Machine Learning Classification of Traumatic Brain Injury Patients and Healthy Controls Using Multiple Indices of Diffusion Tensor Imaging

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Abstract

Background: Diffusion tensor imaging (DTI) indices provide quantitative measures of white matter microstructural changes following traumatic brain injury (TBI). However, there is still insufficient evidence for their use as predictive measures. Recently, there has been growing interest in using machine learning (ML) approaches to aid the diagnosis of many neurological and psychiatric illnesses including TBI. The aim of this study is to examine the potential of using multiple DTI indices in conjunction with ML to automate the classification of healthy subjects and patients with TBI across a spectrum of TBI severity.

Methods: Participants were adult patients with chronic TBI (n=26) and age and gender-matched healthy controls (n=26). DTI images were obtained from all the participants. Tract-based spatial statistics (TBSS) analysis was applied to the DTI images. Classification models were built using principle component analysis (PCA) and support vector machines (SVM). Receiver operator characteristic (ROC) curve analysis and area under the curve (AUC) were used to assess the classification performance of the different classifiers.

Results: The whole-brain white matter TBSS analyses showed significantly decreased FA, as well as increased MD, AD, and RD in TBI patients compared with healthy controls (all p-value < 0.01). The PCA and SVM-based ML classification using combined DTI indices classified TBI patients and healthy controls with the accuracy of 90.5% with an area under the curve (AUC) of 93 +/- 0.09.

Conclusion: This study demonstrates the potential of a joint DTI and ML approach for objective classification of TBI patients and healthy controls.

Introduction

Traumatic brain injury (TBI) is a leading cause of mortality and morbidity worldwide[1]. Individuals with TBI have an elevated risk of developing numerous neurocognitive and psychiatric illnesses [2, 3]. Diffuse axonal injury (DAI) is one of the most common and important pathologic features of TBI [4, 5]. DAI following TBI occurs as a result of acceleration/deceleration trauma to the brain, which results in a shear disruption of the white matter axons [6, 7].

DAI may include extensive microscopic axonal damage, even in the absence of abnormal findings on conventional CT and MR imaging [8]. On the other hand, especially in the case of mild TBI (mTBI), a traumatic accident may result in a psychologically traumatic experience, which can lead to severe stress reactions. In such a case it is often difficult to observe any indication of structural damage on conventional CT and MRI, and it may therefore be difficult to differentiate patient symptoms caused by DAI from those caused by the psychological impacts of the traumatic experience [9]. Unlike conventional imaging techniques, diffusion tensor imaging (DTI) can identify and quantify white matter microstructural changes following DAI, even in the case of mTBI [10–12]. Therefore, DTI has been considered one of the most promising techniques for the study and diagnosis of DAI following TBI.

DTI measures the directional coherence of water diffusion along white matter axons [13, 14]. A variety of parameters can be obtained from a DTI scan (DTI indices), such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). DTI indices reflect the integrity of white matter microstructure and have been extensively applied as neuroimaging biomarkers to study a range of clinical conditions such as multiple sclerosis, Alzheimer's disease, and major depressive disorders. FA measures anisotropic water diffusion within white matter fibers and can be used to indicate axonal structural integrity. Reduced FA is believed to reflect a loss of axonal integrity, indicating possible damage to myelin or the axon membrane and/or decreased axonal coherence. MD describes the average magnitude of water diffusion, regardless of the diffusion direction. Increased MD are thought to reflect overall structural disintegration. FA and MD provide sensitive but not specific measures of white matter microstructural alterations. AD is defined as the diffusion of water parallel to white matter fibers, while RD is the diffusion of water perpendicular to white matter fibers [15]. Both AD and RD are called directionality indices, and they can be used to specifically differentiate axonal injury from demyelination in white matter tracts [16, 17].

Even though many previous studies have used DTI to study TBI, there are currently three main shortcomings that need to be addressed. First, while FA and MD were extensively studied in previous literature, AD and RD have been much less commonly studied [18–20]. Second, to date, few studies have used four DTI indices to investigate whole-brain, white matter changes in TBI patients. Most previous DTI studies focused on studying the main white matter tracts known to be susceptible to damage following TBI (e.g. corpus callosum), rather than studying the whole brain [21–23]. While focusing on susceptible white matter tracts may provide more specific results, it might lead to the loss of information, which might potentially be fatal considering the heterogeneity in the distribution of lesions among patients. The third shortcoming, which may in part be due to the other two shortcomings, is the modest diagnostic accuracy of previous DTI studies; for use as a clinical biomarker of TBI, high diagnostic accuracy is essential [24].

To overcome the aforementioned shortcomings, we used multiple DTI indices to conduct a comprehensive study of white matter alterations in the whole brains of patients with DAI following mild, moderate, or severe chronic TBI. We applied the tract-based spatial statistics (TBSS) method for the DTI indices (FA, MD, AD, and RD) to systematically study DAI-associated changes in white matter tracts across the whole brain. We also used a machine learning (ML) approach to maximally use the DTI indices to classify TBI patients and healthy controls with high accuracy. Recently, there has been growing interest in using Machine Learning (ML) to analyze neuroimaging data to find clinical biomarkers for many neurological and psychiatric conditions [24, 25]. Unlike traditional univariate analysis methods such as voxel-based analyses, supervised ML techniques applying multivariate analyses allow for better predictions and inferences at the level of individuals [26].

When applying ML to neuroimaging data we have to consider the nature of the data and what ML technique is suitable for it. In many neuroimaging studies, the number of observations (subjects) is very low (< 1000) in comparison with the huge number of predictor variables per observation (e.g., over 100

000 voxels in a typical brain scan) [27, 28]. Building a ML or prediction model using high dimensional data may lead to overfitting, resulting in performance degradation and poor generalizability. Therefore, dimensionality reduction is an essential step to improve the prediction accuracy [27]. Principal component analysis (PCA) is a commonly used data-driven non-supervised dimensionality reduction technique. PCA reduces redundant features by linearly transforming correlated variables (e.g. voxels in a neuroimaging scan) into a lower number of uncorrelated variables known as principal components (PCs). High-dimensional neuroimaging data can be transformed into relatively few PCs that maximally explain the variance of the data [29]. PCA has been successfully used for dimensionality reduction in previous neuroimaging classification studies involving schizophrenia, Alzheimer's disease, and major depressive disorder [30].

A support vector machine (SVM) is a supervised ML technique popular in the neuroimaging field, as it can provide a valid classification from high dimensional data [31, 32]. The SVM employs a maximum margin classification algorithm designed to derive the optimal separation between two classes of data (TBI patients group and healthy control group in this study) by identifying a "hyper plane" that crosses the n-dimensional space to separate the training dataset into two pre-defined labels. Each sample within the training dataset is referred to as a vector. The support vectors are defined as the samples that are critical to the positioning of the hyper plane inside the n-dimensional feature space.

In this study, we demonstrate the potential of a joint DTI and ML approach for objective classification of TBI patients and healthy controls. We propose a classification model using combined DTI indices, PCA and SVM that can be used to identify the complex patterns of white matter damage and classify TBI patients and healthy controls with high accuracy.

Material And Methods

Participants

Participants were recruited from the outpatient clinic of the neuropsychology unit at the Department of Psychiatry and the Department of Neurosurgery, Kyoto University Hospital.

Inclusion criteria were: 1) age more than 18 years, 2) an injury sustained through significant trauma; 3) a brain MRI or CT scan showing possible diffuse pathology (without large focal lesions (>10 mm3); 4) the injury occurred ≥ 6 months before the study; 5) ability to give informed consent for participation; 6) ability to undergo MRI. Exclusion criteria were: 1) history of another TBI with altered consciousness; 2) history of drug or alcohol abuse; 3) history of neurological or psychiatric disorder before TBI onset; 4) contraindications to MRI (e.g., implanted metal, claustrophobia). Neuropsychiatrists (UK, TM) specialized in the neuropsychiatric aspects of TBI assessed patients MRI and CT scans and confirmed the information concerning the clinical history and residual symptoms related to the inclusion and exclusion criteria mentioned above.

Twenty-six patients with TBI (20 males, mean age of 40.15 years, standard deviation [SD] 14.93) were recruited to the study. According to the Glasgow Coma Scale (GCS) or Japan Coma Scale (JCS; a measure of the severity of impaired consciousness used in Japan), 5 patients (19.2%) had mild TBI, 2 (7.7%) had moderate TBI, and 19 (73.1%) had severe TBI. The relationship between the JCS score and severity of injury has been explored previously [33]. For comparison purposes, twenty-six age- and sex matched healthy controls (20 males, mean age of 40.08 years, SD 12.82) were recruited to the study.

Imaging acquisition

For DTI, diffusion-weighted volumes were acquired on a 3.0-T whole body scanner (MAGNETOM Tim Trio; Siemens, Erlangen, Germany) using a 40-mT/m gradient and a receiver-only eight-channel phased-array head coil. The scanning parameters were: echo time (TE) = 96 ms, repetition time (TR) = 10 500 ms, matrix = 96 × 96, field of view = 192 × 192 mm, 70 contiguous axial slices of 2.0-mm thickness, 81 non-collinear axis motion-probing gradients, and b = 1500 s/mm2. The b = 0 images were acquired before each set of nine diffusion-weighted images, thus giving 90 volumes in total.

Image processing

DTI data were processed using the FMRIB Software Library (FSL) version 5.2 (FSL; Oxford Centre for Functional MRI of the Brain; www.fmrib.ox.ac.uk/fsl) [34,35]. DTI images were registered to the b = 0 image by affine transformations to minimize distortion due to head motion and eddy currents [35]. Images were then brain-extracted using the Brain Extraction Tool [36]. Using the DTIFIT program, the diffusion tensors were calculated for whole brain volumes and fractional anisotropy (FA) maps, axial diffusivity maps (AD [λ1]), radial diffusivity maps (RD [(λ2+λ3)/2]), and mean diffusivity maps (MD [(λ1+ λ2+λ3)/3]) were generated [37- 40]. MD, AD and RD are in units of mm^2/s, whereas FA is unitless. Tract-Based Spatial Statistics (TBSS) was used for voxel-wise analysis of the DTI indices maps [40]. TBSS is a fully automated whole-brain analysis technique for applying voxel-wise statistics to diffusion indices while minimizing the effects of misalignment that may occur using a conventional voxel-based analysis method [40].

The TBSS procedure included nonlinear registration of all subjects FA images into the common FMRIB58_FA template space [39]. TBSS performs a non-linear registration to align each FA image to every other one and then calculates the amount of warping needed for the images to be aligned. The most representative image is determined as the one needing the least warping for all other images to be aligned to it [41]. The aligned FA images were then averaged to create a 4D mean FA image, which was then subjected to thinning to create a mean FA skeleton representing the center of all white matter tracts, thereby removing partial-volume confounds. The FA skeleton was then thresholded at an FA value of 0.2 to limit the effects of poor alignment across subjects, to exclude areas with extremely low mean FA, and to ensure that grey matter and CSF voxels were excluded from the skeleton. The same non-linear transformation steps were applied to the MD, AD, and RD maps. For statistical analysis, the randomize tool in FSL was used to conduct a non-parametric permutation-based statistics using the Threshold-Free

Cluster Enhancement (TFCE) method with 10,000 permutations to investigate group differences in FA, MD, AD and RD.Voxelwise maps were thresholded at $p < 0.05$ and corrected for multiple comparisons with family-wise error rate (FWE). The significant white matter clusters were identified with reference to the atlas tool JHU ICBM-DTI-81 white matter labels. To qualitatively assess structural difference between TBI patients and healthy controls groups, mean DTI indices for each subject were extracted by averaging FA, MD, AD, and RD for the significant white matter clusters using fslstats tool in FSL.

Dimensionality reduction and feature extraction

PCA was applied to FA, MD, AD, and RD skeletonized maps, in which each voxel represented a variable in the cross validation training dataset, and the same transformation was then applied to the test dataset. A voxel-wise approach was used to combine FA, MD, AD, and RD into one dataset named “ALL”, and PCA was applied to this ALL dataset in the same manner.

Support Vector Machines

A support vector machine (SVM) was used to perform ML analysis using the PCs of the DTI indices. For each DTI index, an SVM classification task was trained to distinguish TBI patients from healthy controls. PCs of the skeletonized maps of each DTI index and the ALL dataset were evaluated. Five-fold cross validation was used to yield an unbiased assessment of the classification method and prevent overestimation. A linear kernel SVM was chosen as a classifier and the hyperparameter (C) of the linear kernel SVM was fixed to 1.0. To evaluate the different classification tasks, the mean accuracy rate and its SD was calculated for the five-fold cross validation for each classification task (Fig.1). To validate the robustness of the classification results, 1000 times permutation tests were conducted to assess the statistical significance of the classification accuracy scores. To further estimate the performance of the different classification task, receiver operating characteristic curves (ROC) were plotted for each classifier and the areas under the curves (AUC) were obtained. The AUC quantifies the overall ability of the classifier to distinguish between the TBI and the healthy subjects. The ML analysis including feature extraction was conducted in Python using the Python library scikit-learn.

Results

Whole brain TBSS analysis of multiple DTI indices

Whole-brain TBSS analysis of the DTI diffusion indices showed a major disruption in the white matter microstructure in the TBI patients group. Significantly decreased FA and increased MD, AD, and RD were present in several major white matter tracts in the TBI group compared with the healthy control group (corrected p value < 0.01) (Fig. 2 & Fig.3). Fig.4 showed boxplots graphical representation for the mean values and standard deviations of FA, MD, AD, and RD for TBI patients and healthy control groups.

Dimensionality reduction and feature extraction

PCA was applied to FA, MD, AD, RD and ALL during cross validation in both training and test datasets. Table 1. Shows average number of PCs that explained 90% of the variance between the TBI and healthy controls group across the five cross validation folds.

SVM Classification

The ML multivariate analysis using SVM with five-fold cross validation was able to classify the TBI patients and healthy control groups using PCs of the skeletonized maps of each DTI index (number of voxels = 97698) and the ALL dataset (number of voxels = 390792). High accuracy (90.5%) was achieved by the classifier trained on the combined indices dataset (ALL) and (86.5%) the classifier trained on the FA maps (all p-value < 0.01) (Table 1).Table 1 below shows the average number of PCs and the mean accuracy score for each classifier.

Table 1: Mean accuracy score for each classification task

Classification task	Average number of PCs	Accuracy (+/- SD)
FA maps	32	0.865 (+/- 0.052)
MD maps	29.4	0.829(+/- 0.073)
AD maps	33.6	0.845(+/- 0.114)
RD maps	29.4	0.845(+/- 0.114)
ALL maps	31.6	0.905(+/- 0.096)

FA: Fractional anisotropy; MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity; ALL: voxel-wise combination of FA, MD, AD, and RD in one dataset; PCs: Principle components; SD: standard deviation

ROC curves for each classifier are shown in Fig. 5. The AUCs were 93% and 89% for the ALL and FA classifier tasks respectively.

Discussion

DTI indices provide quantitative measures of white matter microstructural changes following TBI. However, there is still insufficient evidence for their use as predictive measures. In the current study we studied the potential of using whole-brain multiple DTI indices in conjunction with ML algorithms as a predictive measure to automate the classification of TBI patients and healthy controls. We applied DTI to 26 subjects with chronic TBI and 26 age- and gender-matched healthy controls to obtain values for multiple diffusion indices within the white matter tracts of each subject.

The TBSS analysis of the DTI indices showed significantly decreased FA and increased MD, AD, and RD in the TBI patients in comparison with the healthy control subjects. These results are consistent with previous studies [42-48]. Many studies have reported reduced FA in chronic moderate to severe TBI, even in the absence of visible lesions on conventional CT and structural MRI [8,46,47]. Although FA and MD changes have been extensively reported in TBI, only a limited number of studies compared AD and RD between chronic TBI patients and healthy controls. Kinnunen et.al. conducted a TBSS analysis on 28 TBI patients (8 mTBI and 20 moderate/severe TBI) and 26 healthy controls. They found that TBI patients showed large areas of reduced FA and increased MD, as well as increased AD and RD [48]. Perez et al. studied AD and RD in 16 TBI patientswith chronic moderate to severe TBI. Their results demonstrated disproportionally high AD and RD in TBI patients [49]. Cubon et al. studied a total of 39 subjects with chronic TBI (22 mTBI and 17 moderate/severe TBI), and in both a whole-brain analysis and one using specific regions of interest, they found that moderate to severe TBI patients had increased AD and RD [50].

DTI indices derived from the diffusion images were used together with PCA and SVMs to classify the TBI patients and healthy controls. Five classification models were examined, and the model using the combined indices (ALL) was found to be the most accurate with 90.5% accuracy and a high AUC (93%, SD 0.09). Previous studies that have used ML in conjugation with DTI images to differentiate TBI patients from healthy controls have obtained different approaches. These studies used different ML statistical techniques and different DTI parameters and obtained variable levels of accuracy [51,52]. Mitra et al. applied a decision ensemble ML technique with 10-fold cross validation to DTI data (FA and Network-Based Statistics [NBS]) and revealed an overall classification accuracy of 68% [53]. Lui et al. used other MRI-based imaging parameters in addition to DTI (T1 and rs-fMRI) and tested several different classification approaches on 23 mild TBI patients and 25 healthy controls. They obtained an accuracy of 86% with a multilayer perceptron (neural network) using only relevant variables, and 80% with a Bayesian network using all variables [54]. Fagerholm et al. applied linear SVM analysis to DTI graph metrics of white matter connectivity data from moderate/severe TBI patients and revealed an overall model accuracy of 93.4% [55]. Our model was able to classify TBI patients and healthy controls with 90.5% accuracy. Although Fagerholm et al. obtained higher accuracy than our model, a practical advantage of our method is that it uses well-known DTI indices (FA, MD, AD, and RD), rather than graph metrics of white matter connectivity.

Limitations

The findings of this study should be considered in the context of certain limitations. First, in the case of inaccurate registration of individual images into standard space, partial volume effects can lead to abnormal DTI indices. To eliminate any likelihood of such an error, we applied TBSS preprocessing to minimize this issue and visually checked the registration accuracy. There was a strong correlation between the different DTI indices, and the high classification performance may reflect the underlying variance shared across the different diffusion measures. DTI measures change over time after TBI, and our results are therefore likely to be specific to the chronic phase (> 6 months) post-injury. Investigating

TBI in the chronic phase might potentially be problematic, as patients frequently show some degree of brain atrophy. If this is the case, changes in DTI indices such as lower FA may be due to partial volume effects such as contamination of measurements by cerebrospinal fluid. Again, using the TBSS preprocessing approach should have minimized this potential issue, as the white matter was skeletonized and only the central points of tracts were studied, greatly reducing the risk of partial volume effects [28, 52].

Second, MD is mathematically related to AD and RD and combining them together in one dataset (ALL) might affect the classification performance. However, we combined them together with FA as different DTI indices convey different aspects of white matter microstructure which are potentially complementary for the discrimination power of the classification model [56-59]. Moreover, applying PCA prior to classification removed any redundant information and intercorrelation in the combined DTI indices dataset [59].

Third, our sample size was small, which may have affected the generalizability of our findings, especially regarding mTBI. Therefore, future work with larger patient groups is needed to build a more generalizable predictive model. It is important to note that the sample studied were predominately moderate to severe TBI as recruitment was limited to TBI patients who attend the outpatient clinic of the neuropsychology unit. Although these patients may have detectable abnormalities on clinical MRI, it is important to validate an automated method that can be used as a predictive tool for a wide spectrum of TBI severity.

Fourth, our model needs to be validated against traditional methods; therefore, future work will focus on the statistical validation of the model. Our model did not include many important clinical and social outcomes, and future work should explicitly model other clinical measures such as acute imaging changes, injury severity, neurocognitive consequences, and measures of gray matter atrophy. Finally, our study is cross-sectional, and a longitudinal study would provide better predictions for a clinical application.

Conclusions

We conducted a comprehensive DTI study of patients with mild, moderate, or severe TBI in the chronic stage. Our study results suggest that ML can be used with DTI indices as a predictive tool for the automated classification of TBI.

Declarations

Ethics approval and consent to participate

This study was approved by the Committee on Medical Ethics of Kyoto University and all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later

amendments or comparable ethical standards. Written informed consent was obtained from all individual participants included in the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

All authors contributed to the study conception and methodology. Conceptualization, methodology, investigation, formal analysis and visualization were performed by Hiba Abuelgasim Fadlelmoula Abdelrahman. Gaku Fujimoto, Ubukata Shiho, Ueda Keita and Toshiya Murai have contributed to the conceptualization, methodology and investigation. Naoya Oishi and Toshihiko Aso have contributed to the validation and formal analysis. The first draft of the manuscript was written by Hiba Abuelgasim Fadlelmoula Abdelrahman and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Abbreviations

TBI: Traumatic brain injury

DAI: Diffusion axonal injury

DTI: Diffusion tensor Imagining

FA: Fractional anisotropy

MD: Mean diffusivity

AD: Axial diffusivity

RD: Radial diffusivity

ALL: Voxel-wise combination of FA, MD, AD, and RD in one dataset

TBSS: Tract-based spatial statistics

TFCE: Threshold-Free Cluster Enhancement

FEW: Family-wise error rate

ML: Machine Learning

PCA: Principle component analysis

SVM: Support vector machine

PCs: Principal components

GCS: Glasgow Coma Scale

JCS: Japan Coma Scale

ROC: Receiving operating curve

AUC: Area under the curve

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Figures

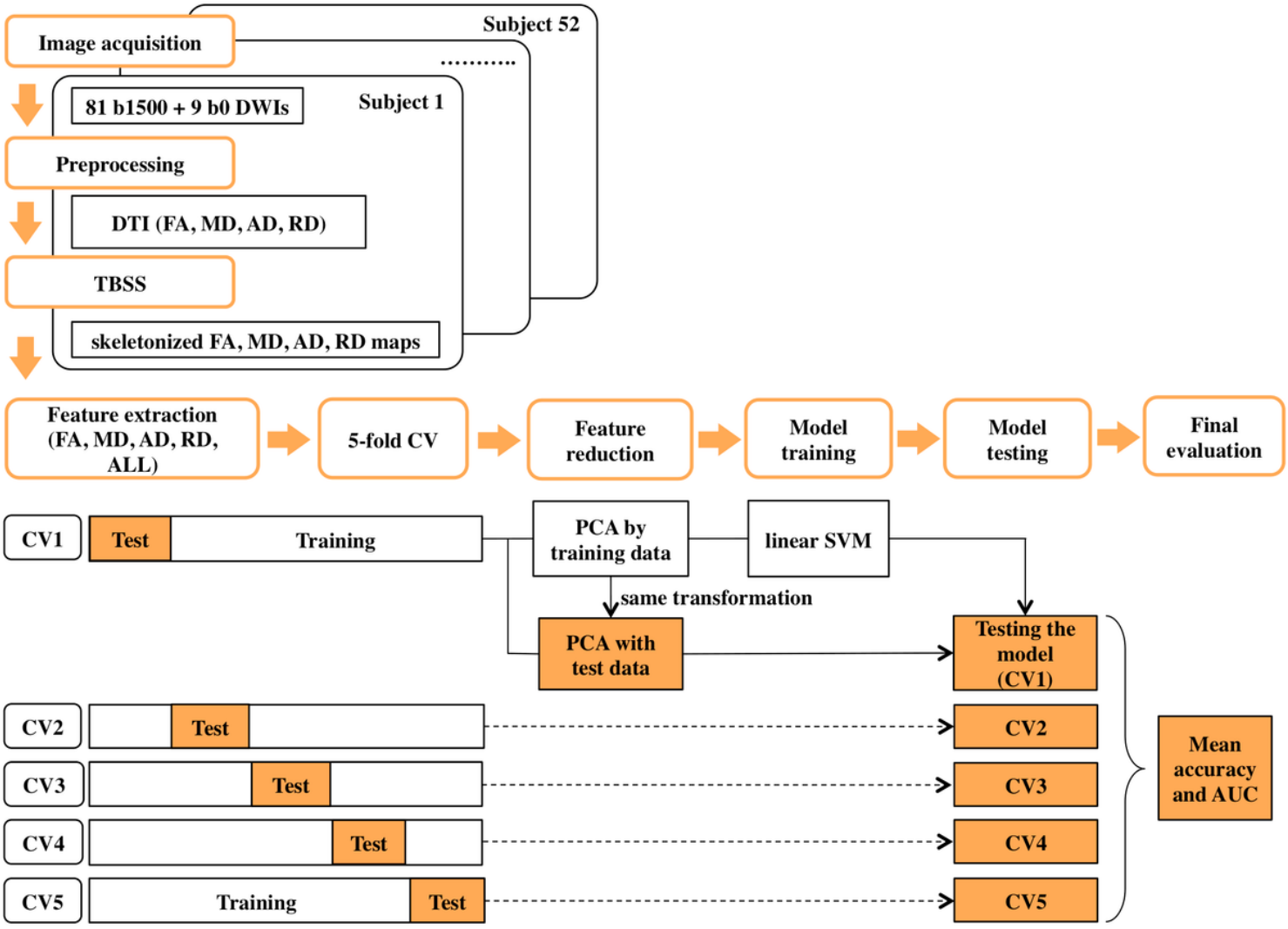

Figure 1

Methods overview. Image acquisition: images were acquired using a 3.0-T scanner. Preprocessing: using the FMRIB Software Library (FSL) and resulted in DTI indices images (Fractional anisotropy (FA), mean

diffusivity (MD), axial diffusivity (AD), radial diffusivity (RD)). TBSS analysis generated skeletonized maps. Features extraction: by extracting mean values of FA, MD, AD, RD and ALL (voxel-wise combination of FA, MD, AD, and RD) from each subject. Five-fold cross validation (CV) for each classification model for model training and model testing. Principle component analysis (PCA) applied for both training data ad testing data during CV. Final evaluation: using classification performance estimator.

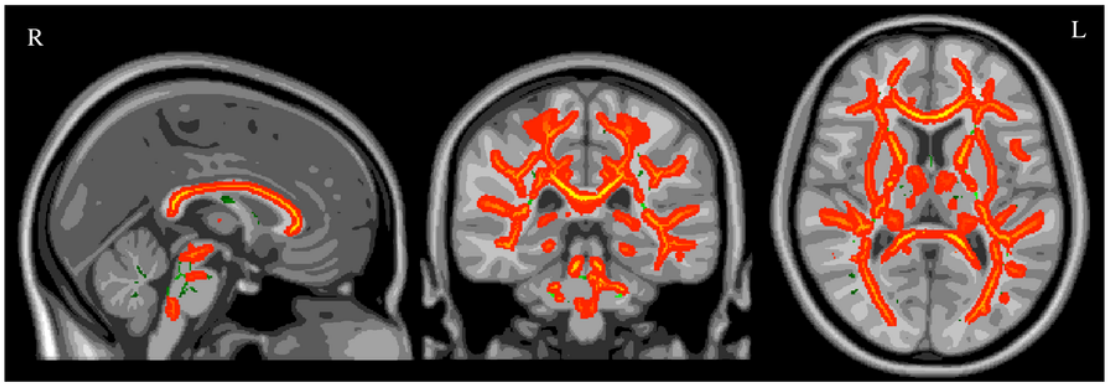

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Figure 2

TBSS analysis showing significant decrease in FA between TBI patients and healthy controls. Voxels with a significant TBI < HC difference are shown in red (corrected p value < 0.05) and yellow (corrected p value < 0.01). The mean FA skeleton threshold with a range of 0.2–0.8 is also shown in green. R = right, L = left

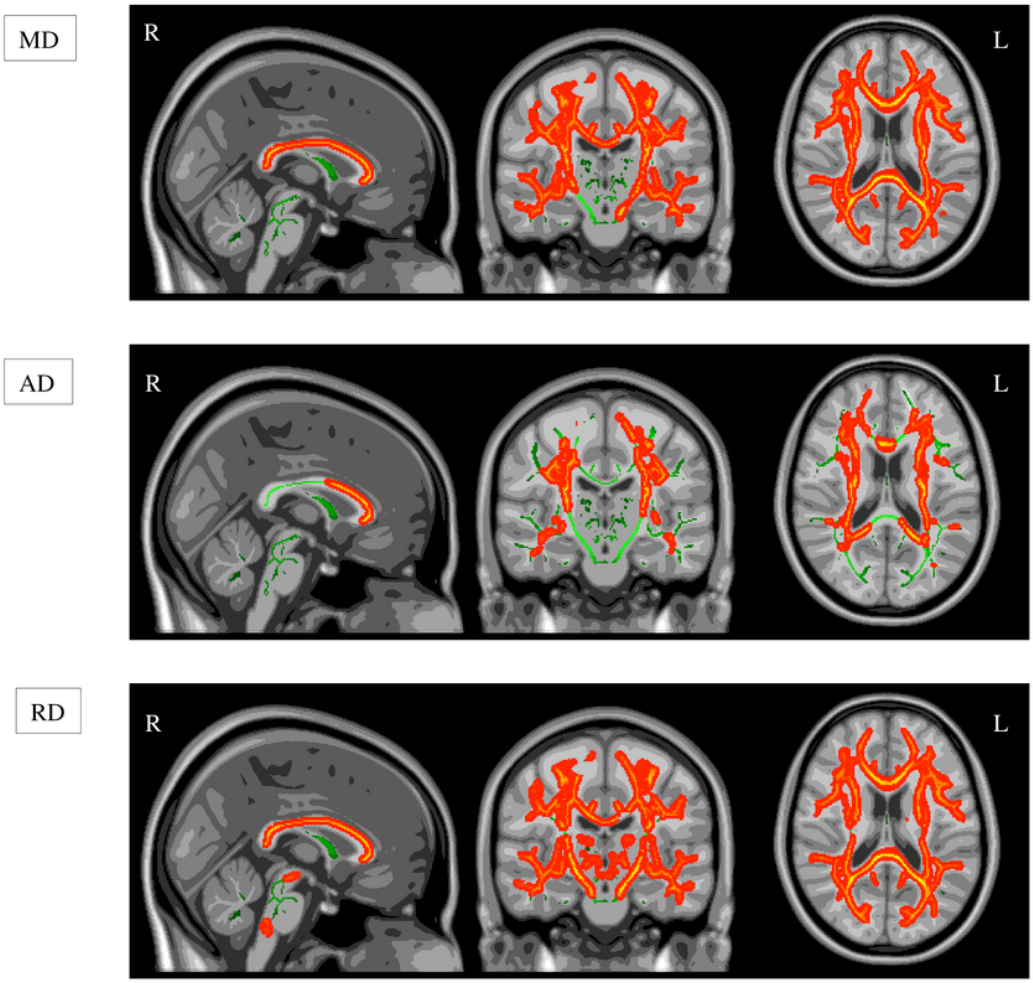

Figure 3

TBSS analysis showing significant increases in MD, AD, and RD between TBI patients and healthy controls. Voxels with a significant TBI > HC difference is shown in yellow (corrected p value < 0.01). MD: mean diffusivity; AD: axial diffusivity; RD: radial diffusivity .The mean FA skeleton is displayed in green for index values of 0.2–0.8. R = right, L = left

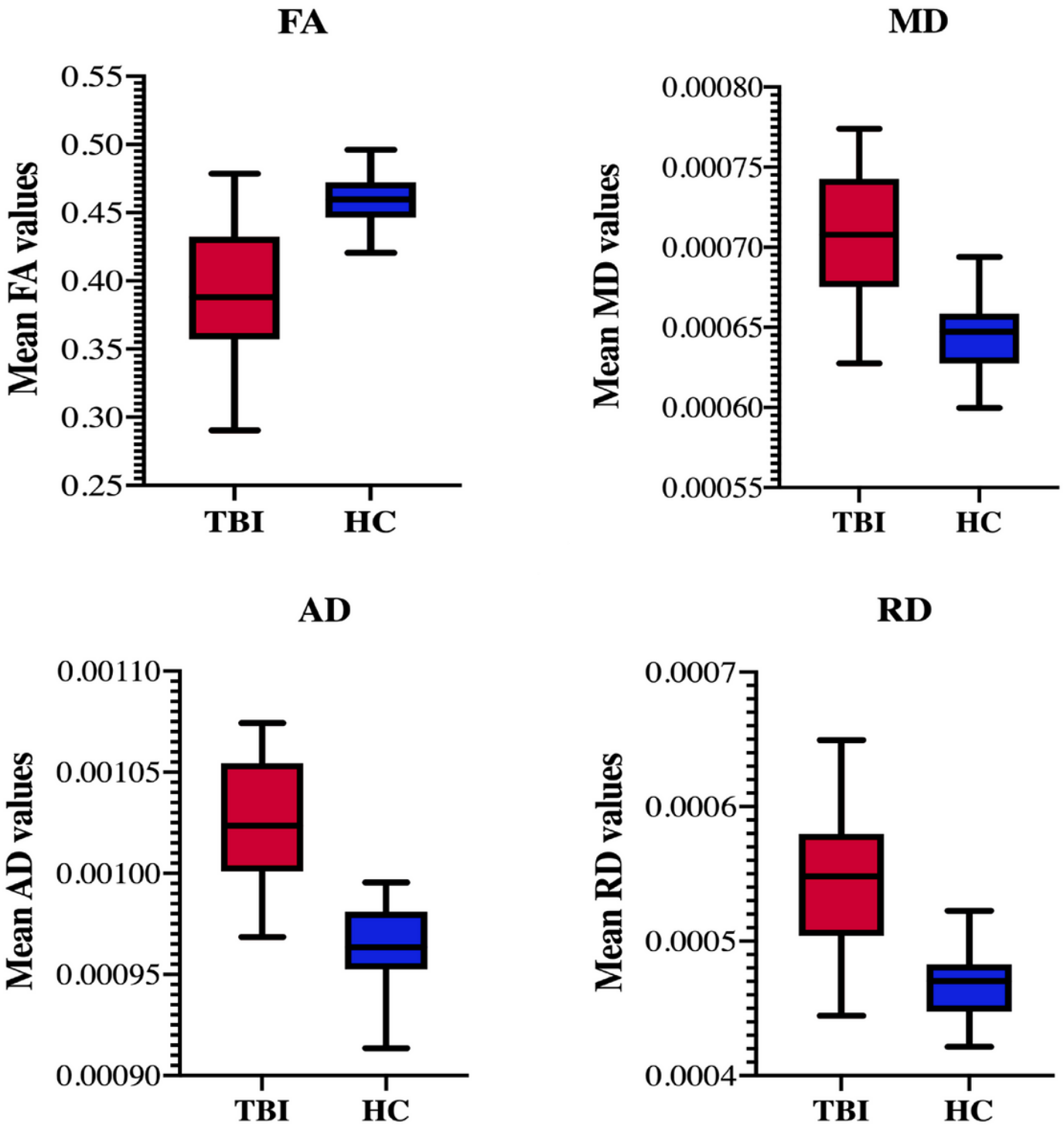

Figure 4

Differences in the Diffusion Tensor Images (DTI) indices. Mean values of Fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) were extracted from each subject in the TBI patients and healthy controls (HC) groups. MD, AD and RD are in units of mm2/s. The horizontal line in the box plot indicates the group mean and the box indicates the upper and lower quartiles, with the vertical lines representing the minimum and maximum values.

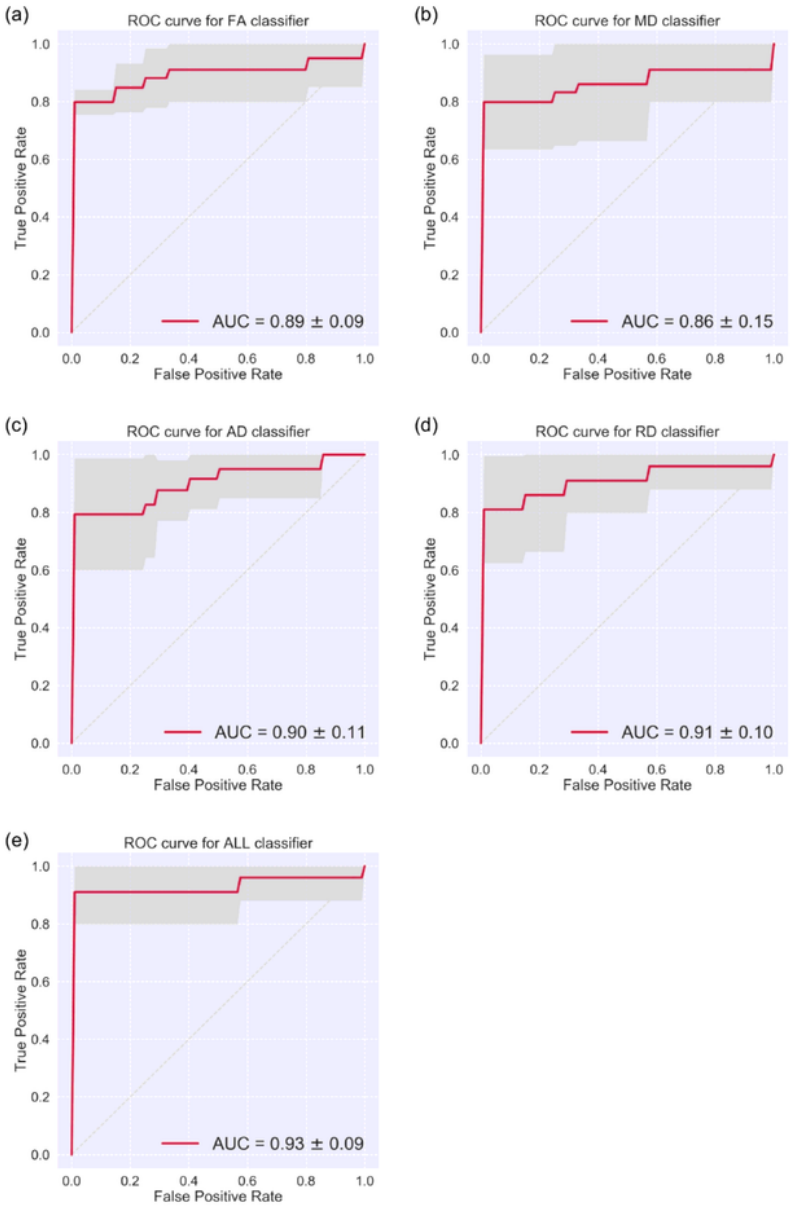

Figure 5

Receiver operating characteristic curves (ROC) for classification of TBI patients and healthy controls. a) Classification using skeletonized fractional anisotropy (FA) maps, (b) classification using skeletonized mean diffusivity (MD) maps, (c) classification using skeletonized axial diffusivity (AD) maps, (d) classification using skeletonized radial diffusivity (RD) maps, (e) classification using combined indices (ALL). AUC: area under the curve