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**RELATION BETWEEN BRAIN LESIONS LOCALISATION AND
CLINICAL OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY:
A DIFFUSION TENSOR IMAGING STUDY.**

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**RELATION BETWEEN BRAIN LESIONS LOCATION AND CLINICAL
OUTCOME IN SEVERE TRAUMATIC BRAIN INJURY PATIENTS:
A DIFFUSION TENSOR IMAGING STUDY USING VOXEL-BASED
APPROACHES.**

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Abstract

The early prediction of consciousness recovery from traumatic brain injury (TBI) is crucial to make decisions about the appropriate use of prolonged intensive care. Diffusion tensor imaging (DTI) has been proposed as a biomarker of white matter injury, that could be used in a classification purpose. Instead of region-of-interest-based approach, we applied voxel-based approaches (voxel-based DTI and Tract-Based Spatial Statistics) on 30 TBI patients to identify, without any prior, the brain regions that were specifically damaged in unfavorable 1-year outcome group compared to the favorable one. DTI were acquired at mean 23 days (5-53 days) and two DTI-derived indices, fractional anisotropy (FA) and apparent diffusion coefficient (ADC) were tested. Our results showed that 1) ADC is not a relevant biomarker for early 1-year outcome prognosis; 2) FA measured in inferior longitudinal fasciculus, in cerebral peduncle, in posterior limb of the internal capsule and in posterior corpus callosum is specifically decreased in unfavorable outcome group compare to the favorable one. 3) a Linear Discriminant Analysis using the FA measured in these four regions showed good classification performance (sensitivity=86% and specificity=86%). These findings confirm the relevance of the use of DTI as biomarkers for consciousness recovery after TBI and support the possible use of these biomarkers for early classification of patients.

Introduction

Severe traumatic brain injury (TBI) is one of the most common cause of long-term disability, among which coma, persistent vegetative or minimally conscious state [Bruns et al. 2003]. In the clinical context, the prediction of consciousness recovery is crucial to make decisions about the appropriate level of initial care. However, clinical experience showed that clinical examinations, conventional CT and morphological magnetic resonance images (MRI) are in most of the cases insufficient to make such decisions, in part because it fails to depict primary lesions such as diffuse axonal injury (DAI) [Coles 2007]. In particular, in the clinical context, the visual examination of the

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2 T2 images is insufficient to differentiate (when they are visible) simple contusions, that are
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4 potentially reversible, and brain parenchyma lesions, that are irreversible.
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7 However, several studies have shown that diffusion-weighted imaging (DWI) [Chan et al.
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9 2003, Huisman et al. 2003, Goetz et al. 2004, Hou et al. 2007] and diffusion tensor imaging (DTI)
10 [Arfanakis et al. 2002, Ptak et al. 2003, Huisman et al. 2004, Nakayama et al. 2006] are sensitive in
11 detecting DAI and white matter disruption without macroscopic lesion. Computed from DTI data,
12 the fractional anisotropy (FA) index express fibers tracts integrity through the relative difference of
13 diffusion across and along axonal fibers, whereas the apparent diffusion coefficient (ADC) index
14 quantify the local averaged diffusion in all directions. In the case of diffuse axonal injury, the FA
15 index allows us to detect white matters fibers disorders (decrease of FA) and the ADC index is
16 sensitive to the movement of water in the tissue, so is sensitive, in particular, to the water diffusion
17 in the intracellular compartment, that is reduced in case of ischemia for instance (decrease of ADC).
18
19 Moreover, a recent study supported the fact that DTI parameters, especially the fractional
20 anisotropy (FA) and the apparent diffusion coefficient (ADC), are relevant biomarkers, which may
21 have prognosis value in TBI [Sidaros et al. 2008]. To do so, the authors manually delineated, for
22 each patient, four white matter regions of interest (ROIs), that were known to be affected by TBI.
23 The FA values reduction in some regions (in the cerebral peduncle in particular) measured few
24 weeks post-injury appeared to be highly correlated with an unfavorable 1-year outcome, whereas
25 the ADC values changed between favorable 1-year outcome and unfavorable 1-year outcome
26 patients only after 12 months. However, this last result was contradictory to the results presented by
27 Hou and colleagues [Hou et al. 2007], that showed that ADC values measured only after few days
28 post-injury in the deep white matter zone consisting of the corpus callosum were significantly
29 different between unfavorable and favorable outcomes and controls. It appears therefore that the
30 main limitation of these approaches was that the choice of the ROIs was based on clinical priors.
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32 Indeed, other white matter tracts affected by TBI could be relevant to improve outcome prediction
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2 by using the DTI biomarkers.
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4 Recently, explorative voxel-based analysis proved its efficiency in detecting unpredicted
5 areas where DTI parameters were altered in Fabry disease [Albrecht et al. 2007], in low-grade
6 hepatic encephalopathy [Kumar et al. 2008] or in amyotrophic lateral sclerosis [Thivard et al.
7 2007]. In the context of TBI, this approach was used to detect FA reduction localization in patients
8 compared to controls [Nakayama et al. 2006] . More recently a study applied voxel-based analysis
9 on DTI and T1-weighted images to compare longitudinal changes (from 2 months to 1 year post-
10 injury) in TBI patients and in controls [Bendlin et al. 2008].
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20 In this context, the goal of the present paper was thus to apply voxel-based analyses to
21 identify the most relevant DTI biomarkers values (FA and/or ADC) measured a few weeks after
22 TBI and the associated white matter tracts, that allow the best 1-year outcome prediction in TBI.
23 The predictive accuracy of the selected biomarkers will then be compared to the classical clinical
24 and morphological parameters.
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35 **Materials and methods**

36 Study patients

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38 30 patients (2 females) with a mean age of 37 ± 12 years and an age range of 15 to 65 years were
39 hospitalized in the Surgical Neuro-Intensive Care Unit of the Pitié-Salpêtrière Hospital, Paris,
40 France between January 2002 and April 2006 and included if they met the following criteria: 1) TBI
41 requiring mechanical ventilation for neurological reasons; 2) persistent disorder of consciousness,
42 defined as the absence of response to simple orders, and not explained by sedation or other medical
43 causes at the time informed consent was signed by the legally authorized representative ; 3) absence
44 of previous neurological disorders; and 4) hemodynamic, ventilatory, and neurological conditions
45 allowing transportation and prolonged supine position without risk to the patient, most notably,
46 stabilized intracranial pressure. Treatment follows the Pitié-Salpêtrière algorithm published in
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1 [Lescot et al. 2008]. DTI acquisitions were performed in these 30 patients and also in 10 healthy
2 controls (4 females) with a mean age of 31 ± 9 years and an age range of 22 to 49 years. No
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7 corticosteroids were used for the patients at the time of DTI scan.

8 9 DTI acquisitions

10 DTI acquisitions was performed on a 1.5T system (Signa, General Electric, Milwaukee, WI) under
11 mechanical ventilation and sedation by sufentanil (20 to 30 $\mu\text{g/h}$) and propofol (100 to 200 mg/h) to
12 ensure immobility of the patient during image acquisition. The acquisition parameters were the
13 following: axial plane; TR/TE = 8000/84.9 ms; 23 directions; diffusion b value = 700 s/mm^2 ; slice
14 thickness = 5 mm; no gap; 20 slices; field of view 32x32 cm; matrix 128x128; and 2 averages. The
15 inferior slice of the DTI acquisition was positioned at the junction between the pons and the
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26 medulla oblongata.

27 28 Clinical evaluation

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30 Age, mechanical ventilation duration, and length of stay in the ICU were recorded. The Glasgow
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Coma Scale (GCS) score was determined by the first physicians upon arrival at the site of the
accident and Marshall scores were determined from initial CT [Marshall et al. 1991]. The Glasgow
Outcome Scale (GOS) score was evaluated for all patients 1 year later by an independent physician.
A GOS score of 3 was assigned to patients in minimally conscious state as defined by Giacino and
Zasler [Giacino and Zasler 1995]. Patients with various disabilities but with normal consciousness,
classified GOS 3 for the most severe of them in several earlier studies, were classified GOS 4 here,
since our goal was to assess the outcome in terms of consciousness recovery. For the analysis, the
patients were divided into two groups based on consciousness recovery (GOS 1-3: unfavorable
outcomes, including death, persistent vegetative state, and minimally conscious state or GOS 4-5:
favorable outcome, including minor or no residual impairments and residual impairments that did
not affect consciousness). Clinicians in charge of the patients were blinded as to the results of DTI
analysis.

DTI data analysis

All processing were done using FSL software (www.fmrib.ox.ac.uk/fsl/). The DTI images were first corrected for distortions due to eddy currents using the b=0 volume as reference. The diffusion tensor was estimated and the fractional anisotropy (FA) and the apparent diffusion coefficient (ADC) were calculated for each voxel from the three estimated eigenvalues [Pierpaoli and Basser 1996], that quantify the water diffusion in three orthogonal directions. Then the FA and ADC images were registered on a 1x1x1 mm standard space image (MNI152 space) using a nonlinear registration procedure and a voxel-based analysis (VB-DTI) were then conducted on both FA and ADC images, which were spatially smoothed using a Gaussian kernel of 3 mm. The differences between the FA and ADC measured in the favorable and unfavorable outcome groups was inferred using a permutation testing procedure (Monte-Carlo permutation test). The group differences maps of the 2-sample unpaired t-test were then thresholded ($p < 0.05$) using the cluster-based thresholding procedure including a correction for multiple comparisons that controls the family-wise error rate.

In addition to the VB-DTI analysis, that did not take into account the residual misalignments between subjects after the nonlinear registration (that is not completely removed by the spatial smoothing), we use the Tract-Based Spatial Statistics (TBSS) approach to test the ADC and FA differences [Smith et al. 2006]. It consists in calculating the FA skeleton from the mean FA image (across the subjects). The FA skeleton is a representation of the alignment-invariant tracts on which the individual ADC and FA images are projected. A voxelwise statistical analysis restricted to the ADC or FA values projected on the skeleton was then applied to test the differences between the favorable and unfavorable outcome groups. Due to the possible strong FA reduction in the patient groups, we calculated the mean FA skeleton from the control group; the FA and ADC values of each patients were then projected onto this skeleton.

Predictive accuracy of DTI-derived biomarkers for the clinical outcome

The former analysis allowed us to determine the biomarkers (FA or ADC) that were the most

1
2 discriminant between favorable and unfavorable 1-year outcome and to localize the brain regions
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4 where the differences were the highest. As the location and the extension of these regions of interest
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6 (ROIs) depend of the group of patients included in the analysis, we tested the spatial variability of
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8 the ROIs depending on the subjects by using a permutation-style analysis. The TBSS approach was
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10 applied 500 times on 12 favorable and 12 unfavorable outcome patients randomly chosen. Each
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12 voxel of the FA skeleton was then characterized by a score between 0 and 500 corresponding to the
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14 number of times this voxel is selected in a ROI.
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19 In the clinical context, our aim was then to test the predictive accuracy for the clinical
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21 outcome of the DTI biomarkers measured in the ROIs, and, to compare them to classical clinical
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23 data : age, GCS and Marshall CT score at admission. To do so, linear discriminant analysis (LDA)
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25 was performed to classify the patients into two categories, favorable and unfavorable outcome,
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27 using DTI biomarkers only, clinical data only (age, GCS and Marshall CT score) or both. The
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29 posterior probability of each patient to belong to each class was calculated by a bootstrap cross-
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31 validation procedure. This approach consisted in, firstly, randomly choosing 3 patients from each
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33 groups (favorable and unfavorable outcome), secondly computing the LDA function using the 24
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35 remaining patients, and, finally, calculating the posterior probability of the 6 testing patients to
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37 belong to the two groups. This procedure was repeated 5000 times. Thus we got 15000 samples of
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39 the posterior probability of favorable (and unfavorable) outcome patients to belong to each group.
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41 To evaluate the classification accuracy, we calculated the sensitivity and the specificity of the two
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43 groups classification according to the threshold of the posterior probability. We especially
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45 compared the results with two thresholds: $p=0.5$ (all cases were classified) and $p=0.95$ (only the
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47 cases with an high level of confidence were classified). In our clinical context, the sensitivity of the
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49 classification was defined as the ratio between the number of correctly classified unfavorable
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51 outcome cases and the total number of unfavorable outcome cases; the specificity was defined as
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53 one minus the ratio between the number of wrongly classified favorable outcome cases and the total
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2 number of favorable outcome cases. Finally, we computed the accuracy, defined as the ratio
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4 between the number of correctly classified cases (both favorable and unfavorable outcome) and the
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6 total number of cases.
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10 11 **Results**

12 13 VB-DTI

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15 Firstly, a VB-DTI analysis was performed on the whole brain to compare the ADC and FA values
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17 between favorable and unfavorable 1-year outcome patients. There was no significant ADC
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19 differences between the two group ($p=0.3$). But the figure 1 shows that the FA was significantly
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21 lower ($p<0.05$) for the unfavorable 1-year outcome group compared the favorable one around
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23 several white matter fasciculi: the inferior longitudinal fasciculus (ILF), the cerebral peduncle (CP),
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25 the posterior limb of the internal capsule (PLIC) and the posterior corpus callosum (PCC).
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33 Voxelwise analysis on the FA skeleton

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35 The TBSS approach, limited to the FA skeleton, confirmed the VB-DTI results. Indeed, no
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37 significant ADC differences were found between favorable and unfavorable 1-year outcome
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39 patients, whereas FA was significantly lower for the unfavorable group around the same white
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41 matter fasciculi (ILF, CP, PLIC and PCC). However, we observed a right lateralization of the
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43 effect, because only the right parts of CP, ILF and PLIC showed significant FA differences between
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45 the two groups (see Figure 2). The study of the spatial variability of these regions depending on the
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47 subsets of subjects used showed that the four regions extracted using all subjects correspond to the
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49 regions that are systematically extracted using the subsets of subjects (see Figure 3). **It showed also**
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51 **that the right lateralization of the PLIC is not systematically observed because the left PLIC is**
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53 **highlighted with almost half of the sampled subsets. On the other hand, the right**
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55 **lateralization of the CP and ILF is confirmed.**
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Predictive accuracy

The FA measured in the four former regions calculated by TBSS (right CP, right ILF, right PLIC and PCC) were the most discriminant between favorable and unfavorable 1-year outcome. We then defined, for each patient and healthy control, four indices as the median value of the projected FA values in each of the four regions as calculated by TBSS (see Figure 2). The distributions of these indices across the three groups (controls, favorable outcomes and unfavorable outcomes) were plotted in the figure 4. Not surprisingly, it appeared that the indices were significantly lower for the unfavorable outcome group than for the control and favorable outcome groups. Moreover, the values of the indices were similar between the favorable outcome and control groups. Therefore, a decrease of the FA values in the regions we selected seemed specifically associated with an unfavorable outcome.

To go further, we looked for the regions where the FA measures on the FA skeleton were significantly different between the favorable outcome and control groups (see Figure 5). It appeared that the highest differences were observed in the anterior corpus callosum (ACC). The distribution of the median of the FA values in this area across the three groups was plotted in the Figure 6. This showed that the FA values in ACC were significantly higher in the control group than in the two patient groups. However, the FA values in ACC were similar in the two groups of patients, suggesting that damages in this area are not predictive of the 1-year outcome.

The predictive accuracy of the four chosen parameters (the median of the FA values in right CP, right ILF, right PLIC and PCC) compared to the clinical parameters (age, GCS and Marshall score) was then tested by a bootstrap cross-validation of the LDA classification. The ROC curves plotted in Figure 7 showed that the classification using only the FA parameters was much better than the classification using only the clinical parameters, and even better than the classification using both FA and clinical parameters. We distinguished two extreme cases depending of the

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2 threshold of the posterior probability p used. For the $p=0.5$ threshold, the sensitivity and the
3
4 specificity using only FA parameters were 86% and 86% respectively (accuracy equal to 86%); for
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6 the $p=0.95$ threshold, the sensitivity and the specificity were 49% and 97% (accuracy equal to
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8 73%). In this last case, where only the patients with a high level of confidence were classified, the
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10 classification was highly specific but only half of the patient has been classified. For the other half,
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12 no answer was given.
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18 Discussion

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20 The main objective of this work was to identify the relevant DTI biomarkers that improve the initial
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22 outcome prediction after TBI. To do so, we applied explorative voxel-based approaches on DTI
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24 images acquired on 30 TBI patients at the early post-injury stage. We tested the FA and ADC
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26 changes between the favorable 1-year outcome group and the unfavorable one, using VB-DTI and
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28 TBSS approaches. Both approaches provided coherent results.
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33 Firstly, no significant ADC difference was observed between the two groups, suggesting
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35 that ADC is not a relevant biomarker for the early 1-year outcome prognosis. These results
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37 generalize those presented in [Sidaros et al. 2007], which indicated no early ADC changes in four
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39 white matter brain regions, but only an increase in the PCC after 12 months post-injury. On the
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41 other hand, the results presented in [Hou et al, 2007] showed significant ADC increase in deep
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43 zones of the corpus callosum for very early acquisitions (from 1 to 24 days). However, the mean
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45 time post-injury of their acquisitions (5 ± 4 days) are significantly lower than ours (23 ± 11 days).
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47 Thus, the post-injury edema might not be reduced enough at the time of the acquisitions, inducing
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49 an increase in ADC values.
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54 Secondly, we showed significant FA differences between favorable and unfavorable 1-year
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56 outcome groups around four FA tracks: in ILF, PLIC, CP and PCC. Thus, the integrity of these
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58 tracks seems to play a key role in the consciousness maintenance. Indeed the ascending reticular
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2 activating system (ARAS), the primary arousal structure, is located in the CP, more precisely in the
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4 mesencephalic reticular formation [Parvizi and Damasio 2001]. Moreover, the ARAS activates
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6 widespread cortical regions through the thalamus, that are linked by fibers of the internal capsule. In
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8 the study by Sidaros and colleagues [Sidaros et al., 2007], PCC, CP and PLIC (in addition to the
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10 centrum semioval) were chosen for the analysis, but significant FA differences with the initial DTI
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12 acquisitions were found only in CP. The absence of FA differences in PCC and PLIC might be due
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14 to the manual delineation of the ROIs that induced partial volume between voxels where FA is
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16 reduced and voxels where FA is unchanged. Moreover, our results in FA reduction showed a right
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18 lateralization of the effect, suggesting that FA reduction in the right parts of CP, ~~PLIC~~ and ILF are
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20 more specific of unfavorable 1-year outcome than the left parts. The specific presence of lateral
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22 lesions (localized with FLAIR and T2* acquisitions) in unfavorable outcome group of patients have
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24 already been described in morphological MRI studies [Weiss et al. 2008]. This study highlighted in
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26 particular the lesions in the right CP.
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33 Compared to the manual delineation of ROIs used in former studies, the voxel-based
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35 approaches we proposed allowed us to automatically choose, without any priors, the most relevant
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37 FA tracks on the FA skeleton for predictive purpose in TBI. Moreover, the use of the FA values
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39 projected on the FA skeleton in TBSS reduced the possible partial volume effect induced by the
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41 manually design of the ROIs or by the spatial smoothing used in VB-DTI. Consequently, the FA
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43 values in the four ROIs were significantly different from one patient group to the other. On the
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45 other hand, the FA values in ACC, that were significantly different from the patients to the controls,
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47 did not discriminate the two groups of patients. This showed that the FA biomarkers in the four
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49 selected ROIs were sensitive and specific for the classification of unfavorable and favorable 1-year
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51 outcome patients.
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56 However, voxel-based methods have limitations, especially for their use in a clinical
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58 context. Indeed, the application of the VB-DTI imposes a spatial smoothing of the data. The choice
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2 for the optimal size of the Gaussian kernel is still an open question, and seems to modulate the
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4 results [Jones et al. 2005]. In particular, when the spatial smoothing is too large, ambiguities over
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6 FA reduction remain: is it due to within-tract FA change or change in tract thickness? Even if such
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8 problems are generally resolved by the TBSS approach, it has also some limitations. Especially, if
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10 the FA is strongly reduced in some areas, these areas may be excluded from analysis because of the
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12 mean FA thresholding on the skeleton. In this case, it is more appropriate to use a target FA
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14 skeleton derived from a control group. Finally, the main limitation of the two methods for their use
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16 on TBI patients is the possible large brain deformations induced by the injury, that are not well
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18 corrected by the nonlinear registration.
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26 To go further, we quantified the accuracy of the FA biomarkers, automatically selected by
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28 TBSS, to predict the 1-year outcome, compared to the association of the clinical and CT parameters,
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30 usually used in the neuro-intensive care unit. More precisely, we focused on the ability of early
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32 detecting the unfavorable 1-year outcome cases. Indeed, in the clinical context, to make decisions
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34 about the appropriate level of initial care, it is important to identify the most unfavorable cases as
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36 unfavorable cases, but it is also crucial to never identify favorable cases as unfavorable cases. That
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38 is why we define the sensitivity and the specificity of the classification according to the unfavorable
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40 cases. Firstly, the bootstrap sampling of the LDA classification showed that the clinical and CT
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42 parameters were not discriminant between favorable and unfavorable 1-year outcome patients. This
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44 confirmed the absolute necessity to find other parameters that would potentially help the clinicians
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46 to make decisions. Thus, the bootstrap sampling of the LDA classification showed that the use of
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48 the FA biomarkers led to a very specific classification of the unfavorable 1-year outcome patients
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50 among all patients. The specificity reached even 97% when only the cases with an high confidence
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52 level were classified (with a posterior probability to belong to a class higher than 0.95). In the
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54 clinical practice, it is essential to make decisions with an high confidence level. In this context, the
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2 drawback is that the markers do not provide any answer concerning the 1-year outcome of one
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4 patient on two.
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7 However, this study involving 30 patients must be considered as a preliminary study. The
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9 relevance of the DTI biomarkers in the four ROIs have to be confirmed using a larger database.
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11 Moreover, the relative small number of patients has constrained us to use the same data to define
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13 the ROIs by TBSS and to test the predictive accuracy for the clinical outcome of the FA value in
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15 these ROIs. The chosen ROIs were thus well adapted to the dataset and our results were
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17 consequently biased. The constitution of a larger database will allow us to quantify the relevance of
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19 these ROIs on a dataset acquired independently.
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27 In addition to the use of large datasets, two improvements could be investigated in future
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29 works. Firstly, Support Vector Machine (SVM) algorithm using nonlinear model is known to
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31 outperformed LDA. Its use in our context would probably increase the predictive performance of
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33 our approach. Secondly, other MR imaging biomarkers (from Magnetic Resonance Spectroscopy
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35 (MRS) and functional Magnetic Resonance Imaging (fMRI) in particular) could be associated to the
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37 DTI to improve the prognosis [Weiss et al, 2007] . MRS allows the study of the brain metabolism
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39 through several markers. N-acetyl-aspartate (NAA), Creatine (Cre), Choline (Cho) and Lactate
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41 (Lac) are of particular interest to evaluate the effect of TBI on cellular metabolism. For instance,
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43 several studies on TBI patients showed that the NAA/Creatine ratio measured in specific brain areas
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45 (thalamus, pons, splenium of corpus callosum, in particular) appeared to be the best outcome
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47 predictor. fMRI, as for it, allows to detect dysfunction of brain regions that look structurally intact
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49 on conventional MRI. The study of the functional integrity of the brain systems involved in
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51 consciousness, such as the reticular activating system or the thalamo-cortical circuits, might provide
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53 additional prognostic factors in TBI.
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Conclusion

This paper confirms that FA measured in several specific brain areas is a relevant biomarker for early outcome prediction in TBI. The use of TBSS approach allowed us to automatically identify the most discriminant regions for classification in a clinical context. However, our results have to be confirmed on a larger dataset and could be improved by adding relevant biomarkers from MRS and fMRI acquisitions.

For Peer Review

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Tables

Patient	Age	Sex	Cause of Injury	GCS	Marshall	ICU	MV	Delay	GOS	Group
1	35	M	MVA	4	2	44	13	16	4	F
2	43	M	Assault	12	6	57	45	29	3	UF
3	55	F	Fall	6	6	19	19	8	1	UF
4	15	F	MVA	7	2	90	18	35	3	UF
5	26	M	MVA	4	3	38	38	31	1	UF
6	54	M	MVA	15	2	8	5	14	5	F
7	30	M	MVA	6	2	32	25	28	5	F
8	20	M	MVA	6	5	43	28	36	4	F
9	65	M	Fall	5	5	6	6	5	1	UF
10	47	M	Fall	3	6	97	72	31	3	UF
11	40	M	MVA	6	6	64	64	53	1	UF
12	38	M	Fall	3	6	32	25	18	4	F
13	46	M	MVA	6	6	36	33	31	1	UF
14	43	F	Fall	8	2	14	14	14	1	UF
15	44	M	Fall	3	5	33	26	15	4	F
16	38	M	MVA	4	3	39	32	13	2	UF
17	45	M	Pedestrian	6	6	101	41	37	4	F
18	52	M	Fall	3	6	11	11	13	1	UF
19	39	M	Fall	4	2	15	8	6	5	F
20	23	M	MVA	5	3	62	48	24	3	UF
21	30	M	Fall	7	3	34	28	34	4	F
22	37	M	MVA	9	5	29	13	19	4	F
23	20	M	MVA	3	3	97	72	31	4	F
24	23	M	Fall	15	5	25	22	23	5	F
25	20	M	MVA	12	5	34	30	23	4	F
26	24	M	MVA	5	5	64	42	23	4	F
27	27	M	MVA	11	5	35	25	32	5	F
28	32	M	MVA	3	2	58	24	24	3	UF
29	45	M	Fall	3	2	67	41	21	3	UF
30	53	M	MVA	3	2	20	21	19	1	UF

Table 1: Patients included in the DTI study. MVA=Motor Vehicle Accident; GCS=Glasgow Coma Scale; ICU=Days in the Intensive Care Unit; MV=Days of mechanical ventilation; Delay=Days from injury to MRI; GOS=Glasgow outcome scale; F=Favorable 1-year outcome; UF=Unfavorable 1-year outcome.

Figure legends

Figure 1: VB-DTI results: orange shows voxels where FA on the skeleton is significantly lower ($p < 0.05$) in unfavorable outcomes than in favorable outcomes. This map is superimposed on

1
2 the mean of all individual FA images of the patients.
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4 **Figure 2:** The four regions where FA on the skeleton is significantly lower ($p < 0.05$) in
5 unfavorable outcomes than in favorable outcomes. This map is superimposed on the
6 mean of all individual FA images of the patients. These regions were used to to define FA
7 biomarkers.
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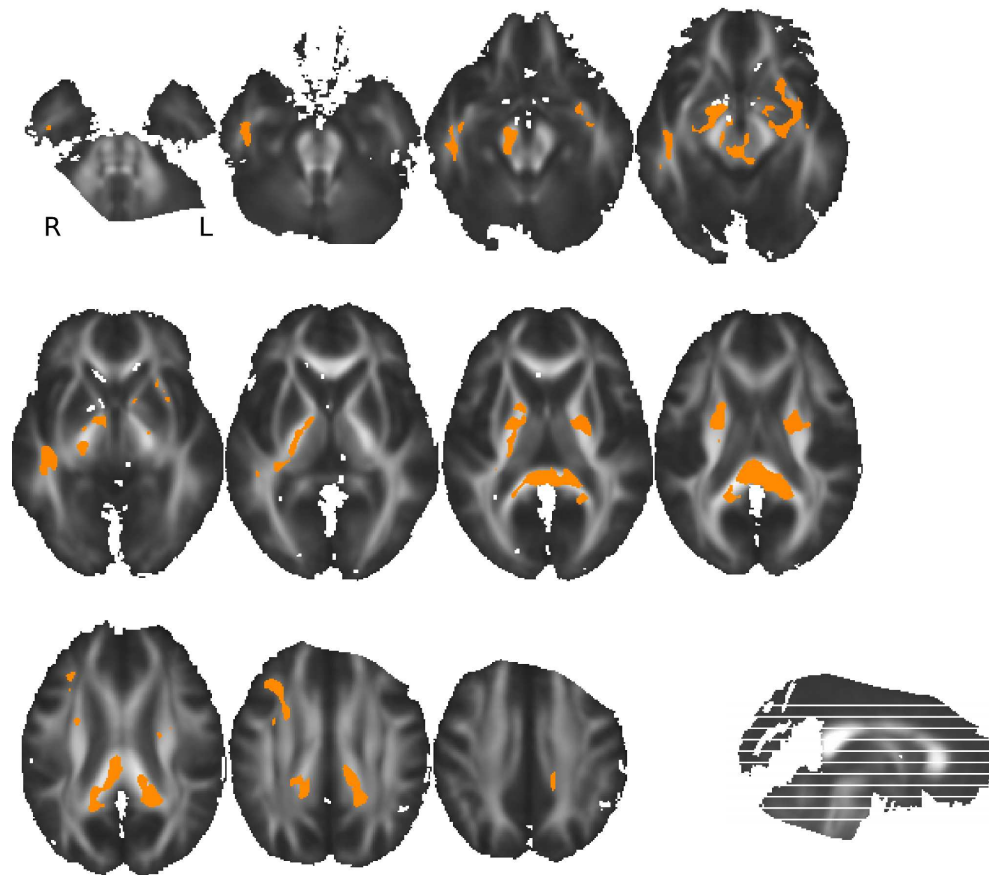
10 **Figure 3:** Spatial variability of the ROIs. The mapped score between 0 and 500 represents the
11 number of times a voxel has been selected as a voxel of interest (over the 500 bootstrap
12 repetitions). This map is superimposed on the mean of all individual FA images of the
13 patients.
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16 **Figure 4:** The distribution of the median of the FA values in the four ROIs across the three groups.
17 The star indicates that the measures for the unfavorable outcomes are significantly lower
18 ($p < 0,0001$) than for the favorable outcomes and the controls.
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21 **Figure 5:** TBSS results: orange shows voxels where FA on the skeleton is significantly lower
22 ($p < 0.05$) in favorable outcomes than in healthy controls. This map is superimposed on the
23 mean of all individual FA images of the patients.
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26 **Figure 6:** The distribution of the median of the FA values in the ACC ROIs across the three groups.
27 The stars indicate that the measures for the healthy controls are significantly higher
28 ($p < 0,0001$) than for the patients.
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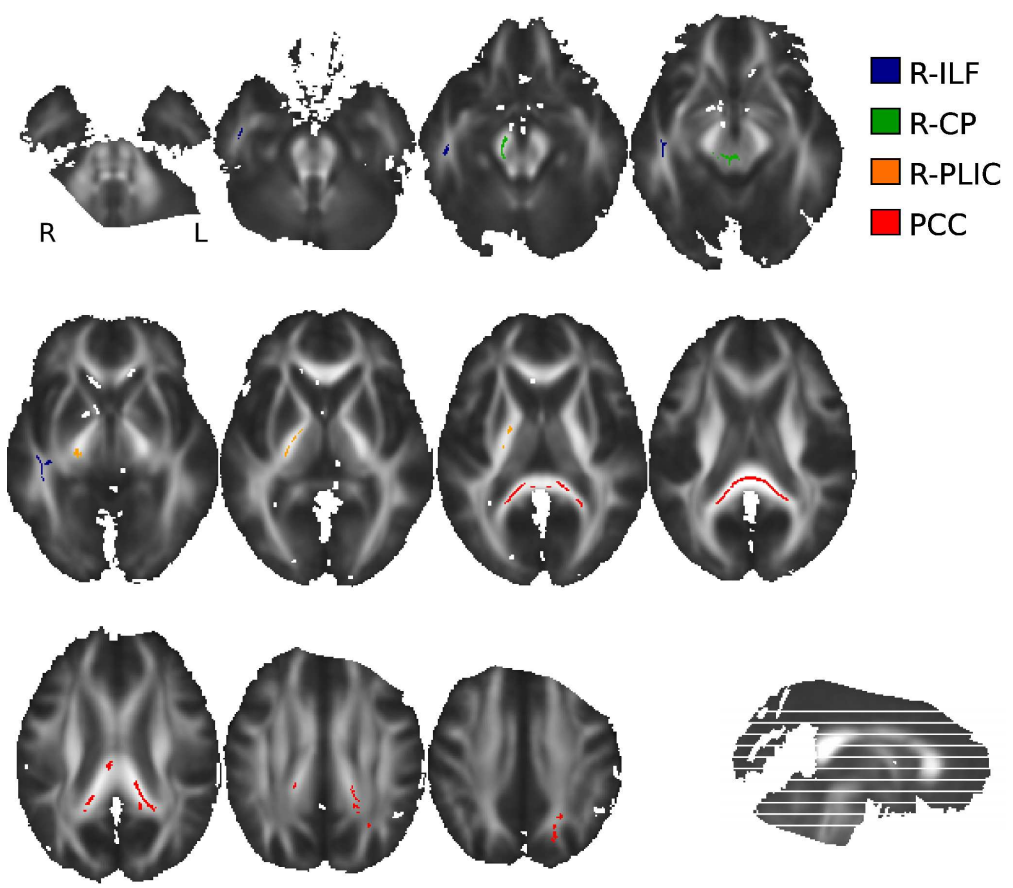
31 **Figure 7:** Bootstrap validation of the LDA classification. The three ROC curves represent the
32 sensitivity function of 1-specificity for various thresholds of the posterior probability p to
33 belong to each class. The squares correspond to the $p = 0.5$ threshold and the circles to the
34 $p = 0.95$ threshold.
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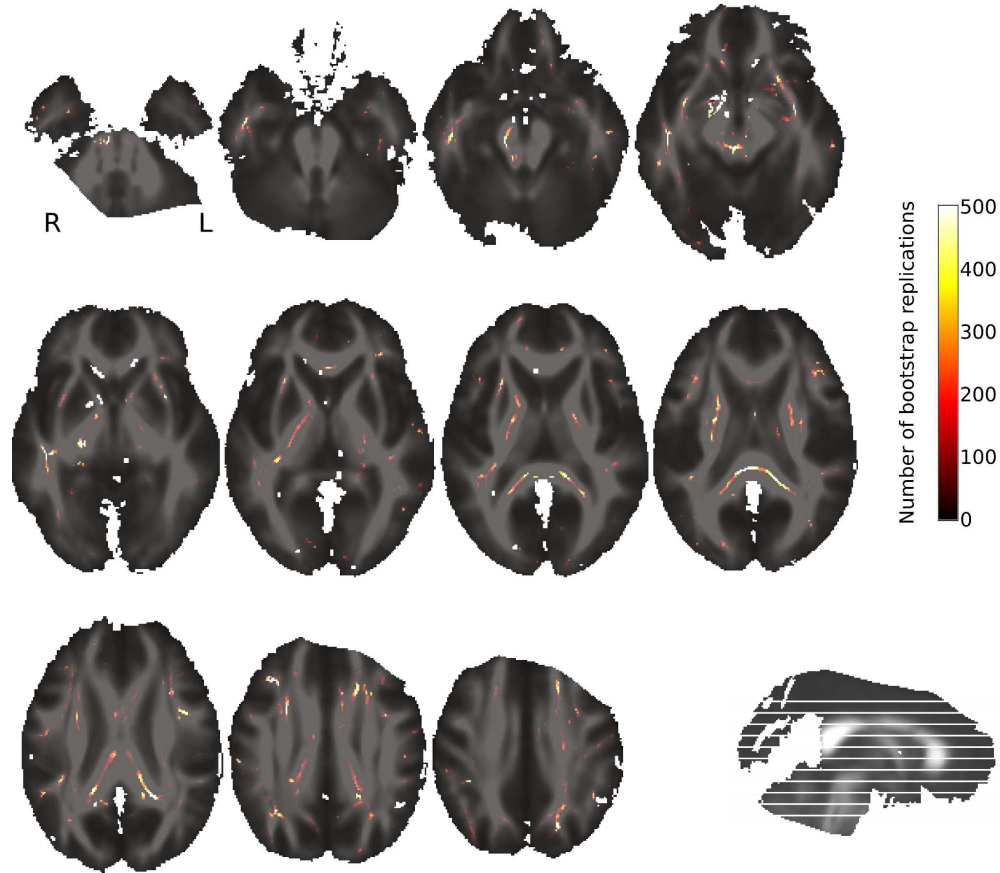
VB-DTI results: orange shows voxels where FA on the skeleton is significantly lower ($p < 0.05$) in unfavorable outcomes than in favorable outcomes. This map is superimposed on the mean of all individual FA images of the patients.



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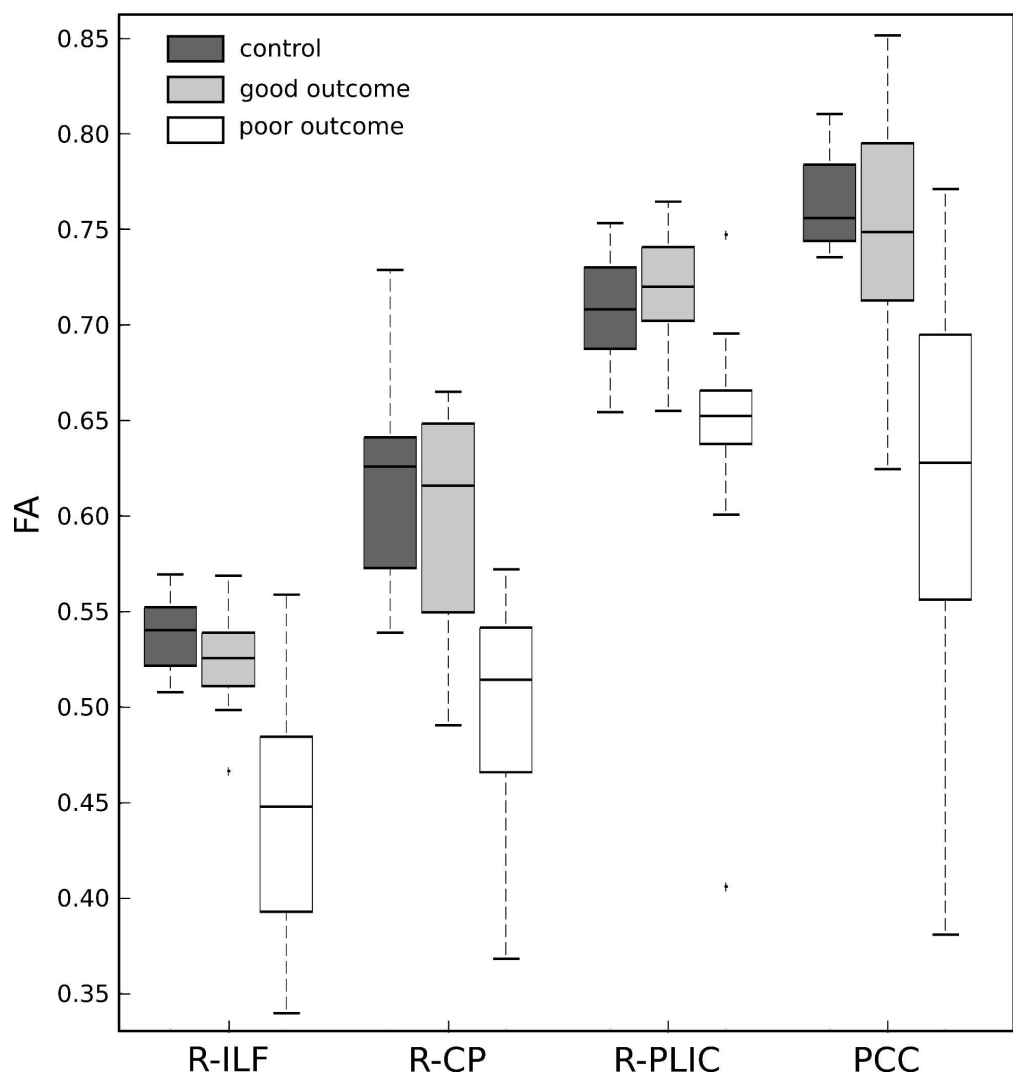
The four regions where FA on the skeleton is significantly lower ($p < 0.05$) in unfavorable outcomes than in favorable outcomes. This map is superimposed on the mean of all individual FA images of the patients. These regions were used to to define FA biomarkers.



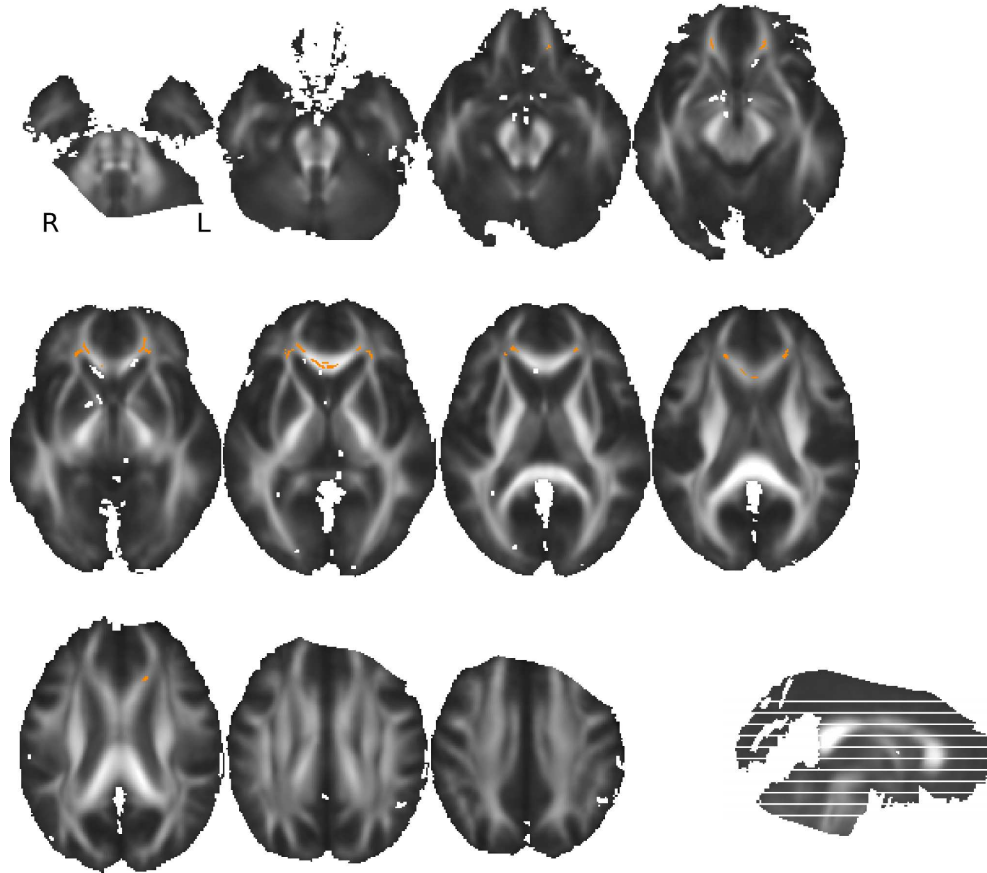
Spatial variability of the ROIs. The mapped score between 0 and 500 represents the number of times a voxel has been selected as a voxel of interest (over the 500 bootstrap repetitions). This map is superimposed on the mean of all individual FA images of the patients.

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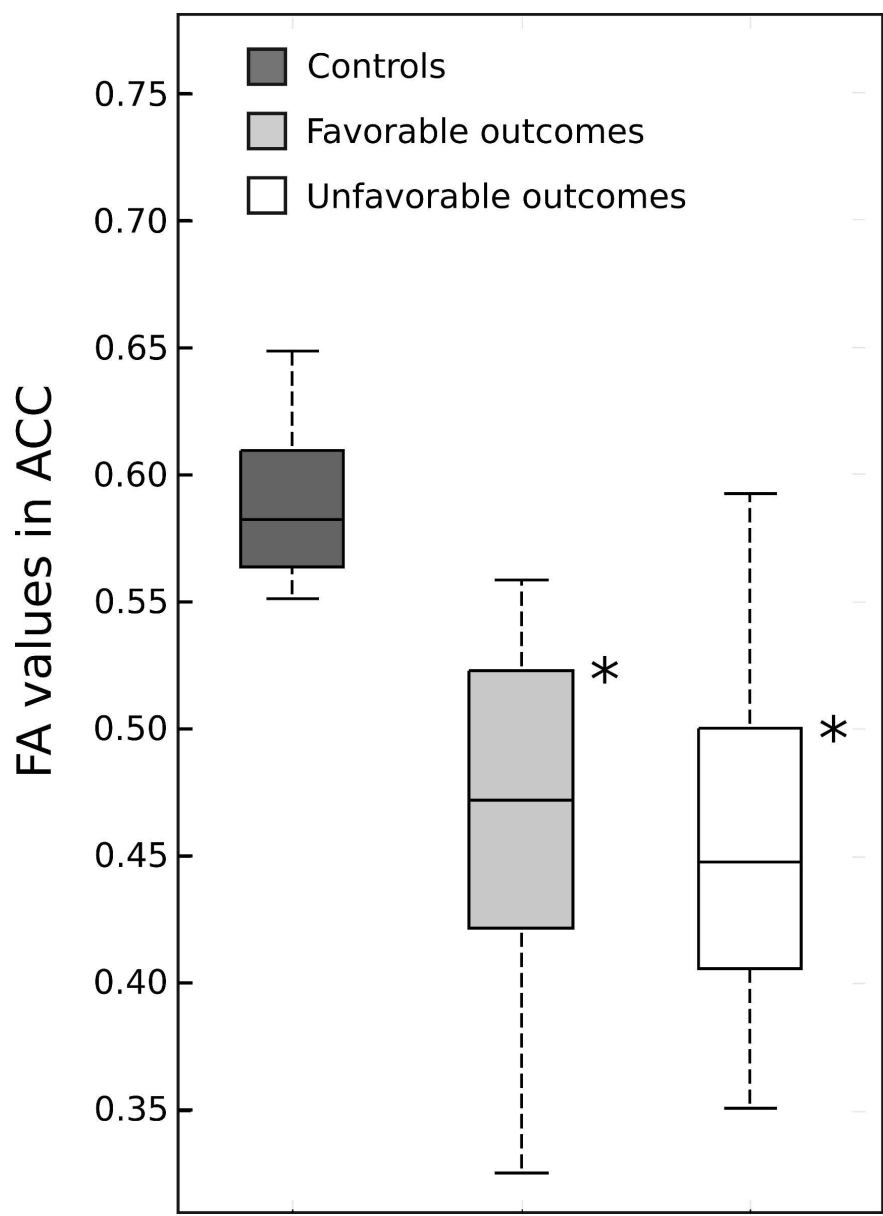


The distribution of the median of the FA values in the four ROIs across the three groups. The star indicates that the measures for the unfavorable outcomes are significantly power ($p < 0,0001$) than for the favorable outcomes and the controls.

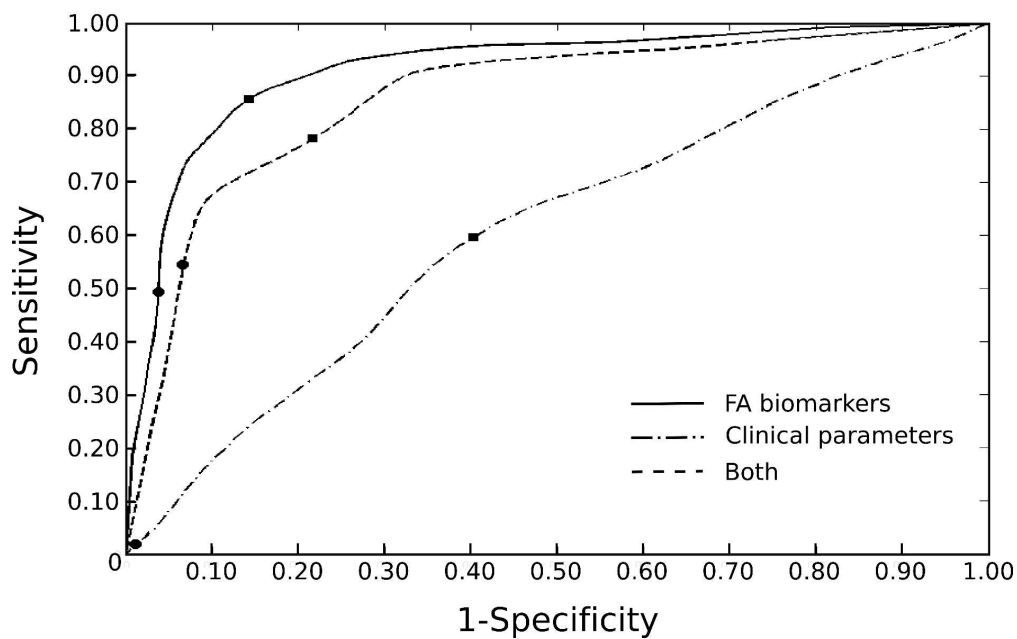


TBSS results: orange shows voxels where FA on the skeleton is significantly lower ($p < 0.05$) in favorable outcomes than in healthy controls. This map is superimposed on the mean of all individual FA images of the patients.

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The distribution of the median of the FA values in the ACC ROIs across the three groups. The stars indicate that the measures for the healthy controls are significantly higher ($p < 0,0001$) than for the patients.



Bootstrap validation of the LDA classification. The three ROC curves represent the sensitivity function of 1-specificity for various thresholds of the posterior probability p to belong to each class. The squares correspond to the $p=0.5$ threshold and the circles to the $p=0.95$ threshold.