corresponding to the largest eigenvalue.

The 95%-quantile of the computed angles between the mean principal eigenvector and the bootstrap eigenvector samples defines the aCU.

Tensor calculation and the bootstrap statistics are part of in-house developed software.

Simulations

To show the bootstrap metric's dependence on the diffusion profile, synthetic data were generated with given MD, FA, and SNR values. For this purpose, the eigenvalues ($\lambda_i, i = 1, 2, 3$) of the simulated diffusion tensors were calculated according to Jones (Jones 2004):

$$\lambda_1 = MD \cdot \left(1 + \frac{2 \cdot FA}{\sqrt{3 - 2 \cdot FA^2}} \right)$$

$$\lambda_2 = \lambda_3 = MD \cdot \left(1 - \frac{FA}{\sqrt{3 - 2 \cdot FA^2}} \right)$$

The diffusion tensor was then given as the 3×3 diagonal matrix $\mathbf{D} = \text{diag}(\lambda_1 \lambda_2 \lambda_3)$. Diffusion signals were computed along the same 15 directions ($\mathbf{g}_i, i = 1, 2, \dots, 15$) as in the in-vivo data with a b-value of 800 s/mm^2 using the basic diffusion attenuation formula:

$$S_i = S_0 \cdot \exp \left(-b \cdot \mathbf{g}_i^T \cdot \mathbf{D} \cdot \mathbf{g}_i \right)$$

As a final step, Gaussian noise was added in quadrature to the diffusion weighted signal (Pierpaoli and Basser 1996). For convenience, the reference signal S_0 was set to unity.

The wild bootstrap was then performed on the synthetic data generated with varying MD, FA, and SNR values in the ranges $0.1 \cdot 10^{-3} \cdot \text{mm}^2/\text{s}$ to $3.0 \cdot 10^{-3} \cdot \text{mm}^2/\text{s}$, 0.1 to 0.9, and 5 to 50, respectively.

The simulations were performed in MATLAB (R2013b, The MathWorks, Inc., Natick, Massachusetts, United States).

Statistical analysis

The independent association of the average aCU in the fornix, along with MD, FA, participant age, and number of voxels with memory functioning was examined with simultaneously-entry multiple regression analysis. As a control, the independent association of the cone of uncertainty, along with the same independent variables with memory functioning was derived in the splenium of the corpus callosum applying the same regression analysis. The splenium of the corpus callosum was chosen because it is typically not related to memory functioning.

Results

aCU contains diffusion information

The bootstrap metric derived from the synthetic data showed clearly how strong the diffusion information is incorporated. Fig. 1 depicts the effect of the MD, the FA and the SNR value on the aCU. Whenever MD, FA, and SNR values are not given explicitly they remain constant and were set to $0.8 \cdot 10^{-3} \cdot \text{mm}^2/\text{s}$, 0.7, and 25, respectively.

Since the bootstrap metric serves primarily as a measure of precision, there was the expected strong correlation with the SNR value (Fig. 1a). However, the simulations with a constant SNR value also showed a strong negative correlation with the FA value (Fig. 1c) and a more complicated relationship between the aCU and the MD value (Fig. 1b). For MD values higher than $0.9 \cdot 10^{-3} \text{ mm}^2/\text{s}$, the aCU increased with increasing MD values. But for MD values below $0.9 \cdot 10^{-3} \text{ mm}^2/\text{s}$, the aCU increased strongly with decreasing MD values instead.

The in-vivo data are in very good accordance with the findings in the simulations. The two scatter plots in Fig. 2 depict the non-linear relationship between aCU, MD, and FA, respectively, in the fornix across subjects.

aCU as predictor

The aCU was correlated with memory performance in the fornix (see Table 1) treating the aCU as the predictor and the memory performance as the dependent variable. This association was independent of the covariates in the model, including MD, FA, number of voxels, and subject age. Of the covariates, number of voxels and subject age, but not MD and FA, were associated with memory functioning. The significant relationship between

aCU in the fornix and memory was confirmed with permutation testing (100,000 permutations), which yielded a p-value of 0.0232.

In Fig. 3, the CUs in the fornix of a participant with a poor memory functioning score and in the fornix of a participant with a good memory functioning score are displayed as examples.

The control measurements in the splenium of the corpus callosum showed no correlation between the aCU with the memory performance (see Table 1). In order to ascertain whether the relationship between the aCU variable and memory was reliably greater for the fornix compared with the splenium of the corpus callosum, a permutation test of 100,000 iterations was conducted. The test statistic was the difference of T statistics for aCU from both separate regressions:

$$\Delta T = T(\text{fornix} - \text{aCU}) - T(\text{splenium} - \text{aCU})$$

The point estimate value for this difference is obtained from the two regressions with the correct assignment of the memory variable to aCU and all covariates. For generating null-conditions, the memory score was randomly permuted with respect to all independent variables, and the two regression analyses were repeated with a computation of T . This process was done 100,000 times to generate the null distribution. If the point estimate for T lies in the tail of the distribution (i.e. less than 5% of null-iterations gave rise to more extreme T values than the point estimate), then the test is significant. The results came out significant with a two-tailed p-value of $p(|T_{\text{null}}| > |T_{\text{point}}|) = 0.0196$.

Discussion

Bootstrap approaches have been introduced to DTI to estimate the uncertainty of tensor derived metrics. One major factor of measurement uncertainty is thermal noise. The first simulation, which showed a decreasing aCU with increasing SNR, is the result of this constructed relationship. However, contrary to the intended purpose of estimating data precision only, the CU is not a simple function of uncertainty but rather it represents a function of the underlying diffusion profile itself. The basic simulations with a constant SNR but varying MD and FA values revealed some of the aCU's characteristics with respect to the diffusion profile.

In the simulations, the aCU decreased with increasing diffusion anisotropy. This effect is directly related to the tensor model since a cigar shaped tensor, for example, defines a principal diffusion direction more clearly than an oblate or spherical tensor. If the FA value is high, the principal direction is less influenced by thermal noise. This effect actually scales with the number of diffusion gradient directions applied. In Fig. 4b the simulation results with 15 gradient encoding directions are depicted together with the results using 64 diffusion directions. Due to the increased number of samples, the uncertainty in general is decreased but moreover the effect of the diffusion anisotropy is reduced.

It is important to note that all acquisition parameters which influence the SNR of the DTI signals, such as the b value, the number of averages for the reference signal, the field strength, the echo time, etc., most likely have a direct influence on the absolute aCU value.

While the relationship between the aCU and the FA is straightforward, the MD has a more complicated influence on the aCU. In this case the aCU is a function of two opposing effects. On the one hand, the MD directly changes the SNR of the diffusion weighted measurements due to the diffusion induced signal attenuation. The constant SNR in the simulations was set with respect to the reference signal S_0 . Hence an increase in MD decreased the SNR in the diffusion signals, which leads to a higher uncertainty reflected by a larger aCU. On the other hand, the difference between the diffusion-weighted signal and the reference signal (i.e. the signal attenuation) scales also with the diffusion strength. If the signal attenuation becomes smaller, the influence of the SNR on the diffusion weighting increases. In this case, the noise starts to dominate the measurements, which leads to higher aCUs. While for MD values above the apparent threshold of $0.9 \cdot 10^{-3} \text{ mm}^2/\text{s}$ the intrinsic decrease of the SNR in the diffusion-weighted signals led to an increase of the aCU, for MD values below $0.9 \cdot 10^{-3} \text{ mm}^2/\text{s}$ the large influence of the noise caused larger aCUs. Since the second effect is more direct, the larger slope below the apparent threshold further supports this explanation. Simulations with a constant SNR of 100 showed a shift of the apparent threshold down to $0.8 \cdot 10^{-3} \text{ mm}^2/\text{s}$ evidencing the given explanation (see Fig. 4b).

While the applied simulations showed the direct influence of the diffusion strength and the diffusion anisotropy on the aCU, there are many scenarios that are not covered. For example, a voxel with two crossing fiber bundles and a voxel with a single fiber bundle, but less tightly packed, might lead to the same FA value but the aCU might be affected differently. In the former case, the tensor is a poor model, which will have a direct influence on the aCU. However, the goodness of the tensor model cannot be captured by the aCU which requires a more complex model such as diffusion kurtosis imaging (Jensen et al. 2005). Moreover, to investigate how the aCU is exactly influenced by the goodness of the tensor model, more exhaustive simulations are required, such as particle based Monte-Carlo simulations (Hall and Alexander 2009; Yeh et al. 2013).

Previous studies among older adults with Alzheimer's disease reported reduced FA values in the fornix (Mielke et al. 2009; Ringman et al. 2007; van Bruggen et al. 2012). In the current study, which included non-demented participants, aCU was the only diffusion derived metric that correlated with memory performance. A relationship between the FA value or the MD value in the fornix and memory functioning was not observed. Thus, the in-vivo measurements indicate that the aCU is more sensitive than the FA value. The present analyses focused on the fornix because it has been implicated in memory functioning among older adults; indeed, all findings confirm this specific relationship, as a relationship between the control region and memory functioning could not be observed.

Next to the MD and FA, there is a variety of eigenvalue-based diffusion metrics proposed in the literature, such as the enhanced (or exponential) apparent diffusion coefficient (eADC) (Provenzale et al. 1999), the axial (AD) and radial diffusivity (RD) (Song et al. 2002), the rational anisotropy (RA) and the volume ratio (VR) (Basser 1995), or the linear (C_1), planar

(C_p), and spherical (C_s) measures proposed by Westin (Westin et al. 2002). It might be that one of these DTI parameters is sensitive enough in this particular case to show a significant correlation with memory functioning in the fornix. While a thorough investigation of all available parameters might be very interesting, an extensive listing would distract from the actual finding of the present study. The focus of the present study is not to find the best DTI parameter to investigate the relationship of the fornix and memory functioning but rather to demonstrate the potential of a bootstrap derived metric to serve as a sensitive diffusion measure.

Apart from the subject age, the number of voxels, which reflects the size of the fornix in subject space, was a reliable predictor of memory performance. Since the aCU is much larger in the surrounding tissue than in the fornix itself, the question rises if the significant correlation of the aCU with memory performance is just an artifact. In smaller structures, the influence of a single voxel wrongly assigned is more severe and may distort the results disproportionately. However, the same holds for the MD and the FA value. At least in the case of the FA the impact of non-fornix voxels would be of the same magnitude as for the aCU parameters. Furthermore, the exemplarily chosen subjects in Fig. 3 contradict the argument that the results are artifactual. In both subjects, the region of interest seems to contain a few voxels outside the fornices. If these voxels were removed from the analysis, the difference between the two subjects would be larger and the change of the aCU would be even more significant.

In Fig. 3, the average principal diffusion direction is very coherent for the subject with a good memory score but very incoherent for the subject with a bad memory score. To provide a good visual example, subjects with extreme values were chosen. Thus, the FA value in the subject with a bad memory score is very low and, as described above, the computation of the principal diffusion direction is therefore more influenced by thermal noise which again leads to a high aCU.

It is important to keep the original intended purpose of bootstrap derived metrics in mind: to estimate precision. How is it possible to distinguish between a significant change in the diffusion profile and a significant change in data quality? Since the same question arises also for conventional DTI parameters and for MRI signals in general, visual inspection is very important. Moreover, the suitability of bootstrap metrics for quality control has to be put into perspective with the diffusion profile.

When using the aCU as a diffusion parameter rather than as a precision metric, a reference measurement should be computed in a region where no effect is expected. In the present in-vivo analysis this was performed in the splenium of the corpus callosum. In doing so, it is possible to exclude a global change in data quality, e.g. due to movement, as the driving factor of a significant effect.

In conclusion, bootstrap metrics, such as the CU, provide sensitive diffusion information next to the common DTI parameters and should be incorporated in ongoing and future DTI studies to provide more extensive insight.

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Fig. 1.

The aCU as a function of SNR (a), MD (b), and FA (c).

Fig. 2.

The scatter plots of the parameter pair (aCU, MD) and of the parameter pair (aCU, FA) in the fornix across the subjects show the same non-linear relationship as revealed by the simulations.

Fig. 3.
Exemplary CUs (red double-cones) in the fornix overlaid onto the FA map. The images are examples of a subject with large aCUs (left) and of a subject with small aCUs (right).

Fig. 4.

The relationship between the aCU and the underlying profile depends on the number of applied gradient encoding directions (a) and on the actual SNR (b).

Table 1

Multiple Regression Analysis

predictor	fornix		splenium	
	standardized β	p-value	standardized β	p-value
aCU	-0.233	0.037	0.041	0.701
MD	-0.158	0.429	0.040	0.712
FA	0.034	0.850	0.206	0.187
number of voxels	0.304	0.008	0.047	0.426
subject age	-0.187	0.002	-0.227	<0.001

Results of the multiple regression analysis. The aCU is significantly correlated with memory functioning in the fornix whereas the FA shows no correlation. In the splenium of the corpus callosum no correlation with memory is reported at all.