Diffusion Magnetic Resonance as the Basis of Novel Biomarkers Using Multidimensional Statistics in the Brain

PhD thesis

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Table of contents

List of abbreviations

2D Two Dimensional

3D Three Dimensional

3T Three Tesla

ACE Addenbrooke's Cognitive Examination

AD Alzheimer's Disease

ADC Apparent Diffusion Coefficient

AFROC Alternative Free-Response Receiver-Operator Characteristics

aMCI Amnestic Subtype of Mild Cognitive Impairment

ANOVA Analysis of Variance

AUC Area Under the Curve

BOLD Blood Oxygen Level Dependent (signal)

CHARMED Composite Hindered and Restricted Model of Diffusion

CNR Contrast–to–Noise Ratio

CNS Central Nervous System

CSF Cerebrospinal Fluid

CSD Constrained Spherical Deconvolution

D^2 Squared Mahalanobis–Distance

DARTEL Diffeomorphic Anatomical Registration using Exponentiated Lie Algebra

DDF Diffusion Displacement Function

DKI Diffusional Kurtosis Imaging

dMRI Diffusion Magnetic Resonance Imaging

DNT Disembryoplastic Neuroepithelial Tumor

DRE Drug Resistant Epilepsy

DSI Diffusion Spectrum Imaging

DTI Diffusion Tensor Imaging

DWI Diffusion Weighted Imaging

EPI Echo Planar Imaging

FA Fractional Anisotropy

FCD Focal Cortical Dysplasia

FDR False Discovery Rate

FLAIR Fluid Attenuated Inversion Recovery

fMRI Functional Magnetic Resonance Imaging

fODF fiber Orientation Distribution Function

FOV Field Of View

FPR False Positive Rate

FWE Family–Wise Error Rate

FWHM Full Width at Half Maximum

GLM General Linear Model

GM Grey Matter

HARDI High Angular Resolution Diffusion Imaging

HTP Heterotopia

HME Hemimegalencephaly

JHU Johns Hopkins University

LEAT Long–Term Epilepsy–Associated Tumor

MD Mean Diffusivity

MCI Mild Cognitive Impairment

MCD Malformation of Cortical Development

MNI Montreal Neurological Institute

MMSE Mini Mental State Examination

MRI Magnetic Resonance Imaging

naMCI Non–Amnestic Subtype of Mild Cognitive Impairment

NODDI Neurite Orientation Dispersion and Density Imaging

PAL Paired Associates Learning

PET Positron Emission Tomography

PFGSE Pulsed Field Gradient Spin Echo

PMG Polymicrogyria

QSI q–Space Imaging

RAVLT Rey Auditory Verbal Learning Test

RD Radial Diffusivity

RESTORE Robust Estimation of Tensors by Outlier Rejection

ROC Receiver–Operator Characteristics

ROI Region of Interest

SD Standard Deviation

SE Spin Echo

SMVND Standard Multivariate Normal Distribution

T_1 and T_2 Characteristic Relaxation Time for Longitudinal and Transverse Magnetization

TBI Traumatic Brain Injury

TBSS Tract–Based Spatial Statistics

TFCE Threshold–Free Cluster Enhancement

TE Echo Time

TI Inversion Time

TPM Tissue Probability Map

TPR True Positive Rate

TPRB True Positive Rate Binary

TR Repetition Time

VBA Voxel–Based Analysis

VBM Voxel–Based Morphometry

VLOM (Verbal Fluency + Language Score / Orientation + Memory Score) Ratio in the ACE

VLPFC Ventrolateral Prefrontal Cortex

WM White Matter

I. Introduction

1. Foreword

The development of magnetic resonance imaging (MRI) in the last two decades have propelled the investigation of the central nervous system (CNS) at an unprecedented rate. With the increasing availability of high–quality equipment and the inventions of novel imaging and processing techniques, MRI has been pushed to the forefront of brain research, facilitating several large–scale initiatives, such as the Human Connectome Project [1-3], the Human Brain Project [4], or the UK Biobank Project [5], and imaging was also given due attention in the Hungarian Brain Research Program (NAP).

The ever–growing amount of multimodal brain imaging data, especially with the introduction of diffusion and functional MRI, has been driving the development and use of novel processing and statistical methods. Since different modalities, even distinct MR contrast mechanisms, provide complementary information on brain structure and function, methods combining data from various approaches could aim for more accuracy and sensitivity by leveraging their advantages.

The work behind the present Thesis was aimed at developing methods and new biomarkers using combinations of state of the art neuroimaging techniques with diffusion MRI. Although the machine learning–based methods for image processing and analysis (some of which are referred to with the alluring term 'radiomics'), that received an exponentially growing interest in the past few years are promising optimized, data–based, automated feature selection, their general use is still hampered by, among other factors, the need for vast amounts of well–annotated training data. The author firmly believes that knowledge–driven studies addressing specific research questions, such as the ones presented in this Thesis, still hold merit, at least by forming basis for and interpreting the results of such endeavors.

In the first study of the thesis, conventional whole brain two sample parametric statistics and correlation analyses, followed by subsequent white matter region–level analyses were used to identify the brain structures where mild cognitive impairment inflicts substantial alterations on the diffusion profile, and measurements from these

structures were fed into stepwise logistic regression. Our results demonstrated that combining volumetry measurements from anatomical scans with robust region–level diffusion tensor metrics significantly aids distinguishing patients from healthy subjects, and improves the differentiation between amnestic and non–amnestic subtypes of mild cognitive impairment even more.

In the second study a novel approach was proposed and demonstrated for single subject whole brain voxel–level analyses, based on the squared Mahalanobis–distance with analytically derived critical values. The problem of identifying epilepsy–related structural abnormalities was implemented as a data–driven detection problem, treating diffusion tensor eigenvalues from lesion voxels as outliers compared to the distribution derived from healthy controls. The expected detection rate and sensitivity to different effect strengths and lesion volumes was explored through simulations, and verified in select cases with malformations of cortical development.

2. Diffusion Magnetic Resonance Imaging

2.1 Basics of diffusion MRI

Diffusion magnetic resonance imaging (dMRI) is a general term referring to a group of methods widely used for the non–invasive examination of biological samples and porous materials [6-8]. The term diffusion in dMRI refers to the random thermal motion of water molecules in the extracellular space, described by Einstein's theory: the ensemble average translation is proportional to the elapsed time, and the ratio is called the diffusion coefficient:

$$< (\boldsymbol{r'} - \boldsymbol{r})^2 >= 6Dt \qquad (Eq.\,1)$$

By using spatially varying magnetic fields (referred to as diffusion encoding gradients), the magnetic resonance (MR) signal can be made sensitive to the microscopic motion of water molecules [9, 10]. An 'encoding gradient' means that the magnetic field component parallel to the polarizing field (B_0) changes linearly across the sample space. This is achieved by generating additional magnetic fields much smaller than B_0, using coils with special geometry. The gradient of the parallel component, denoted as **g,** describes the change in magnetic field along the direction of the pulsed magnetic field. By employing the encoding gradient, the Larmor frequencies (ω) of the nuclear magnetic spins of water molecules (at coordinates **r**) also vary linearly along the direction of **g**:

$$\omega(\boldsymbol{r}) = \gamma B_0 + \gamma \boldsymbol{g} \cdot \boldsymbol{r} \qquad (Eq.\,2)$$

where γ is the gyromagnetic ratio. The use of the gradient over an evolution time t results in an accumulated phase shift dependent on the position: $\Delta\varphi = \exp(i\gamma \boldsymbol{g} \cdot \boldsymbol{r}t)$.

In practice, most diffusion–weighted MR sequences follow the Stejskal–Tanner encoding scheme [11] with a spin echo (Fig 1).
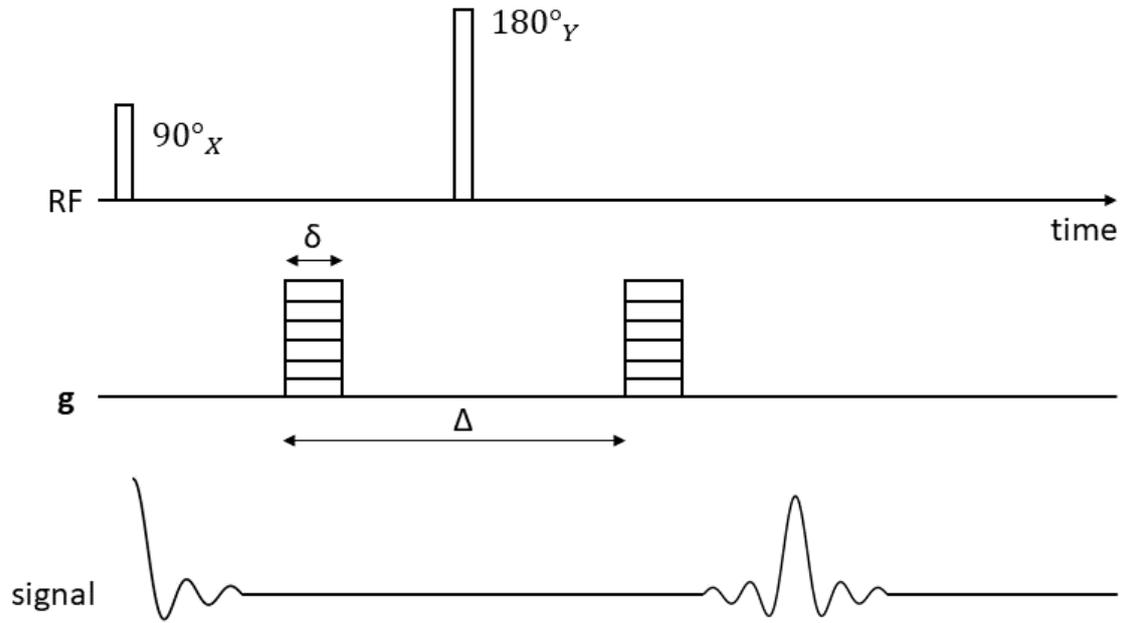
Fig 1 The Stejskal–Tanner diffusion encoding scheme

Two identical diffusion encoding gradients (**g**) are used, with pulse length δ and diffusion time Δ. The 180° RF pulse inverts the phase shift accumulated during the first gradient, thereby the second gradient effectively rewinds the phases for stationary spins, but displacement along the direction of the gradient results in remaining phase error.

Diffusion encoding is achieved by two identical pulsed gradients preceding and following a *180°* spin–echo (SE) pulse. The SE–pulse inverts the phase shift resulting from the first gradient, so the second one completely recovers the phase for stationary spins. For moving spins, with displacement R along the direction of the gradients, the remaining phase error is $\Phi = \gamma G \delta R$, with gradient pulse strength G = |**g**|, and pulse length δ. The signal attenuation in a pulsed field gradient spin echo (PFGSE) sequence with short, rectangular gradient pulses and echo time TE, as shown in [11], is:

$$A(TE) = \exp\left[-\gamma^2 G^2 D \delta^2 \left(\varDelta - \frac{\delta}{3}\right)\right] \qquad (Eq.\,3)$$

Parameters describing the diffusion encoding are generally merged in order to simplify the equation, defining the so–called *b*–value:

$$b = \gamma^2 G^2 \delta^2 \left(\varDelta - \frac{\delta}{3}\right) \qquad (Eq.\,4)$$

11

As diffusion means the flux of particles through a surface during a given period of time, its' dimension is in the form of [area/time]. In order for the exponent $-bD$ to be dimensionless, b is expressed as [time/area]. In practice, b–values are given in units of s/mm^2, in the range of $0 - 10000$. From the attenuated signal (S_b) corresponding to a given b–value, and a reference measurement (S_0) without diffusion encoding, the apparent diffusion coefficient (ADC) along the direction of the gradient can be calculated:

$$ADC(b) = \frac{\ln\left(\frac{S_b}{S_0}\right)}{b} \qquad (Eq.\,5)$$

It is important to note, that the mono–exponential signal attenuation in (*Eq.3) is* only accurate for rectangular gradient pulses and *free* diffusion. In practice, gradient shapes are trapezoidal and the b–values given by MR scanners are calculated slightly differently, accounting for the finite rise times and the auxiliary effects of imaging gradients as well. Free diffusion means that the displacement of water molecules can be described as a simple Gaussian process (i.e. the probability distribution of spin displacement can be described with a three dimensional Gaussian function). Strictly, this is only true for pure, homogenous liquid samples with infinite size, but the approximation also holds for water molecules in the extracellular space with most b–values used in human studies, except for those specifically chosen to measure the non–Gaussian behavior of the dMRI signal (see subsection 2.2.3).

2.2 Diffusion MRI approaches in neuroimaging

Even though diffusion only results in displacements on the microscopic scale, the degree, at which water molecules can move in the three–dimensional space of the extracellular environment may be hindered due to the physical arrangement of obstacles in one, two, or all three directions, resulting in restricted, and in many cases anisotropic diffusion [12]. Therefore, the measured signal attenuation in biological samples reflects properties of tissue microstructure [6-8]. Measurement and data processing approaches can be described according to the level of information extracted about the diffusion pattern. By measuring ADC–values in several directions, one can define the diffusion profile as a three dimensional surface describing the orientation distribution of the observed displacement in each voxel (Fig 2).
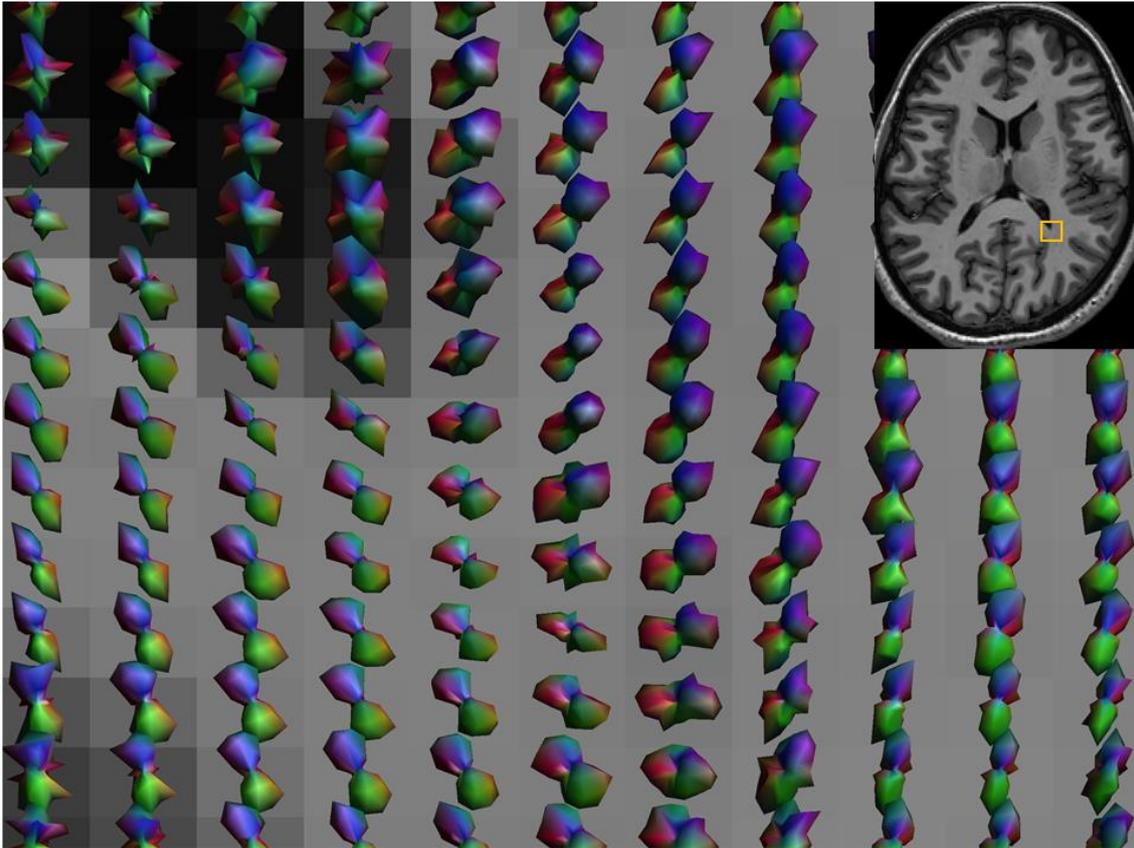
Fig 2 Diffusion profiles of several voxels in the deep parieto–occipital white matter

Apparent diffusion coefficients in each measured direction can be used to construct 3D surfaces, visualizing the orientation distribution of the observed mean displacement of extracellular water molecules. The difference between white matter structures with a single main orientation (e.g. the callosal fibers on the middle on the left side), with two or three orientations (on the bottom in the middle and the right side), in gray matter with no clear maxima (lower left corner), and in the cerebrospinal fluid (CSF – upper left corner) can be measured and visualized.

2.2.1 Diffusion weighted imaging

The simplest approach of dMRI, called diffusion weighted imaging (DWI), quickly gained interest in the clinical field for its superior sensitivity detecting cerebral ischemia through the restricted diffusion signal of cytotoxic edema, appearing in minutes after the occlusion [13]. DWI has also been proven useful in onco–radiology. In DWI, diffusion–encoding gradients are applied separately in three perpendicular directions; restricted diffusion can be identified as high signal intensity after averaging the corresponding images. Due to averaging, directional, and therefore anisotropy information is not extracted; DWI can be viewed as measuring only the volume enclosed by the diffusion profile (with the three orthogonal directions, the corresponding surface is a cuboid). By

acquiring a reference image and calculating the ADC–values from the averaged images, other biological and physics–related phenomena (e.g. differences in T_2–relaxation times) can be disentangled from the effects of the diffusion process.

2.2.2 Diffusion tensor imaging

The most widely known (and simplest) technique, capable of handling anisotropy information, used in both clinical neuroradiology and for innumerable research questions about the CNS, is diffusion tensor imaging (DTI) [14, 15]. Since DTI was the method of choice in both research projects of the present Thesis, this section contains a detailed explanation of the approach, with emphasis on its strengths and limitations.

In the DTI representation, the 3D Gaussian model uses a 3–by–3 tensor D to describe diffusion anisotropy, instead of a scalar ADC:

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix}$$

Using the observed properties of molecular diffusion, the tensor describing the physical process must be real and symmetric, therefore $D_{xy} = D_{yx}$, $D_{xz} = D_{zx}$, and $D_{yz} = D_{zy}$. By writing the diffusion encoding b–vectors in matrix format, and utilizing this symmetry, (*Eq.5*) takes the following form for DTI:

$$\ln\left(\frac{S_b}{S_0}\right) = -\left(b_{xx}D_{xx} + 2b_{xy}D_{xy} + 2b_{xz}D_{xz} + b_{yy}D_{yy} + 2b_{yz}D_{yz} + b_{zz}D_{zz}\right) \quad (Eq.6)$$

The six unknowns in (*Eq. 6*) means that at least six measurements with diffusion encoding in non–collinear directions are required in a dMRI measurement indented for DTI processing. In typical DTI–studies *30 – 40* directions are used [16] and tensor fitting usually forgoes simple least squares methods; iterative approaches with outlier rejection strategies [17] benefit from the higher number of measurements.

This representation means that the diffusion profile is modeled as an ellipsoid in each voxel (Fig 3), which is understandable after the eigenvalue decomposition of the tensors:

$$D = \begin{bmatrix} - & v_1 & - \\ - & v_2 & - \\ - & v_3 & - \end{bmatrix} \begin{bmatrix} \lambda_1 & 0 & 0 \\ 0 & \lambda_2 & 0 \\ 0 & 0 & \lambda_3 \end{bmatrix} \begin{bmatrix} | & | & | \\ v_1 & v_2 & v_3 \\ | & | & | \end{bmatrix} \qquad (Eq.7)$$

The lengths of the ellipsoids half–axes are the eigenvalues (λ_1, λ_2, λ_3) of D and the corresponding eigenvectors (v_1, v_2, v_3) determine their orientation.

The principal eigenvector (v_1) signals the direction in which the measured diffusion displacement is largest and is used by convention for color coding the voxels: right–left direction is red, anterior–posterior is green, superior–inferior is blue, and their mixtures represent in–between orientations (Fig 3).
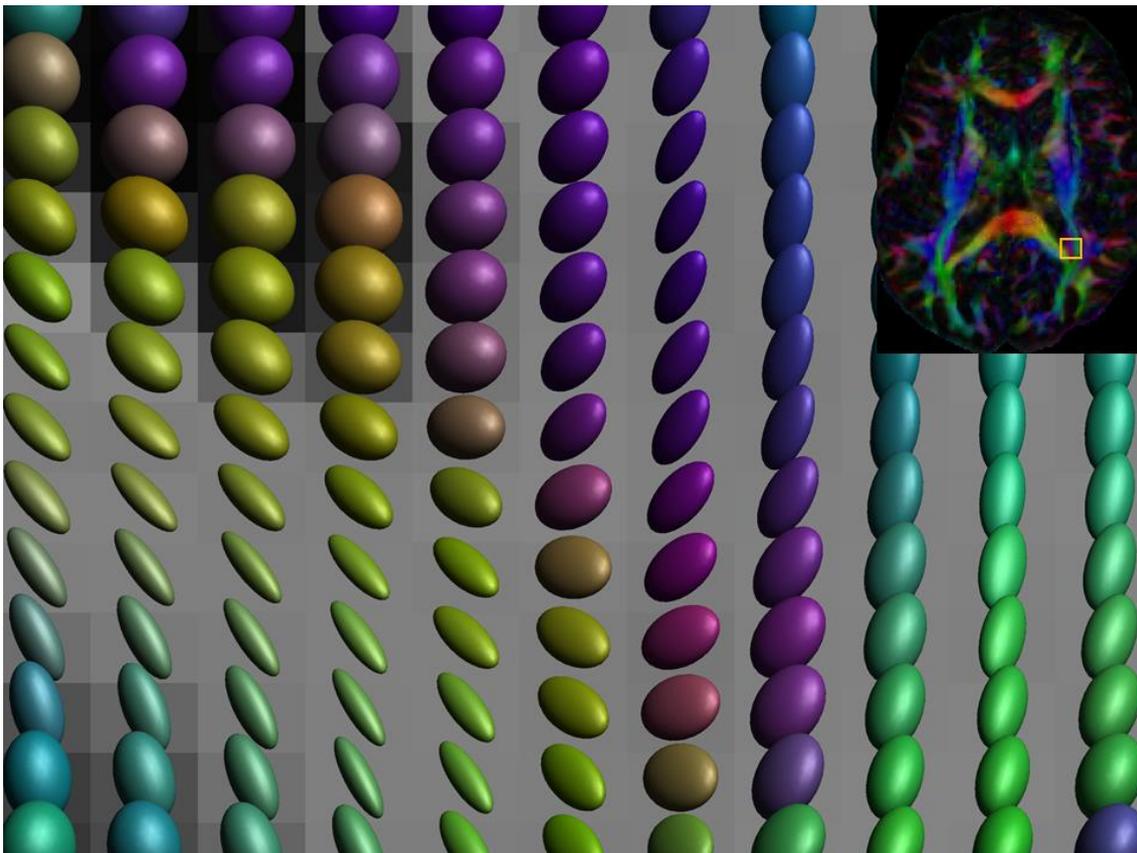
Fig 3 Diffusion ellipsoids in the deep parieto–occipital white matter

The tensor representation in DTI means that the 3D diffusion displacement profile is approximated as an ellipsoid in each voxel. This approach handles the anisotropy and directionality information, measured in dMRI, but fails to resolve the geometry of crossing fibers and to capture the signal behavior of non–Gaussian diffusion processes.

Diffusion tensor data can be utilized with two distinct approaches: the orientation information facilitates tractography, while the eigenvalues can be used to derive anisotropy and diffusivity–related measures that reflect tissue microstructure.

In tractography, neighboring voxels are linked sequentially, following the ellipsoids angulation, to form fiber tracts (i.e. supposed axonal bundles in the white matter of the brain and spinal cord), using interpolation with sub–voxel step size [18]; methods similar to those describing flow patterns in fluid dynamics.

Tracts are identified through the following logic: so–called seeds voxels act as starting points, and tracts are propagated while considering limits on anisotropy and geometric parameters (e.g. angulation). There are two distinct approaches for propagation: deterministic [19], when a single tract follows the direction determined by $\mathbf{v}_1$ and probabilistic [20, 21], when a large number of tracts are observed simultaneously, sampling the diffusion profile for the selection of propagation direction in each step following a Monte Carlo procedure. Tractography results have been used in innumerable clinical and research applications, e.g. studying specific white matter regions for neurosurgical planning [22] and in developmental studies [23, 24]. By defining seed points throughout the entire brain parenchyma, whole brain tractography (Fig 4) enables network–studies with quantitative measures on connectivity between different structural or functional regions [25, 26].
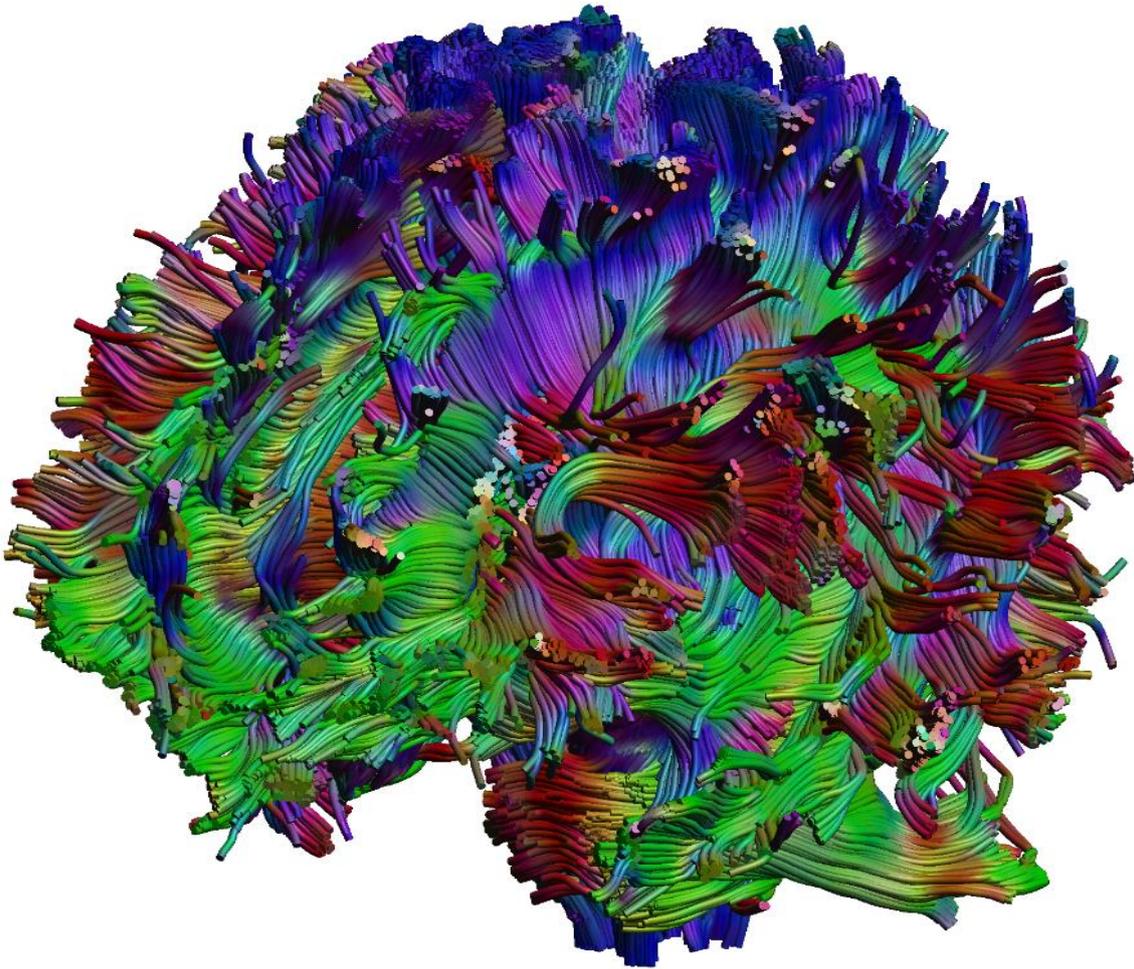
Fig 4 Result of whole brain, deterministic DTI tractography on a healthy volunteer

Conventional color–coding, defined by the direction of the primary eigenvector: right–left direction is red, anterior–posterior is green, and superior–inferior is blue

Although after its introduction, DTI–based tractography gained substantial interest, it has been shown that its approach of identifying one primary direction per voxel is overly simplistic, since the vast majority of white matter voxels contain two or more distinct fiber bundles [27]. A brief overview on the more recent approaches surpassing these limitations is given in subsection 2.2.3.

DTI data has also been used to probe tissue microstructure through rotationally invariant scalar metrics, derived from the tensor eigenvalues [28]. The most well–known are the diffusivity measures and fractional anisotropy (FA). The first eigenvalue, representing diffusion strength along the primary direction, is usually referred to as axial diffusivity. Following the same logic, the arithmetic mean of λ_2 and λ_3 is radial diffusivity (RD), measuring diffusion perpendicularly to the main direction; and the average of all

17

three is mean diffusivity (MD), which can be interpreted similarly to the ADC–value in DWI, but, with the high number of measurements and subsequent model–fitting, is less prone to imaging errors and noise. FA measures diffusion anisotropy in the voxel in the range *[0, 1]*, with FA = 0 representing isotropic, FA = 1 perfectly anisotropic diffusion. Defining equations for the above described diffusivity measures and FA are as follows:

$$RD = \frac{\lambda_2 + \lambda_3}{2}; \; MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3}; \; FA = \sqrt{\frac{3}{2} \frac{(\lambda_1 - MD)^2 + (\lambda_2 - MD)^2 + (\lambda_3 - MD)^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

A vast number of DTI–based studies have used these metrics as indicators of neuropathological progress with popular interpretations for various findings. FA is generally viewed as a measure of fiber coherence in the white matter (WM), and has been shown to increase with brain maturation [29], supposedly reflecting axon myelination. The same process results in concordantly observed decreases in MD and RD. On the other hand, neurodegenerative diseases has been shown to inflict opposing changes in white matter: reduced FA and increased RD, possibly indicating demyelination [30]. Decreased axial diffusivity has also been confirmed in cases with axonal damage [31]. More details and examples regarding DTI–related findings and interpretations concerning our research topics, i.e. mild cognitive impairment and malformations of cortical development, are given in subsections 5.1.2 and 5.2.1.

The straightforward interpretations and seemingly clear connections between various pathological processes and the observed changes in these scalar parameters made DTI popular in the field of neuroimaging, but limitations of the tensor representation also stand for such microstructural applications, and must be considered when discussing highly diverse or even controversial findings. These limitations stem from the fact that scalar metrics are calculated from the volume–averaged signal attenuation, which reflects the mixed behavior of the various contents of voxels. A simple example is when a voxel contains two perpendicular fiber populations, and the demyelination of one results in increasing FA [32]. Such considerations do not necessarily undermine past or novel findings using the DTI approach, but instead demonstrate the limits on the complexity of processes it can interpret.

With the various diffusivity and anisotropy measures calculated from the same three eigenvectors, deciding which of them are of interest in any given study has also been a highly debated topic, especially considering the problem of multiple comparisons. In [33], the second article behind this thesis, we proposed a novel and more straightforward approach for statistical evaluation of DTI data that works with the raw eigenvalues themselves and utilizes all of the scalar information in the diffusion tensor using multidimensional statistics.

2.2.3 Outlook on dMRI methods beyond DTI

Several, more complex methods have been proposed to surpass the above described limitations of DTI [34]; the common prerequisite for all is the need for collecting more data, i.e. more diffusion encoding directions and strengths [35]. For the complete description of the three dimensional diffusion displacement function, especially the non–monoexponential signal attenuation at high b–values, the so–called q–space imaging formalism was introduced [36]. The q–vector describes the encoding strength, similarly to the previously described b–vector: $\boldsymbol{q} = \boldsymbol{\gamma}\boldsymbol{\delta}\boldsymbol{g}/2\pi$, and can be used to describe the Fourier–relationship between signal attenuation ($A(\Delta, \mathbf{q})$) and the average displacement function ($\bar{P}(\boldsymbol{R}, \varDelta)$) for given mixing time Δ and net displacement $\mathbf{R}$:

$$A(\Delta, \mathbf{q}) = \int \bar{P}(\boldsymbol{R}, \varDelta) \exp(i2\pi\boldsymbol{q} \cdot \boldsymbol{R})\, d\boldsymbol{R} \qquad (Eq.\,8)$$

In theory, the displacement function itself can thus be measured by sampling the whole of q–space in a Cartesian fashion and subsequently applying the three dimensional Fourier–transform – analogously to the sampling and reconstruction of k–space in MR image formation. Such a measurement, however, would require short gradient pulses that cannot be fully achieved with clinical scanners, and total scan times that are not tolerable, even to highly motivated subjects. Therefore, complete q–space imaging (also referred to as diffusion spectrum imaging – DSI [37]) has only been seldom applied in human studies [38], but several, more or less simplified approximations has been proposed, which may all be illustrated in the q–space formalism (Fig 5).

19
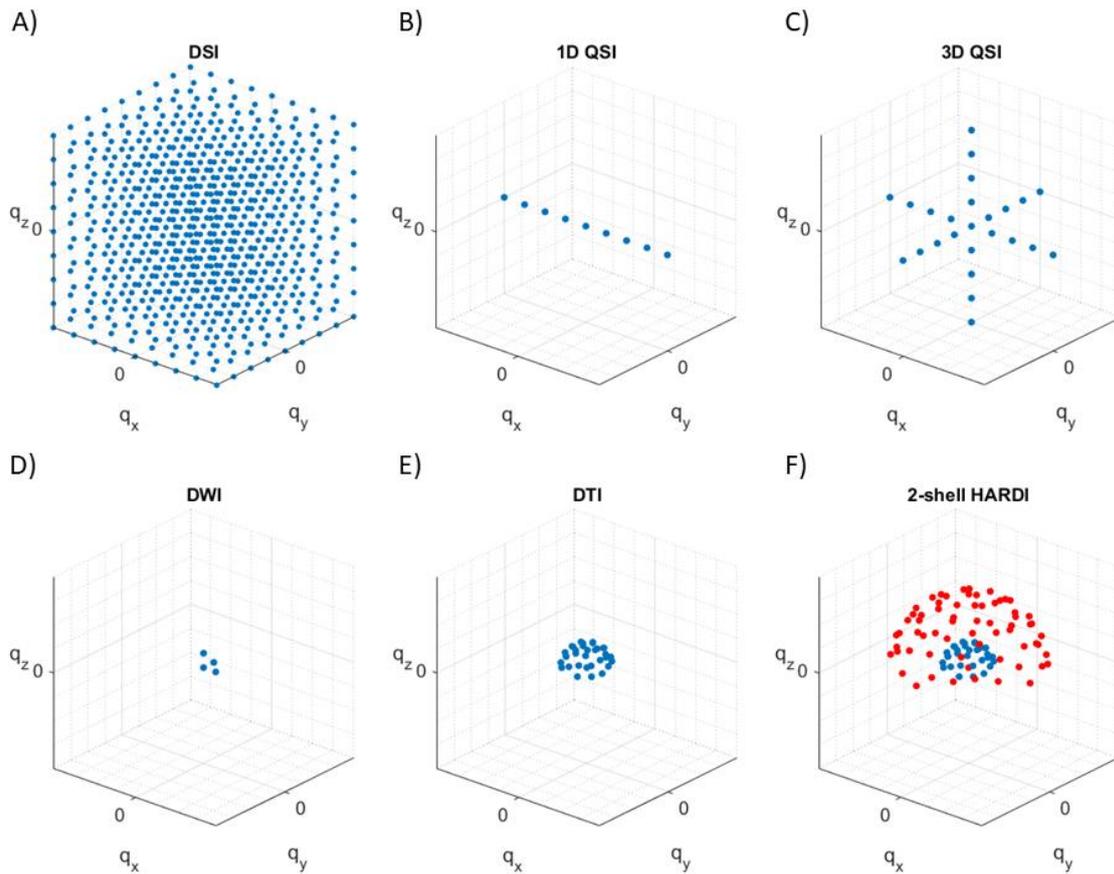
Fig 5 The q–space sampling schemes of different dMRI methods

A: Diffusion spectrum imaging (DSI) aims to sample the whole q–space to reconstruct the complete diffusion displacement function (DDF). B and C: with less demanding scan times, q–space imaging (QSI) resolves displacement along one and three (or more) directions. D: Diffusion weighted imaging (DWI) samples only four points in q–space (one along each main axis plus the origin). E: a typical measurement for diffusion tensor imaging (DTI) essentially means the sampling of a half–sphere (shell) in q–space and the origin. F: the majority of recent dMRI processing methods use data with one or multiple q–shells (multiple b–values) along many encoding directions; common terms are q–ball imaging (QBI), or high angular resolution diffusion imaging (HARDI).

With measurements along one or several axes with different q–values (Fig 5, panels B and C), the diffusion displacement function (DDF) for the corresponding direction(s) can be reconstructed. This model–free approach, called q–space imaging (QSI) has been used in examining certain diseases of the central nervous system, e.g. multiple sclerosis [39, 40]. From the q–space sampling patterns, it is evident how little of the available information is collected in conventional DWI (Fig 5, panel D) and even in typical measurements for DTI (Fig 5, panel E).

With technical and methodological improvements, such as parallel imaging and, more recently, simultaneous multi–slice imaging, the acquisition time needed for a single whole brain image has been substantially reduced, enabling tolerable scan times for high angular resolution (typically around $60 - 130$ directions) and multi–shell dMRI data [41-43], with b–values in the order of $0 - 10000 \ s/mm^2$ [44] (Fig 5 panel F). The term 'high angular resolution diffusion imaging' (HARDI) became generally accepted for such measurements over the last two decades [45], and numerous processing approaches and models were proposed leveraging the increased quality and quantity of information.

The higher number of encoding directions facilitates higher order fitting methods that can resolve complex fiber geometry (e.g. crossing fibers) in tractography. Examples of such methods are Q–ball imaging [46] (the name referencing the fact that measurements with a single b–value along several directions correspond to a sphere or shell in q–space), or the more recent and currently most popular constrained spherical deconvolution (CSD) approach [47, 48], in which the fiber orientation distribution function (fODF) is reconstructed using symmetrical spherical harmonic functions.

With at least three different b–values or even more complex encoding schemes, tissue microstructure can be described more accurately, as well. A relatively simple extension to DTI is diffusional kurtosis imaging (DKI) that requires at least three different b–values (e.g. 0, 1000, and $2000 \ s/mm^2$) and is able to separate multiple water compartments by quantifying the non–Gaussian behavior of the diffusion signal [49]. Several model–based methods has also been proposed, such as the straightforward biexponential model [50], or geometric models using ensembles of spheres, cylinders, ellipsoids, and planes to describe the microstructural environment of neural tissue, with or without exchange of water molecules between various compartments. A few notable examples are CHARMED [51], NODDI [52], and the diffusion tensor distribution approach by Szczepankiewicz et al. [53].

Although in both papers providing the basis of this theses the processing of dMRI data was performed with DTI, the proposed multidimensional statistical approaches are also applicable when working with more advanced methods, yielding more sophisticated descriptions of tissue microstructure or connectivity.

2.2.4 Imaging, correction, and data processing in dMRI

Image formation for dMRI acquisitions is a complex problem since several conflicting requirements have to be met simultaneously. The use of the diffusion sensitizing gradients and the need for adequate mixing time demands longer echo times (in the order of *100 ms*), which requires a spin echo (SE) based technique. Conventional SE, or fast SE sequences would be preferential for their high signal to noise ratio, excellent image contrast, and since they are mostly free form geometric distortions, but their use is inadequate for multiple reasons.

First, the diffusion weighting brings a new set of steps into the pulse sequence that needs to be performed for each k–space line; this would naturally lead to intolerable acquisition times. More importantly, the diffusion sensitizing gradients cause random, spatially varying phase differences over the field of view (FOV), therefore multi–shot techniques would be tainted by these phase errors between k–space lines, resulting in uncontrollable image ghosting and signal voids. Thus, the need for a single–shot imaging approach is evident; historically the most popular of such sequences has been echo planar imaging (EPI) [54].

In EPI, all the two dimensional (2D) k–space data is read after a single excitation, thereby diffusion weighting only needs to be performed once for each slice, facilitating short acquisition times and ghost–free images. On the other hand, single–shot EPI has several limitations and inherent artefacts that need to be acknowledged and/or corrected. Since the whole k–space is to be acquired in one readout, the number of phase encoding steps, therefore spatial resolution is limited: typical dMRI acquisitions for whole brain imaging achieve *2 mm* isotropic voxel size by the aid of parallel imaging or partial Fourier techniques.

The consecutive reading of k–space lines leads to the accumulation of phase errors, resulting in distortions along the phase encoding direction. These errors are most severe in brain regions with strong variations in magnetic susceptibility, for example, around the edges of the frontal and temporal lobes.

Furthermore, the strong diffusion sensitizing gradients often induce eddy currents in the gradient coils and other conductive elements of the MRI scanner. These eddy currents generate spatially and temporally varying magnetic fields that could taint the EPI readout, resulting in shifting, shearing, or scaling of the image, visible over the whole FOV.

These image distortions, as well as other types of artefacts, such as insufficient fat suppression, ghosting from timing errors, patient motion, gradient nonlinearities etc. all lead to inaccuracies in dMRI processing, hindering all types of inference [55]. Fortunately, most systemic errors can be aided to some degree and typical dMRI processing pipelines usually include corrections, preferentially also conserving the directional information of the diffusion measurement while performing various spatial transformations on the data [56]. By using the non–diffusion weighted ($b = 0$) image(s) as reference, distortions caused by eddy–currents or patient motion can be mitigated through linear and non–linear transformations. If an additional image, preferentially a high–resolution, T_1–weighted, anatomical scan is available in the processing pipeline, it can be used as a target for registration in order to correct susceptibility and EPI–related distortions.

With sophisticated interpolation approaches, the description of tissue microstructure and tractography can even benefit from the higher resolution [57]. Both studies of the present thesis leveraged this and a further advantage of this approach: the spatial correspondence between dMRI and anatomical data enables high performance coregistration between subjects and identification of various brain regions by using methods that were developed for anatomical scans [58].

3. Statistics in brain MRI studies

3.1 Univariate statistics

Since the inception of brain MRI, numerous approaches has been employed to utilize its superior image quality and various contrast mechanisms for studying brain structure, morphology, maturation, and the effects of various diseases. The simplest methods measure the size or volume of specific structures, e.g. the hippocampus and either compare it between individuals or cohorts of different diseases [59, 60] and healthy control subjects; or correlate it with specific, often neuropsychology–related measures [61]. Information about tissue microstructure, e.g. average DTI scalar metrics can also be extracted from manually or automatically delineated regions of interest (ROIs), and compared with conventional parametric or non–parametric tests [62].

Explorative methods also emerged for identifying systemic effects throughout the brain. Structural and functional atlases have been proposed as the extension of the ROI–based approach, yielding automated labeling of white [63] or gray matter structures [64]. In conjunction with the advances in processing functional MRI data, standard coordinate systems gained wide acceptance for identifying brain structures: so called template spaces, of which the most well–known were the single subject – based Talairach–space [65, 66] and the Montreal Neurological Institute (MNI) template [67], the latter created from the average of the structural images from hundreds of subjects. Nowadays, the latter became almost exclusively used, being the default coordinate system of the two most popular MRI processing software: FSL [68] and SPM [69].

Templates are used by spatially registering the individual's data through linear and non–linear volumetric transformations [70, 71], and the resulting spatial correspondence across subjects not only means that the structures can be labeled automatically with the use of atlases, but also facilitates statistical inference on the voxel level. Such methods are called voxel–based analysis (VBA) or, particularly, when working with measures describing gray matter structure, voxel–based morphometry (VBM) [72]. Along the VBA methods that work with scalar values, other approaches have also been proposed to utilize the information of the spatial deformations called deformation–based morphometry [73] and tensor–based morphometry [74, 75].

In cohorts with certain diseases or specific age groups, the widely used templates may not be accurate, as they were derived from images of healthy adult brains. Such could be the case e.g. with the atrophied GM of the elderly or patients with Alzheimer's disease. In these avenues of research, study–specific templates yield better spatial coregistration performance and therefore more homogeneous samples. The DARTEL method [58] for defining such specific common coordinate systems was used in both studies of the present thesis.

3.2 The problem of multiple comparisons

With the high number of ROIs in finer atlases and even more so with VBA methods, the problem of multiple comparisons has severe impact on neuroimaging studies [76, 77]. Performing a large number of statistical tests simultaneously (mass univariate testing) inherently degrades the reliability of the inference as the likelihood of false positives increases. Remedies for this problem generally follow one of the following three approaches: (1) reducing the number of the performed tests by the limiting the number of examined structures or volume, (2) utilizing the fact that the measured values in the brain are not independent, or (3) applying conservative thresholds for inference in order to control the rate of false positives.

An example for the first approach, designed for dMRI–studies is the tract based spatial statistics (TBSS) [78] method, which projects DTI–scalars onto the center of WM regions, defined as the so–called FA–skeleton, and performs statistical inference on this limited volume. Methods of the second approach, such as the cluster–level inference based on random field theory in SPM, are widely accepted in functional MRI (fMRI) processing, when the assumption holds, that the observed blood oxygen level dependent (BOLD) signal alteration of neighboring voxels is linked, as it follows from the nature of hemodynamic response [79].

Historically the oldest, simplest, and most conservative is the third approach, generally associated with the name of Bonferroni, and is based on simple probability. With n measurements converted to probability values using some null distribution, if all n samples are from the null distribution, then, with a threshold (level of significance) α,

the probability of all tests being less then α is $(1 - \alpha)^n$. The probability of one or more of the n test values being greater than α is called the family–wise error rate (FWE):

$$P^{FWE} = 1 - (1 - \alpha)^n \qquad\qquad (Eq.\,9)$$

This can be approximated for a small α as $P^{FWE} \leq n\alpha$, from which it follows that in order to achieve a given desired error rate, the probability threshold has to be adjusted as $\alpha = P^{FWE} / n$. This procedure, called the Bonferroni–correction was used in in both studies of the present thesis.

Another method with similar logic, which was also employed in our work as a more liberal point of reference, is controlling the false discovery rate (FDR). In FDR–correction, instead of constraining the probability of one false positive result, only the rate at which type I error occurs is controlled, resulting in less conservative testing and yielding less false negatives.

Although it has been demonstrated that when spatial correlation is present in the samples, therefore the performed tests are not independent, FWE and even FDR–correction methods tend to be overly strict. Thus, several, more liberal approaches have been proposed to deal with the problem of multiple comparisons, yet both FWE and FDR are both still widely used as conservative approaches to retain specificity in statistical testing. Moreover, results 'surviving' Bonferroni–correction are generally considered to signal substantial effects.

3.3 Multivariate approaches

Multidimensional studies aim to combine information from independent sources in order to raise statistical power; a feat sought after in the neuroimaging literature. Several strategies were employed to implement such combination at different levels of statistical analysis throughout the past two decades, using (and sometimes combining) voxelwise, surface–based, or ROI–level methods. The performance of this pooling of information has been evaluated on the level of p–values [80, 81], T–score maps [82], and by using multivariate [83, 84] and, as in the first study, logistic regression [85] analyses.

The lowest level at which neuroimaging information can be combined is achieved by working with raw data, or derived parameter maps. Such was the approach e.g. in [86], working with voxelwise MD and volumetry data. More recently, the performance of machine learning based classifiers in the scope of lesion detection was demonstrated with satisfying performance, e.g. on the voxel level, working on T_1–weighted data using a one–class support vector machine–based classifier and outlier detection approach [87]; or on the vertex–level, working with morphologic and intensity–based metrics, using surface–based methodology [88] [89].

Although the aforementioned models and studies demonstrated (further detailed in subsection 2.1) that multidimensional approaches can increase statistical power by combining the sensitivity profiles of independent modalities, their usage is often complicated, computationally expensive, and includes arbitrary choices (for example the choice of combining functions in [82] or the selection of weighting factors for multivariate linear regression).

The second study of the Thesis was aimed at developing a more straightforward and easier to use method, based on the Mahalanobis–distance for testing neuroimaging (specifically DTI) data in the context of lesion detection when comparing a single patient to a group of healthy controls.

4. The Mahalanobis–distance

4.1 Definition

The Mahalanobis–distance is a measure of dissimilarity, commonly used in multivariate outlier detection problems [90-92], which we employed in our second study as the basis for epileptic lesion detection, searching for abnormal voxels as outliers when comparing a single subject to a group of controls.

Following the original definition by Mahalanobis [93], in a P dimensional statistical field (constructed from P separate variables) the squared distance between an observed distribution with mean $\mu = (\mu_1, \mu_2, ..., \mu_P)$ and covariance matrix $\underline{S}$, and any point $X = (X_1, X_2, ...X_P)$ is expressed in the form:

$$D_M^2 = (\boldsymbol{X} - \boldsymbol{\mu})^T \underline{\underline{\boldsymbol{S}^{-1}}}(\boldsymbol{X} - \boldsymbol{\mu}) \qquad (Eq.\,10)$$

Multiplication with the inverse of the covariance matrix maps the inter–point distances to a standard L^2 – norm (i.e. Euclidean space), cleared of any possible correlations and differences in standard deviations $(\sigma_1, \sigma_2, ... \sigma_P)$ between the dimensions (Fig 6); therefore D^2 values reflect how far a given point is from the underlying multivariate distribution.
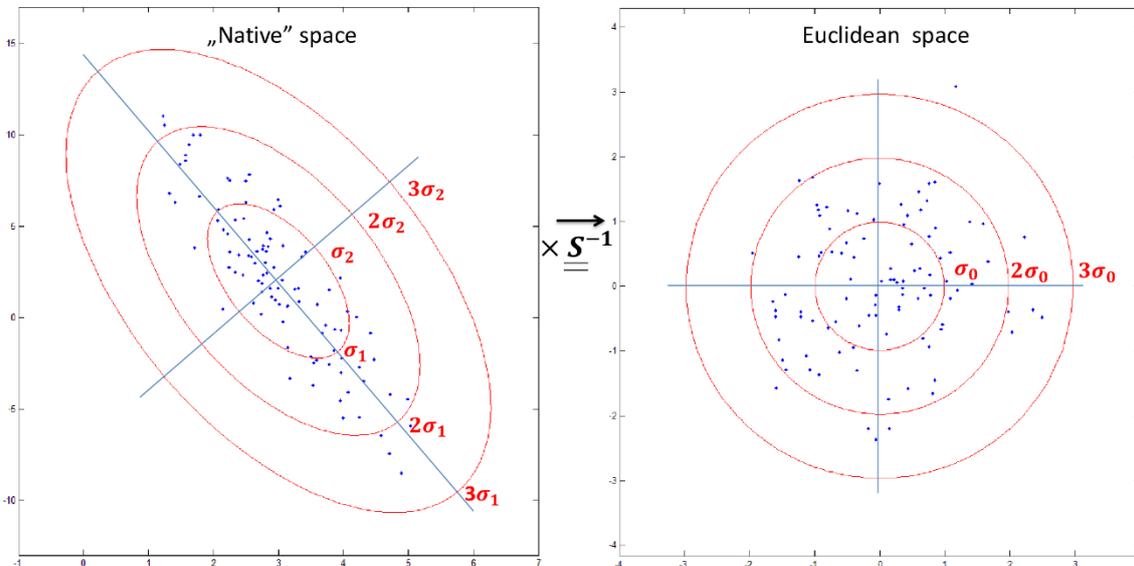
Fig 6 The effect of the multiplication with the inverse of the covariance matrix.

The multidimensional distribution is cleared of possible correlations and differences in standard deviation, therefore the distances are effectually calculated in a Euclidean space.

This mapping feature is potentially useful in diffusion weighted image processing and the detection of pathological tissue microstructure in the DTI framework, as different tensor eigenvalues are sensitive to different pathologies but they generally exhibit strong correlations [94-96].

By definition, the Mahalanobis–distance is related to Hotelling's T^2 (e.g. used in [86]) with the exception that the latter compares a group of subjects to the reference distribution, by using $\overline{X}$ (the group average of $X^i = (X_1, X_2, ...X_P)$ vectors, each corresponding to an individual subject) instead of a single X. Like Hotelling's T^2 is often referred to as the multidimensional equivalent of Fischer's two–sample T–test, one may view the squared Mahalanobis–distance as a multidimensional one–sample T–statistic.

4.2 The Mahalanobis–distance in neuroimaging

The Mahalanobis–distance has been employed in neuroimaging in relation to various disorders and at different levels of information processing: in discrimination between normal tissue types and brain tumors [97]; in ordering the eigenvectors of discriminatory principal component analysis, differentiating Schizophrenia patients from controls using whole brain FA [98]; in combining DTI–scalar metrics with T_1 and T_2–weighted images in WM–ROIs, quantifying brain maturation [99]; in discerning subtypes of mild cognitive impairment based on T_1, T_2, and proton density–weighted images [100]; and, more recently, in quantifying the difference between patients with autism spectrum disorder and subjects with normal aging, using different sets of DTI scalars from major WM tracts [101].

In [33], the second study behind the thesis, 3 dimensional distributions were constructed in each voxel from the eigenvalues of the diffusion tensor, and the voxelwise squared Mahalanobis–distance was calculated using empirical μ and $\underline{S}$ from samples containing one patient and a group of control subjects (Fig 7).
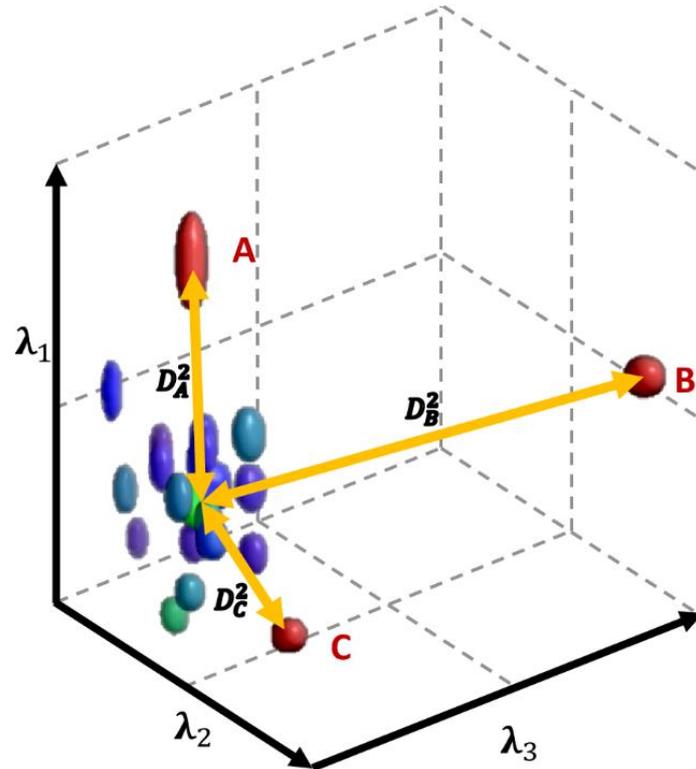
Fig 7 Mahalanobis–distance in the 3D space of DTI eigenvalues.

Outlying diffusion profile in a given voxel of a single subject under examination (red) is detectable through the distance (D^2) from a group of controls (blue and green) in the three dimensional parameter space of the diffusion tensor eigenvalues. Common alterations of the diffusion profile, such as a higher first eigenvalue (as in the case of point A; usually detected through increased fractional anisotropy in univariate tests); an increase in all three eigenvalues (B; commonly observed as increased mean diffusivity); or an altered diffusion profile with normal–appearing diffusion strength (like in the case of C, when MD equals to the average MD of the controls, but the eigenvalues differ) are all detectable in the multivariate framework with a single test.

4.3 Statistical inference based on critical values

Critical values for detecting a single multivariate outlier at a desired level of significance, as shown in [102], can be calculated using Wilks's criterion [103], with the following formula:

$$D^2_{crit} = \frac{p(n-1)^2 F_{p,n-p-1;\frac{\alpha}{n}}}{n\left(n-p-1+pF_{p,n-p-1;\frac{\alpha}{n}}\right)}, \qquad (Eq.\,11)$$

where p is the number of dimensions, n is the number of observations (subjects) and F is the distribution function of the F statistics, with the appropriate numerator and denominator degrees of freedom at the desired significance level α. By selecting a sufficiently conservative α, i.e. one aiming to control the FWE or the FDR, the problem of multiple comparisons (high number of voxels under examination) may also be addressed. Although the distributions of the diffusion tensor eigenvalues are usually not strictly Gaussian, this generally does not affect the calculation of Mahalanobis–distance significantly, however, it may result in an overestimation of the critical values somewhat reducing sensitivity with the unintendedly more conservative inference. With the analytically derived critical values accounting for sample size, statistical significance is not likely to be affected by the bias described in [104], however, as with conventional statistical approaches, using larger control samples is desirable to increase specificity.

5. Research topics – Clinical importance

5.1 Mild Cognitive Impairment

Alzheimer's Disease (AD) is the most common neurodegenerative disorder among the aging population [105], which is already an enormous but still a growing economic burden in western societies such as countries of the European Union or the United States.

While we do not have effective treatment for AD at the moment, but future interventions will likely be effective in an early stage of the disease, many research efforts are focused on the early detection of symptoms. Converging evidence from many previous investigations revealed that pathologic process of AD starts decades before the first symptoms of cognitive decline [106]. Therefore, the intermediate stage between the mild decrease of cognitive functioning in physiological aging and the severe decline in dementia known as 'mild cognitive impairment' (MCI) has gained a lot of interest in the last decade. "In MCI mild impairment of cognitive skills can be revealed by neuropsychological tests, while global cognitive functions and everyday activities are preserved" [107]. The higher conversion rate to AD in MCI gives the clinical significance of this pre–disease condition. The annual conversion rate is *10 – 15%* in MCI compared to the annual rate of *1 – 4%* in the average elderly population; hence, most MCI patients develop clinical AD [108, 109]. Further subtypes of MCI can be differentiated such as the amnestic (aMCI) and non–amnestic subtypes (naMCI) with distinct structural features [110]. The conversion rate from the aMCI subtype to Alzheimer Disease is much higher [111] compared to the naMCI subtype, which underlines the significance of differentiation between the two. Patients with the naMCI subtype tend to develop other dementia variants (e.g. vascular).

5.1.1 MRI diagnostics of MCI

Though atrophy of grey matter (GM) structures in the medial temporal lobe have been the most studied feature [110, 112-114], degradation of white matter tracts, especially the fornix may precede it [115, 116] and has become detectable in preclinical states with use of DTI and other complimentary imaging techniques [117]. Indeed, the cingulum and the fornix carry the axons projecting from the CA1 and CA3 pyramidal neurons of the

hippocampus, and there is further published evidence underlining their predictive potential [118, 119].

5.1.2 The role of DTI in MCI diagnostics

DTI is a relatively new and promising neuroimaging technique in the early diagnosis of Alzheimer Disease and in the identification of early at–risk groups such as patients with MCI. FA and MD were found to be good indices of fiber density, axonal diameter and myelination, and proved to be useful as early signals of cognitive decline [120, 121]. FA is greater and MD is decreased in organized white matter tracts, while both measures go to the opposite direction in CSF and disorganized fibers [122, 123]. Findings of previous studies suggest a specific pattern in MCI and AD where white matter damage begins in the core memory network of the temporal lobe and cingulum and spreads beyond these regions in later stages [124].

5.2 Drug resistant epilepsies (DREs)

Drug resistance affects about *20 – 30%* of the epileptic patient population, causing severely impaired quality of life and a difficult to treat situation [125, 126]. Most of the drug resistant cases (~*60%*) are focal epilepsies; nevertheless, there are generalized forms. Malformations of cortical development (MCDs) and long–term epilepsy–associated tumors (LEATs) are among the most frequent etiological factors causing DRE [127-130]. Subtypes of MCDs include focal cortical dysplasia (FCD), polymicrogyria (PMG), heterotopia (HTP), hemimegalencephaly (HME), while subtypes of LEATs include gangliogliomas, and disembryoplastic neuroepithelial tumors (DNTs) [131]. Most of these entities may exhibit variable features on MR images collected with an epilepsy protocol.

DRE patients are often candidates for surgical intervention; however, the probability of postoperative seizure freedom is remarkably lower in cases lacking any identifiable lesions on conventional MRI [132]. Therefore better visualization of MCDs and LEATs e.g. as shown in [87, 88, 133-137] can be crucial for improving surgical outcomes.

5.2.1 DTI in the diagnosis of epilepsy

DTI has been proven sensitive to the disrupted tissue microstructure, identified in MCDs. Abnormalities tend to extend beyond the lesions themselves, for example [138] identified decreased FA and increased MD and RD in regions spanning *5 – 20 mm* around the nodules in children with periventricular nodular heterotopia. Widespread decrease of FA was also demonstrated in major WM tracts in both hemispheres (e.g. in the cingulum, forceps minor, anterior thalamic radiation, superior longitudinal fasciculus, uncinate fasciculus, and the inferior fronto–occipital fasciculus) in a group of patients with frontal FCDs, using TBSS [139].

More sophisticated models such as DKI [140] or the NODDI [52] approach may further improve lesion detection based on diffusion weighted MRI [141-143]. Once again, since DTI is still the most widely used approach, mainly because of its simplicity and clinically feasible acquisition and processing time, we chose to demonstrate our proposed statistical method using DTI data, however, the framework we introduced in the second study may be applied to all kinds of voxelwise variables derived from any meaningful model.

II. Aims

1. DTI and Mild Cognitive Impairment

The primary aim of the first study was to find the possible differences between the subgroups of MCI, which may increase prognostic capability at an early stage, and a further aim was to confirm the recent findings regarding the DTI differences observed between controls and MCI subjects [118, 119]. Based on previous evidence [118, 119], the most prominent between group differences and the strongest correlations with memory functions were expected in the cingulum and the fornix. The secondary aim of the study was to determine in which brain regions and DTI measurements can expand the findings of previous volumetric examinations [110], to help the differentiation between patients with aMCI, naMCI, and healthy subjects.

2. Mahalanobis–distance in MCD lesion detection

The main aim of the second study was to evaluate the performance of a novel, Mahalanobis–distance–based statistical approach using DTI data, –for detecting microstructural abnormalities; by simulations using data from standard multivariate normal distribution (SMVND − $\mathcal{N}_P(0,1)$) and from healthy controls. Based on the simulation results we also aimed to demonstrate the utility of the approach in select cases of patients with MCDs.

III. Materials and Methods

1. DTI and Mild Cognitive Impairment

Briefly, in this study different statistical approaches were applied to (a) identify those white matter structures which are the most sensitive to early impairment in pathological aging, and (b) to estimate if diffusion metrics can extend the differentiation performance of volumetry. First, we performed voxelwise correlation analyses between neuropsychological tests and the above mentioned DTI parameters to assess and demonstrate whether these tests capture the examined aspects of cognitive performance and that the DTI metrics under consideration do reflect the state of tissue microstructure in relation to them. Next, we compared subgroups of healthy individuals, and at–risk subgroups of amnestic and non–amnestic mild cognitive impairment on the voxel–level to solidify the results of the correlation analyses and to identify the regions showing significant between–group differences. With voxel–level calculations being extended to the whole of the brain parenchyma, the earliest signs of alterations in GM cellular structure may be detected. We then performed both correlation and between group analyses in predefined regions of interest (the *48* ROIs of the 'JHU White–Matter Atlas' [63, 144-146]). With less independent tests to perform and thereby being able to apply more liberal thresholds for multiple comparisons correction, the ROI–level approach may exhibit higher sensitivity. Even more so, with the method being used on WM ROIs, its results may prove to be more stable (as DTI is most sensitive to changes in the WM), rendering this approach better suited for discriminative models.

Finally, In order to prove our hypothesis that DTI measures of these regions can improve the differentiation performance achievable with GM volumetry, logistic regression analysis was performed with a K–fold cross–validation approach [147], combining volumetric data from the same patient population [110] with the DTI measures.

1.1 Study data and Participants

MR imaging data of *65* subjects (*18* with amnestic MCI, *20* with non–amnestic MCI, and *27* healthy controls) acquired at *3T* (Philips Achieva scanner, Philips Medical Systems, Best, The Netherlands) was included in this study; the subjects were the same as those in [148], except for three additional healthy controls.

Brain dMRI images were collected with a single shot SE–EPI sequence, with $b = 800 \, s/mm^2$ diffusion weighting in *32* directions and one $b = 0$ image. In–plane resolution was *1.67×1.67 mm*; whole brain coverage was achieved with 70 consecutive, *2* mm thick axial slices; repetition time *TR = 9660 ms* repetition time, *TE = 75.6 ms* echo time, and *90°* flip angle was used; the total acquisition time was 8:32min. High resolution T_1–weighted images were also acquired for registration purposes with *1 mm* isotropic voxels, using a 3D gradient–echo sequence.

All subjects enrolled in the study participated in a cognitive training program announced in a Retirement Home and among general practitioners (The study is registered at ClinicalTrials.gov, identifier is 'NCT02310620'). Demographics of the three groups of subjects are summarized in Table 1. A detailed description of the neuropsychological tests can be found in the Supplementary Material of [85].

Subjects included in the study were categorized as aMCI, naMCI, and healthy controls according to the Petersen criteria [107]. The Petersen criteria include subjective memory complaint corroborated by an informant together with preserved everyday activities, a memory impairment based on a standard neuropsychological test, preserved global cognitive functions and finally the exclusion of dementia. It does not specify a neuropsychological test for the assessment of memory impairments; therefore, we applied the Rey Auditory Verbal Learning Test (RAVLT), which is the most frequently used test in the literature [149]. For the differentiation between aMCI and healthy controls, we applied a cutoff score of one standard deviation (SD) under population mean standardized for age and gender. Participants, who scored under the cutoff value, either in the delayed recall subscore or in the total score, was assigned to the aMCI group. The applied criteria are based on the recommendations of the National Institute on Aging – Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease [150]. Subjects

who were not in the aMCI group, but scored one SD under the population mean standardized for age and gender/education either in the Trail making Test B or in the Addenbrooke's Cognitive Examination (ACE), were assigned to the naMCI group. An additional criterion for the naMCI group was a lower than 3.2 VLOM (verbal fluency + language score / orientation + memory score) ratio in the ACE to exclude possible aMCI subjects from the naMCI group (these subjects were excluded from the study).

Subjects with dementia according to the Mini Mental State Examination (MMSE) scores standardized for age and education [151] were excluded from the study, similarly to subjects with history of head trauma, epilepsy or stroke, or with the diagnosis of acute psychiatric disorder, schizophrenia or mania, or alcohol dependence. One aMCI patient was left out of the calculations who was found to be an outlier, performing significantly worse on each test, thereby biasing the calculations. None of the subjects enrolled in the study had a history of any neurological disorder.

Table 1 Demographic data and result of basic neuropsychological tests.

	control (n=27)	naMCI (n=20)	aMCI (n=18)	p value
Age	65.2 (7.2)	71.1 (8.2)	69.8 (11.3)	n.s.*
Education [a]	7%/33%/59%	20%/30%/50%	17%/22%/61%	n.s.*
Gender (Female)	70%	65%	61%	n.s.*
Rey Auditory Verbal Learning Test 1 -5 sum [1]	53.4 (7.7)	46.6 (10.0)	29.5 (7.4)	p<0.0001
ACE Total Score [c]	94.0 (3.1)	89.5 (4.6)	82.1 (7.7)	p<0.0001
ACE VL/OM-ratio [d]	2.6 (0.4)	2.5 (0.4)	3.1 (0.8)	p=0.002
Mini Mental State Examination Total Score [e]	28.5 (1.3)	28.4 (0.9)	27.4 (1.8)	p=0.025
Geriatric Depression Scale Score [f]	3.3 (2.9)	4.5 (2.7)	4.4 (3.3)	n.s.*
STAI Score [g]	37.3 (9.8)	36.4 (9.3)	36.7 (8.3)	n.s.*

aMCI: Amnestic mild cognitive impairment, naMCI: non amnestic mild cognitive impairment ACE:
Addenbrooke's Cognitive Examination, STAI: state-trait anxiety inventory

a: Participants were categorized into three education groups: 1=less than 12 years; 2=high school
graduation (12 years education); 3=more than 12 years education

b: Sum of all words in the first five trials.

The maximum score is 75.

c: The maximum score is 100

d: VL/OM: verbal fluency and language points/orientation and delayed recall ratio can be defined based
on ACE. Result below 2.2 indicate frontotemporal dementia and result over 3,2 indicate Alzheimer's
disease.

e: The maximum score is 30.

f: The maximum score is 15.

g: State-Trait Anxiety Inventory. The maximum score is 80.

* n.s. (not significant) = p > 0.05

1.2 Preprocessing and diffusion tensor fitting

dMRI data was preprocessed using the Matlab–based (MATLAB 8.3, The MathWorks Inc., Natick, MA, 2000) ExploreDTI software package [152]. Processing steps included coordinate system transformation, rigid body transformations for correcting subject motion, non–rigid transformations for correcting susceptibility–related and EPI–induced distortions, with the local rotation of the b–matrix (the diffusion weighting directions) to avoid angular inaccuracies [56]. The high–resolution T_1–weighted images were used as templates for registration to correct the distortions inherent to the EPI–acquisition method [153]; thereby dMRI–images were spatially aligned to the T_1–weighted images.

After tensor fitting, using the RESTORE (Robust Estimation of Tensors by Outlier Rejection) [17] algorithm, two voxelwise DTI–measures FA and MD [14, 154, 155] were calculated from the tensor eigenvalues, following their well–established definitions, to be used in voxel–level and ROI–based analyses.

1.3 Voxelwise analysis

Images containing the DTI scalar values were 'normalized', i.e. transformed into a common coordinate system using the DARTEL tools [58] of the SPM12 toolbox [69]. The DARTEL method is a common approach e.g. in VBM studies [156, 157] using T_1–weighted images. This method creates a template in several iteration steps that is the closest to each individual subject's anatomy. This way the common coordinate system is study–specific, resulting in more efficient handling of macroscopic anatomical differences (such as possible GM–atrophy), compared to other widely used approaches, for example those utilizing the MNI152 space [158].

Once the template image was calculated and the transformations ('flow fields') linking each subject's native space to the common space were determined, we used these transformations on the DTI parameter images ('warping').

The 'warping' function of DARTEL includes a 'modulation' step to account for macroscopic anatomical differences. As the method was developed to examine cortical

thickness and structure, when e.g. the transformation means merging three voxels in two, the addition of tissue probability values keeps the information of cortical thickness.

However, when working with DTI scalar parameters, this addition (preserving the 'concentration') would falsify the original diffusion traits, thereby we omitted the 'modulation' option in our processing framework.

The performance of the spatial alignment was assessed by visual inspection and the 'Check Data Quality' function of the Computational Anatomy Toolbox ('CAT12', an extension to SPM12) [159]. This tool calculates a three dimensional spatial correlation coefficient between images; misaligned data is easily identified by the decreased level of correlation. Three subjects (two controls and one aMCI patient) were removed from the voxelwise calculations following the corresponding results of the two quality assurance methods. The resulting normalized data was used unsmoothed for assessing the correlation between neuropsychology and microstructure, while, for between group analyses, Gaussian smoothing (with full width at half maximum: *FWHM = 8 mm*, isometric) using SPM was applied.

Use of the widely acknowledged TBSS [78] method was also considered for its higher statistical power, but because of its inherent loss of spatial information (especially from the cortex) due to constraining analysis to the FA skeleton (the supposed center of white matter tracts), and its recently discovered poor spatial alignment performance in regions with complex WM structures [160], this option was omitted.

The whole brain voxelwise analysis, used in both between group and correlation analyses was extended to grey matter voxels, hypothesizing that small changes in GM microstructure which may precede macroscopic symptoms manifest in noticeable differences in DTI scalar values [161-163].

1.3.1 Voxelwise correlation analysis

In order to accurately localize the brain regions related to cognitive dysfunction, we calculated partial correlation coefficients in each voxel between the (non–smoothed) values of DTI parameters and the results of neuropsychological tests across all subjects using a high performance Matlab–based algorithm, including subject's age and sex as

covariates. Statistical significance of the correlations was assessed using Student's T–distribution.

Two types of corrections for multiple comparisons were employed: FWE control was achieved by the Holm–Bonferroni method [164], while the less conservative FDR control was achieved by the Benjamini–Hochberg step–up algorithm, which is considered to have more statistical power at the cost of controlling only the proportion of type I. errors [165]. Due to the large number of voxels in the calculations (*280315* grey or white matter voxels, defined using the DARTEL template), achieving a FWE rate or FDR of *0.05* meant statistical p–values in the order of $10^{-8} – 10^{-6}$.

In order to distinguish between true and false positive results in the cases of small clusters spanning the volume of only a few voxels, we also checked the underlying trends using an exploratory threshold of $p < 0.001$, uncorrected. True positive result would appear as the most significant voxels (the focal points) of larger regions achieving significance with the exploratory threshold, while false positives could show as single voxels spread in random fashion.

Moreover, similar, homogeneous behavior, or emerging patterns of correlation coefficients in specific anatomical regions (e.g. the same sign and scale of R–values in a specific gyrus) could also support the identification of true positives as the most significant voxels would be identified as the peaks of such regions.

1.3.2 Voxel–based between group statistical analysis

A large number of studies have confirmed the connection between various types of dementia and the changes in diffusion tensor parameter values in several brain regions [123, 166-171], using voxel–based analysis (VBA) methods typically in group–level comparisons. In order to confirm that our patient groups exhibit such significant differences, and therefore the identified correlations are meaningful, smoothed diffusion parameter maps (isometric Gaussian smoothing with *FWHM = 8 mm*) were examined, using SPM's 'Second–level' general linear model (GLM) functions.

Four calculations were performed on both diffusion parameters, using each individual's age and sex as covariates: one–way analysis of variance (ANOVA) test on

42

all three groups and two sample T–tests between pairs of groups. Each test was performed with FWE correction for the conservative treatment of the problem of multiple comparisons.

1.3.3 Visualization

Resulting raw images of the VBA and the correlation analyses were in the DARTEL Template space; however, in order to easily compare our results to those of previous publications, FWE or FDR corrected T and R–score maps were transformed to MNI152 space [158] using SPM's DARTEL tools.

1.4 ROI–based statistics

ROI–s were defined by transforming the *48* regions of the JHU White–Matter Atlas [63, 144-146] into each patient's own image–space, using the 'Get diffusion metrics from ROI labels' tool of 'ExploreDTI'. This plugin utilizes the 'Elastix' [172] software for label registration and exports the average DTI–parameter values (MD, FA) for each region. Spatial alignment of the ROI labels was validated by visual inspection. In the further analyses, data obtained from *36* cerebral ROIs was imported into SAS (SAS 9.4 software, SAS Institute, Cary, NC); *12* ROIs outside the cerebrum, such as cerebellar white matter tracts, were excluded.

1.4.1 ROI–based correlation analyses and between–group comparisons

Correlations with neuropsychological tests were analyzed by calculating Pearson's correlation coefficients (proc. CORR in SAS), and also Spearman partial correlations as independent confirmation of the monotonous and linear nature of the relationships.

The three study groups were also compared by Analysis of Covariance (ANCOVA) using FA and/or MD data from these ROIs with age and gender as covariates; followed by post hoc between group comparisons using general linear models (proc GLM in SAS). In order to control for multiple comparisons, Bonferroni correction was applied: the level of significance was adjusted to $p = 0.05 / 36 = 0.0013$.

1.4.2 ROI–based logistic regression analysis for a combined cortical thickness and DTI based differentiation between study groups

GM volumetric data (cortical thickness and subcortical brain structure volumes) obtained using the freely available Freesurfer 5.3 image analysis suite (http://surfer.nmr.mgh.harvard.edu/) with its default processing pipeline and parcellation settings were then analyzed jointly with the DTI–derived metrics in a logistic regression analysis ('proc LOGISTIC' in SAS, stepwise variable selection) to assess if the combination of GM and WM DTI data leads to better differentiation between aMCI subjects and healthy controls than using the GM data alone. Three healthy controls and one subject with naMCI were excluded from the logistic regression analyses due to missing volumetric measurements. The Freesurfer–based processing pipeline for the grey matter data were described in detail in [148].

Combined MD/GM volume and FA/GM volume models were analyzed separately; further details on the logistic regression analyses and how measurements were selected to be included in the model are described below. Discrimination between each pair of subject groups was tested using a ten–fold cross–validation approach [147] (K–fold testing in SAS):

First, an independent test–set of four subjects (two from each group, representing *10%* of the sample population) was assigned; the features of the logistic regression model were selected on the remaining *90%* of the subjects. In the second step, the resulting model was tested on the small test subset, independent from the model creation. This method was repeated ten times (nine times when discriminating between aMCI and naMCI) as each subject was assigned once to a test–subgroup. The resulting ten (nine) independent models, their selected effects and corresponding discrimination performances were then summarized.

2. Mahalanobis–distance in MCD lesion detection

2.1 Study data and participants

Diffusion and T_1–weighted MR imaging data of *45* healthy control subjects (*25.6* years average age, range: *20 – 37* years, *17* males) and *13* patients (*21* years average age, range: *7 – 46* years , with two children under *10*, *7* adolescents between *14* and *18, 9* males) with MCDs was acquired at 3T (Philips Achieva scanner, Philips Medical Systems, Best, The Netherlands). dMRI images were collected with a single shot SE–EPI sequence, with diffusion weighting in *32* directions with $b = 800 \, s/mm^2$ and one $b = 0$ image. In–plane resolution was *2×2* mm (reconstructed to *1.67×1.67* mm with zero filling); whole brain coverage was achieved with *84* (adjusted when necessary), *2* mm thick axial slices and no gap; *TR = 9660* ms repetition time, *TE = 75.64* ms echo time, and *90°* flip angle was used; the total acquisition time was *8:32* minutes. High–resolution 3D T_1–weighted images were also acquired for registration purposes (*1* mm isotropic voxels), using a standard 3D gradient–echo sequence. 2D fluid attenuated inversion recovery (FLAIR) sequences (*0.43×0.43* mm in plane resolution, *3.3* mm thick coronal slices, tilted perpendicular to the axes of the hippocampi, *TR = 9000* ms, *TE = 125* ms, *TI = 2800* ms, flip angle = *90°*) were also acquired for aiding the visualization of the MCDs.

Patients were selected retrospectively, with several different types of MCDs and other abnormalities: MCD subtypes included polymicrogyria (in two patients) schizencephaly (two patients), subependymal heterotopia (in three patients), FCD (in six patients), cortical dysgenesis (in three patients) and other, not clearly identifiable malformations (in four patients). Several other types of abnormalities were also identified in the patient group, such as DNT (in one patient, later confirmed by histopathology), ischemic WM lesions (in two patients), a gliotic cyst (in one patient), focal gliosis (in one patient, also confirmed by subsequent histopathology), hippocampal sclerosis (in four patients), and malrotation of the hippocampus (in one patient). Diagnoses of MCD subtypes were based on neuroradiology report; the supplementary Table S10 contains detailed information on each lesion and abnormality, along with the results of neuroradiology assessment and lesion detection calculations.

The study was approved by the Scientific and Research Ethics Committee of the Medical Research Council, Budapest, Hungary (ETT TUKEB - 20680-2/2012/EKU (368/PI/2012)) for patients and (ETT TUKEB 23609-1/2011-EKU, 23421-1/2015-EKU) for controls; all participants provided written informed consent. Following publication requirements, anonymized T_1–weighted images (facial structures removed using the 'mri_deface' function of Freesurfer – https://surfer.nmr.mgh.harvard.edu/fswiki /mri_deface) and coregistered DTI–eigenvalue maps of the patients and controls were made available in the 'GIN' public repository under the DOI 10.12751/g-node.80dd9a.

2.2 Data processing

dMRI data was preprocessed using the Matlab–based ExploreDTI software package [152]. Processing steps included the transformation into ExploreDTI's coordinate system, rigid body transformations for correcting subject motion, and non–rigid transformations for susceptibility–related and EPI–induced distortion–correction, while also rotating the b–matrix (the directions of diffusion–weighting) accordingly, in order to avoid angular inaccuracies [56]. T_1–weighted images were used as templates for registration to correct the distortions inherent to the EPI–acquisition method [153]; thereby DW–images were spatially aligned to these T_1–weighted images. After robust tensor fitting, using the RESTORE [17] algorithm, the tensor eigenvalues were calculated and exported for the voxel–level analysis.

We used the DARTEL method with default parameters for the group–level coregistration of the eigenvalue images, as described in detail in 1.3, with some variations:

The DARTEL template was created from the T_1–weighted images of only the control subjects; patient data was subsequently registered to this common space. As a byproduct of the registration, 'flow–fields' describing the transformation between each individual's native space and the template space were obtained and used to coregister the eigenvalue images. Finally, the DARTEL template was used to generate a brain mask and subsequent calculations were limited to this volume.

This way, the reference distribution of voxelwise DTI eigenvalues in the common coordinate system (control data) had low observed sample variance, unbiased by patient anatomy, and provided a solid basis for sensitive lesion detection. On the other hand, this subsequent transformation of patient data may have amplified registration artefacts, especially in cases when a patient was highly different from the controls (e.g. when the patient was significantly younger, or had large anatomical abnormalities).

This processing pipeline contains only two interpolation steps. First, in the motion and distortion–correction step, the DWI data is interpolated to the finer resolution of the T_1–weighted images [173], while the second is performed in the coregistration step of the DARTEL method, to a coarser, *1.5* mm isotropic resolution. This is the necessary minimal number of interpolations when each individual's T_1–weighted images are used for DWI distortion correction, and statistical inference is made in a common space.

Spatial alignment was once again assessed by visual inspection and the 'Check Data Quality' function of the Computational Anatomy Toolbox ('CAT12', an extension to SPM12) [159].

The resulting coregistered whole brain tensor eigenvalue images of the healthy subjects were used for three purposes: (a) as data basis for simulations in a 'bootstrap' manner, (b) in a leave one out examination to measure the performance of coregistration and its effect on false positives, and (c) as controls when patient data was examined.

2.3 Independent automatic evaluation of MCDs

As part of our epilepsy post–processing protocol we also used the MAP07 toolbox that performs single subject vs. control group comparisons on volumetric T_1 data derived 3D feature maps regarding the GM–WM junction (junction map), cortical gyration (extension map), and cortical thickness (thickness map). The resulting *Z*–score maps can be thresholded and/or combined (combined map) in order to pinpoint areas with suspected pathologies [135-137].

We analyzed all our cases using the default processing parameters of the MAP07 toolbox, the feature map comparisons were performed against a generic normal database provided with the software, which consists data of *150* healthy controls scanned on five different MRI systems [136]. The resulting Z–score maps were thresholded at the default *Z > 4* value and then combined and converted to ROIs.

The resulting ROIs were used to signify locations being suspicious of malformation of cortical development in the general neuroradiology workup. They have all been re–evaluated by the neuroradiology expert, and those without underlying pathology were discarded. The ROIs deemed relevant were then edited to completely cover the respective pathologies. Additional ROIs were created manually to cover lesions that were not identified by the MAP07 toolbox; finally the ROIs served as ground truth signaling the lesions in further analysis.

2.4 Mahalanobis–distance related calculations

We have implemented the calculation of the voxelwise Mahalanobis–distance (D^2) from the DTI eigenvalue maps according to (Eq. 10), the statistical inference based on critical values determined by (Eq. 11), and cluster size thresholding, in Matlab scripts and functions (MATLAB 9.2, The MathWorks Inc., Natick, MA United States). Eigenvalue maps are being read in nifti format, transformed to vector format for efficient parallelized calculations, inference is performed voxel–by–voxel, followed by cluster identification, and size thresholding (also see the bottom half of Fig 8). The same framework was used for subsequent calculations, including simulations, leave–one–out examination of controls and patient evaluations.

2.5 Simulations

The performance of the method was evaluated using simulations with two distinct sets of data: (a) Gaussian random images and (b) real diffusion tensor eigenvalue maps. Following the fashion described in [174], alternative free–response receiver–operator characteristics (AFROC) analyses were carried out on both sets.

As the critical values calculated by (Eq. 11) depend on sample size, and the aim of the simulation study was to provide grounds for later analyses; the same number of control observations (*45* subjects) were modelled in both simulations.

In order to evaluate the method's performance as a lesion detection tool, simulations were carried out with different contrast–to–noise ratios (*CNR* − i.e. effect strengths: difference between mean values of the 'lesions' and the 'background', measured in units of standard deviation with $\sigma_{lesion} = \sigma_{background}$), and lesion sizes, with a variable cluster size threshold for controlling the rate of false positives. An overview 'flow–chart', describing the steps of the simulations is shown in Fig 8.

2.5.1 Simulations with Gaussian distributions

A group of *45* 'control subjects' were generated following 3D Gaussian distribution, with zero mean and unit standard deviation in all three random variables ($\mathcal{N}_3(0,1)$, SMVND) in each voxel (upper left part of Fig 8). The spatial dimensions matched those of the real coregistered DTI data, described in subsection 'Data processing'.

True positive images were generated, starting from similar random 'noise' data and adding simulated 'lesions': 3D patches with predefined sizes, randomly generated shape, and voxel values from a distribution with the mean shifted from the background values, according to the predefined CNR. Each true positive image had one 'lesion' with a center randomly selected from *25* different locations; coordinates were defined on the template, close to the frontal, temporal, and occipital GM–WM boundary, in view of the second set of simulations with real eigenvalue data. One thousand such positives and another thousand negatives (i.e. just SMVND 'noise') were generated to calculate true and false positive rates (upper left part of Fig 8).
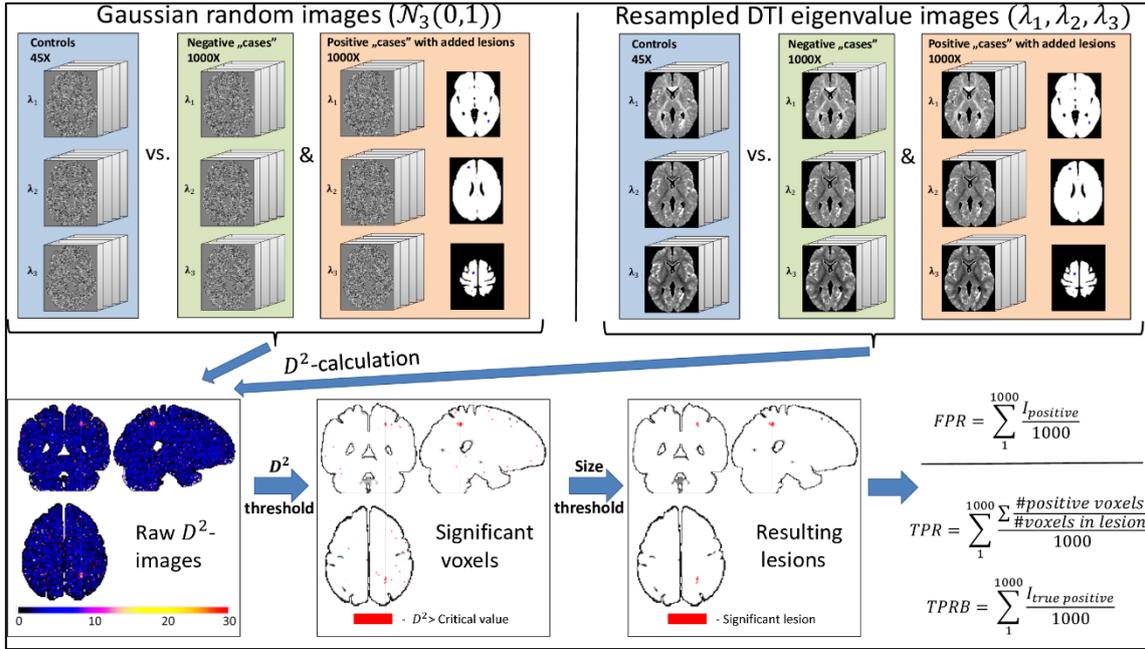
Fig 8 Flow chart demonstrating steps of the simulations.

Eigenvalue maps of standard multivariate normal distributions (SMVND – upper left) and random resampling of the real eigenvalue maps of the control subjects (upper right) were used as reference data. True negative and true positive 'cases' (with added artificial 'lesions', i.e. patches of voxel values of shifted distributions, compared to the background) were generated and the squared voxelwise Mahalanobis–distance (D^2) was calculated in relation to 45 control cases. D^2–images were subjected to thresholding using FDR– or FWE–corrected critical values (for multiple comparisons) and cluster size thresholding. False positive rates (FPR) were calculated from hits in true negative 'cases' ($I_{positive}$), while true positive rates (TPR) and hit rates (TPR–binary, i.e. TPRB) resulted from hits in the positive cases ($I_{true\ positive}$) .

After the calculation of voxelwise D^2–values, thresholding was performed using critical values calculated to control the FWE rate (i.e. Bonferroni bounds) or the FDR (using the Benjamini–Hochberg step–up algorithm on P–values calculated by the inverse of (Eq. 10)). The surviving supra–threshold voxels were subjected to cluster–size thresholding following third–neighbor (26 neighbors) cluster definition (Middle panels in the lower half of Fig 8).

The resulting binary images were used to calculate the true positive rate (TPR) in positive, and the false positive rate (FPR) in negative cases. Two types of TPR were defined, the first as the ratio of identified positive voxels (i.e. the identified lesion volume ratio, averaged over the pool of positive cases), following the definition of alternative

fractional receiver operating characteristics (AFROC) TPR as used in [174] (rightmost panel in the lower half of Fig 8).

As lesion detection is a binary problem (i.e. identifying only a part of the region of pathological tissue is also considered a positive result) any true positive voxel was counted as a hit ($I_{true\ positive}$) in the second definition of true positives (TPR – Binary – TPRB). False positives were defined similarly, as any positive cluster in a true negative (only noise) image was considered a false hit ($I_{false\ positive}$).

$$TPR = \sum_{1}^{1000} \frac{\Sigma \frac{\#positive\ voxels}{\#voxels\ in\ lesion}}{1000} \qquad (Eq.\,12)$$

$$TPRB = \sum_{1}^{1000} \frac{I_{true\ positive}}{1000} \qquad (Eq.\,13)$$

$$FPR = \sum_{1}^{1000} \frac{I_{false\ positive}}{1000} \qquad (Eq.\,14)$$

The same sets of simulations were performed for each combination of the controlled parameters with FDR and FWE critical values. TPR, TPRB and FPR values corresponding to each set of controlled parameters were used for the creation of ROC curves and the calculation of 'area under the curve' (AUC) values, using the *0 – 0.05* FPR–range, using trapezoids under the curve and the *FPR = 0.05* point determined with linear interpolation. AUC values were scaled up to the *[0, 1]* range to compensate for the limited range of interpretation. This constrained FPR–range means that in our simulations, the Family–Wise Error rate was also controlled at the subject level (above the voxel–level FWE or FDR), resulting in thorough correction for multiple comparisons.

Values of the three varied parameters are summarized in Table 2.

Table 2: CNR lesion size and cluster size threshold values used in the simulations.

CNR [σ]	1	$2\sqrt{2\ln(2)}$ [a]	3	$4\sqrt{2\ln(2)}$	-	-	-
Lesion size [#voxels]	19	35	50	100	200	-	-
Cluster size threshold [#voxels]	1	2	3	4	5	6	7

[a] Note that CNR $= 2\sqrt{2\ln(2)}$ contrast to noise ratio equals to 1 FWHM distance between the peaks of the distributions.

The desired CNR was calculated by setting the difference between means, in units of standard deviations. In SMVND simulations *σ = 1* was used, while unique values were calculated in each individual 'lesion' volume and for each eigenvalue in the second set of simulations with real DTI data.

In an exploratory analysis, additional simulations were performed with smaller effect sizes (down to *CNR = 0.1*); however, since the lesion detection performance did not exceed chance level, these results were omitted. Larger cluster size thresholds of *19, 27* and *50* voxels were also used, but, as no false positives were identified above the size of *4* voxels (*7* voxels in the second set of simulations; see subsection 2.5.2) these results are not detailed either.

2.5.2 Simulations with real eigenvalues

The second sets of simulations were performed based on the diffusion tensor eigenvalue maps of the control group using bootstrap approach, i.e. *2000* resamples considered as individual 'subjects' were generated by random resampling of voxel values from the pool of *45* control subjects (upper right part of Fig 8). Similar to the first set, half of these resamples were designed to be 'positive' with added simulated 'lesions', while the other half of the resamples was 'negative'. Finally, the same subsequent TPR, TPRB, and FPR calculations were performed as with the SMVND data, and corresponding AUC and optimal threshold vales were obtained.

While the first set of simulations used Gaussian random values in the whole brain, the bootstrapping in the second set was performed on the voxel level, thereby these values followed the distribution of tensor eigenvalues in the particular 'lesion' volume. Thus the CNR in each artificial 'lesion' was determined using a volume–specific *σ* (representing

the distribution around the GM–WM boundary), assuming $\sigma_{lesion}= \sigma_{background}$. Although this may be considered a limitation, as true MCDs are likely to exhibit atypical distribution of tensor eigenvalues, since the statistical decision is made independently in each voxel with no cluster–level inference, this assumption does not affect the detection performance directly.

2.6 Leave–one–out examination of controls

The simulations demonstrated that lesions with sufficiently high effect strengths (CNR) and volumes are detectable using the proposed Mahalanobis–distance based method, with satisfying sensitivity. On the other hand, this high sensitivity makes the approach susceptible to registration artefacts and strong individual variability, resulting in false positive clusters. In order to measure the impact this effect has on patient evaluation, data of the control subjects was also used in a leave–one–out examination, comparing each individual to the remaining *44*. Calculation of D^2–values, inference with critical values (with FWE or FDR correction), and cluster size thresholding (with the size of *7* voxels) were performed in the same manner as with the simulations. Resulting thresholded D^2–maps, indicating regions of significantly outlying diffusion profiles were transformed back to the native space of each patient's original T_1–weighted image.

2.6.1 Cluster description based on tissue probability maps (TPMs)

The results contained several clusters, in many cases obvious false positives, likely resulting from the aforementioned registration inaccuracies and individual variability in gyration patterns. In order to distinguish such false positives and increase the specificity of our method, clusters were subjected to additional post–processing in the following manner:

From each individual's Tissue Probability Maps (resulting from the initial segmentation step of the DARTEL–pipeline), we defined a new parameter describing voxel position, by subtracting the WM TPM from the CSF TPM: $\delta = P(CSF) – P(WM)$ (Fig 9). This way a δ–value was assigned to each voxel from the *[-1, 1]* range, with positive values indicating voxels closer or belonging to CSF, and negative values indicating voxels closer or belonging to WM.
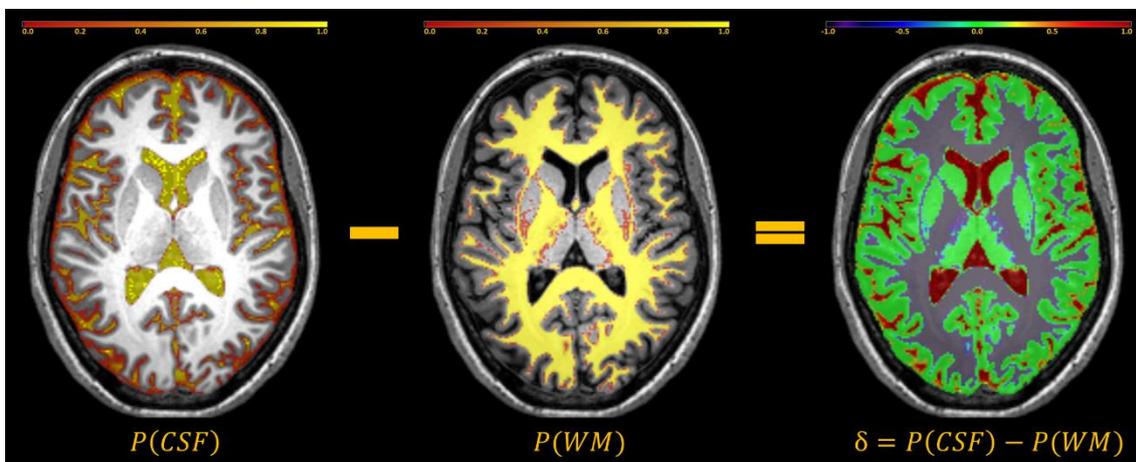
Fig 9 Definition of 'tissue probability' used for cluster filtering.

δ– values were calculated in each voxel by subtracting the probability of a voxel belonging to the white matter (WM) from the probability of it belonging to the cerebrospinal fluid (CSF), using the tissue probability maps obtained in the initial segmentation of the T_1–weighted images. The resulting δ–value indicates the voxels' position along the centrifugal WM–GM–CSF axis.

Registration artefacts around the brain surface would mainly contain voxels with positive values ($\delta > 0$; meaning that the majority of voxels are from the CSF). On the other hand, MCDs under consideration typically occur around the GM–WM boundary, thereby true clusters would contain negative values close to zero ($\delta \lesssim 0$), the distribution

of the δ–values in any given cluster could be used as an indicator of cluster position along the centrifugal WM–GM–CSF axis.

In the second step, clusters with more than half of the voxels with $\delta > 0.1$ were eliminated from the analysis. This cutoff, signaling clusters with the majority of voxels from the CSF, was determined based on the results of leave–one–out examination of controls.

2.7 Representative cases of MCDs

As described in subsection 2.2, DTI eigenvalue maps of patients with MCDs were registered to the DARTEL–template created from control data. D^2–calculation and thresholding using FWE–corrected critical values (see the corresponding subsection 2.3 for the reasoning behind using the more conservative correction), cluster size thresholding (again with 7 voxels threshold size), and the δ–value–based post–processing of the clusters were performed in the same manner as described above.

Results were qualitatively evaluated by comparing the anatomical images and D^2 'heatmaps' along with the Z–scored junction maps, resulting from independent calculations by the MAP07 toolbox [135], as described in 2.3. Clusters of outlying diffusion profile, remaining after the thresholding and artefact removal steps were considered true positive, when good spatial concurrence with the underlying pathology (as observed on anatomical scans) and the reviewed and corrected results of the MAP07 toolbox was ascertained.

An additional step included the calculation of the clusters' centers of mass (using the D^2–values as weights), and their (physical) distance from the lesion masks; created as described in 2.3.

IV. Results

1. DTI and Mild Cognitive Impairment

1.1 Voxelwise analyses

1.1.1 Voxelwise correlation analysis

Voxelwise correlation of the FA and MD values with the results of the four neuropsychological tests was found to be significant ($p < 8.4 \times 10^{-7}$) in several clusters with FDR and FWE correction. Table 3 contains the list of these clusters, while the following paragraphs also highlight the peaks of the underlying test distributions (i.e. the locations that exhibit the strongest correlation), represented by their corresponding statistical values and $[x, y, z]$ coordinates in MNI space [158].

The most significant correlation between FA values and the paired associates learning (PAL) test results was identified in the pars triangularis of the right inferior frontal gyrus ([-38, 19, 27], *R = –0.67, p < 1.36×10⁻⁷*) (Fig 10/ Panel A).

Neither the ACE–score values nor the RAVLT or the Trail Making test showed any significant correlation with FA.

Correlation of MD with three of the four tests was found to be significant in several clusters. The RAVLT score was found to be correlated to MD in the left parahippocampal gyrus ([-25, 3, -30], *R = –0.63*) (Fig 10 / Panel B).

The ACE score correlated significantly (*p < 1.53×10⁻⁷*) to MD in the left parahippocampal gyrus ([-23, 2, -30]) and in the pole of the left middle temporal gyrus ([-34, 5, -47], *R = –0.62*) with FWE correction (Fig 10 / Panel C), and in two additional clusters with FDR correction.

Ten clusters with significant correlation between the Trail Making test and the MD values were identified with FDR (*p < 5.4×10⁻⁶*) and two with FWE (*p < 2.7×10⁻⁸*) correction: one in the angular gyrus ([48, -60, 28], *R = –0.65*) (Fig 10/ Panel D) and one in the right superior temporal gyrus ([61, -46, 14], *R = +0.66*) showed the most significant correlation.

Table 3 Results of the voxelwise correlation analyses

		FA FDR				FWE	
	Number of clusters	Peak p	Cluster size [voxels]	R-score	Region [175]	Peak p	Cluster size [voxels]
PAL Test	1	8.40×10^{-7}	3	-0.63 / -0.64 / -0.64	Posterior Corona Radiata R [-29,-29,26]	-	-
ACE	-	-	-	-	-	-	-
Rey Auditory	-	-	-	-	-	-	-
Trail Making Test A	-	-	-	-	-	-	-

		MD FDR				FWE	
	Number of clusters	Peak p	Cluster size [voxels]	R-score	Region [175]	Peak p	Cluster size [voxels]
PAL Test	-	-	-	-	-	-	-
ACE	4	6.30×10^{-7}	2	-0.61 / -0.63	Para Hippocampal L [-23,2,-30]	1.53×10^{-7}	1
Rey Auditory	8	5.00×10^{-6}	19	-0.64 / -0.58	Para Hippocampal L [-25,3,-23]	1.70×10^{-7}	4
			3	-0.55 / -0.57	Hippocampus L [-31,-20,-16]		-
			2	-0.55 / -0.56	Fusiform L [-29,-11,-33]		-
Trail Making Test A	10	5.40×10^{-6}	11	+0.55 / +0.58	Temporal Mid R [56,-28,-9]	2.70×10^{-8}	1
			2	+0.56 / +0.57	Fusiform L [-39,-17,-21]		-
			7	+0.56 / +0.59	Thalamus L [-16,-28,12]		-
			3	+0.65 / +0.56	Angular R [48,-60,28]		1
			2	+0.56 / +0.57	Occipital Mid L [-31,-81,11]		-

FA: fractional anisotropy, MD: mean diffusivity, ACE: Addenbrooke's Cognitive Examination, FDR: false discovery rate control, FWE: familywise error rate control, Peak p: the highest significant p–value in a cluster, R–score: Pearson's correlation coefficient, [175]: coordinates in Montreal Neurological Institute template space.
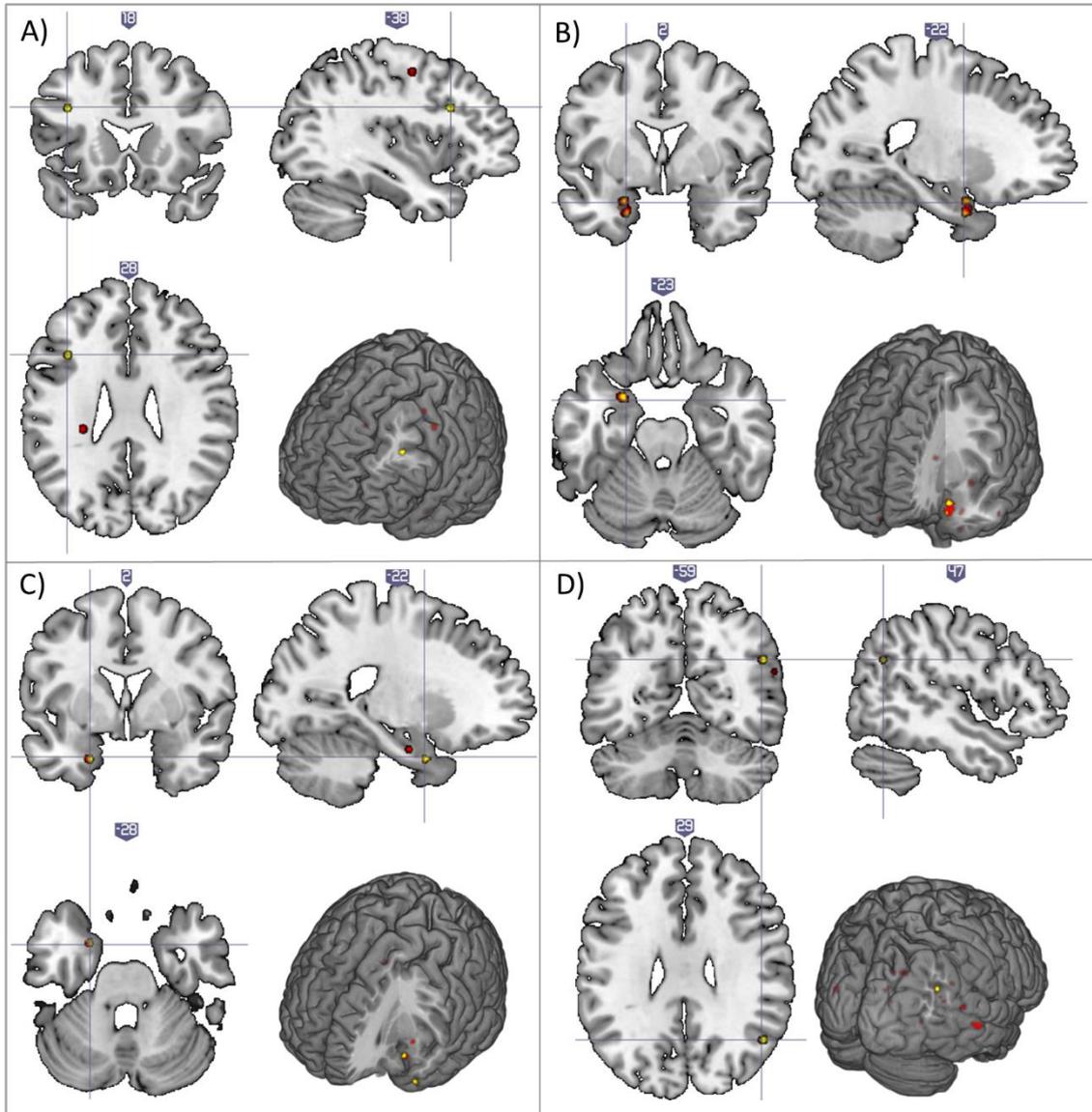
Fig 10 Results of the voxelwise correlation analyses between DTI scalar values and neuropsychological tests of healthy subjects and patients with Mild Cognitive Impairment

Regions of significantly (FWE = 0.05 in yellow, FDR = 0.05 in red) correlated DTI−scalar values: in the pars triangularis of the right inferior frontal gyrus (R = −0.67) between fractional anisotropy (FA) and the PAL test scores (Panel A); in the left parahippocampal gyrus (R= −0.63) between mean diffusivity (MD) and the RAVLT score (Panel B) and the ACE score (Panel C); and in the right angular gyrus (R = +0.65) between MD and the results of the Trail Making test (Panel D). Thresholded 1−p value maps transformed to MNI152 space and overlaid on a single subject T_1−weighted image, shown following neurological convention (left side on left). Small clusters of significant correlations emerged as peaks of larger regions with trend−like behavior; see Fig 11 for details.
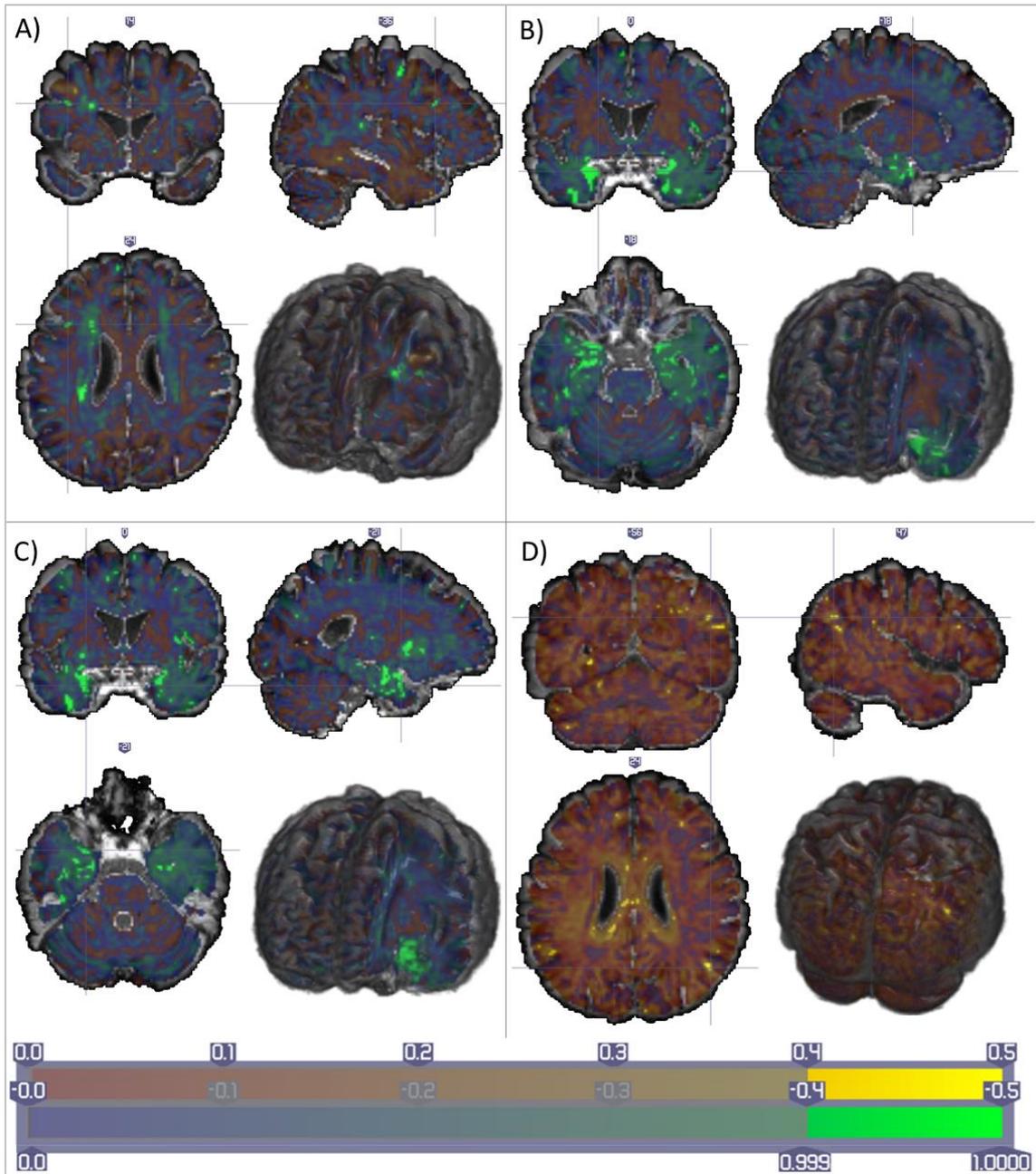
Fig 11 Voxelwise partial correlation between DTI measures and neuropsychological tests

Maps of positive (red–yellow) and negative (blue–green) partial correlation coefficients in the DARTEL Template space overlaid on a single subject T_1–weighted image (shown following neurological convention, i.e. left side on left) show clear spatial trends of correlation between fractional anisotropy (FA) and PAL Test values (Panel A), mean diffusivity (MD) and RAVLT values (Panel B), MD and ACE score values (Panel C) and MD and Trail Making Test scores (Panel D). Smaller clusters of few voxels with correlations deemed significant with FWE or FDR corrections are all located at the focal points of larger regions achieving significance at exploratory thresholds $((1-p) > 0.999)$.

The small clusters of significant correlations (p–values in the order of 10^{-7}) were identified as peaks of trend–like behavior, (as presented on Fig 11), therefore we chose not to employ cluster size thresholding, but rather eliminate voxels that did not belong to significant cluster with an exploratory threshold of $p < 0.001$, uncorrected. For example, Panels B and C of Fig 11 demonstrate that the whole left parahippocampal gyrus exhibited negative correlation (in correspondence with the underlying anatomical structure) between MD and the RAVLT or ACE scores, where the peaks spanning a few voxels were deemed significant after the strict correction for multiple comparisons.

1.1.2 Voxelwise ANOVA and between-group differences

Between-group comparison of mean diffusivity values yielded several significant results with FWE correction, while no regions showed significantly different FA. The one–way ANOVA confirmed MD differences in seven clusters of voxels, with p–values below 2.3×10^{-6}. A list of all the resulting clusters is summarized in Table 4; the largest and easily interpreted ones are once again presented in the following paragraphs with MNI–coordinates and T–values of their peaks.

Seventeen regions showed increased MD in patients with aMCI compared to controls ($p < 2.3 \times 10^{-6}$). A left inferior temporal cluster of *206* voxels ([-47, -9, -35], $T = 6.5$) and a right middle temporal cluster of *72* voxels ([59,-33,-3], $T = 5.8$) were the largest and most significant (Fig 12/ Panel A and B), while another cluster in the left superior frontal gyrus had *12* voxels (Fig 12 / Panel C; [-15, 28, 50], $T = 5.6$).

Higher MD in the naMCI group compared to the controls was confirmed with the post–hoc T–tests, in a precuneal ([-9, -66, 52], $T = 7$) and a smaller temporal ([-50, -9, -39], $T = 5.4$) cluster (*124* and *3* voxels, $p < 8.5 \times 10^{-9}$), (Fig 12 / Panel D), however, no significant difference was identified between the DTI scalar values of the two groups of MCI patients on the voxel level.

As expected, all the regions deemed significant with FWE correction emerged as peaks of the T–score "landscape" (Fig 13): focal points of regions with trend–like MD differences.

Table 4 Results of the voxelwise ANOVA and between group differences

	Number of clusters	Peak p	FA-smoothed Cluster size [voxels]	F/T-score	Region [175]
ANOVA	-	-	-	-	-
aMCI > Control	-	-	-	-	-
naMCI > Control	-	-	-	-	-

	Number of clusters	Peak p	MD-smoothed Cluster size [voxels]	F/T-score	Region [175]
ANOVA	7	2.3×10^{-6}	130	28.3	Precuneus L [-10,-68,49]
			17	18.7	Frontal Sup L [-14, 28,51]
			15	16.9	Temporal Mid R [59,-33,-3]
			67	21.6	Temporal Inf L [-48, -7, -39]
			25	21.9	Temporal Inf L [-58,-11,-32]
			13	18.6	Supra Marginal L [-56, -49, 33]
aMCI > Control	17	2.3×10^{-6}	206	6.5	Temporal Inf L [-47,-9,-35]
			13	5.5	Fusiform L [-30,-43,-19]
			39	5.2	Fusiform L [-25,-34,-14]
			72	5.8	Temporal Mid R [59,-33,-3]
			3	5.3	Cingulum Post R [3,-48,32]
			4	5.4	Angular L [-55,-50,34]
			4	5.3	Supra Marginal R[50, -41, 40]
			4	5.4	Supra Marginal R[61, -23, 39]
			26	6.0	Frontal Mid L [-31, 23,41]
			12	5.6	Frontal Sup L [-15, 28,50]
			43	6.0	Precuneus L [-9,-68,50]
			39	5.5	Precuneus L [-14,-50,62]
			4	5.4	Parietal Inf L [-52,-49,38]
naMCI > Control	2	8.5×10^{-9}	124	7	Precuneus L [-9,-66,52]
			3	5.4	Temporal Inf L [-50,-9,-39]

FA: fractional anisotropy, MD: mean diffusivity, Peak p: the peak p–value in a cluster in voxelwise calculations, ANOVA: analysis of variance, MCI: amnestic mild cognitive impairment, naMCI: non amnestic mild cognitive impairment, [175]: coordinates in Montreal Neurological Institute template space.
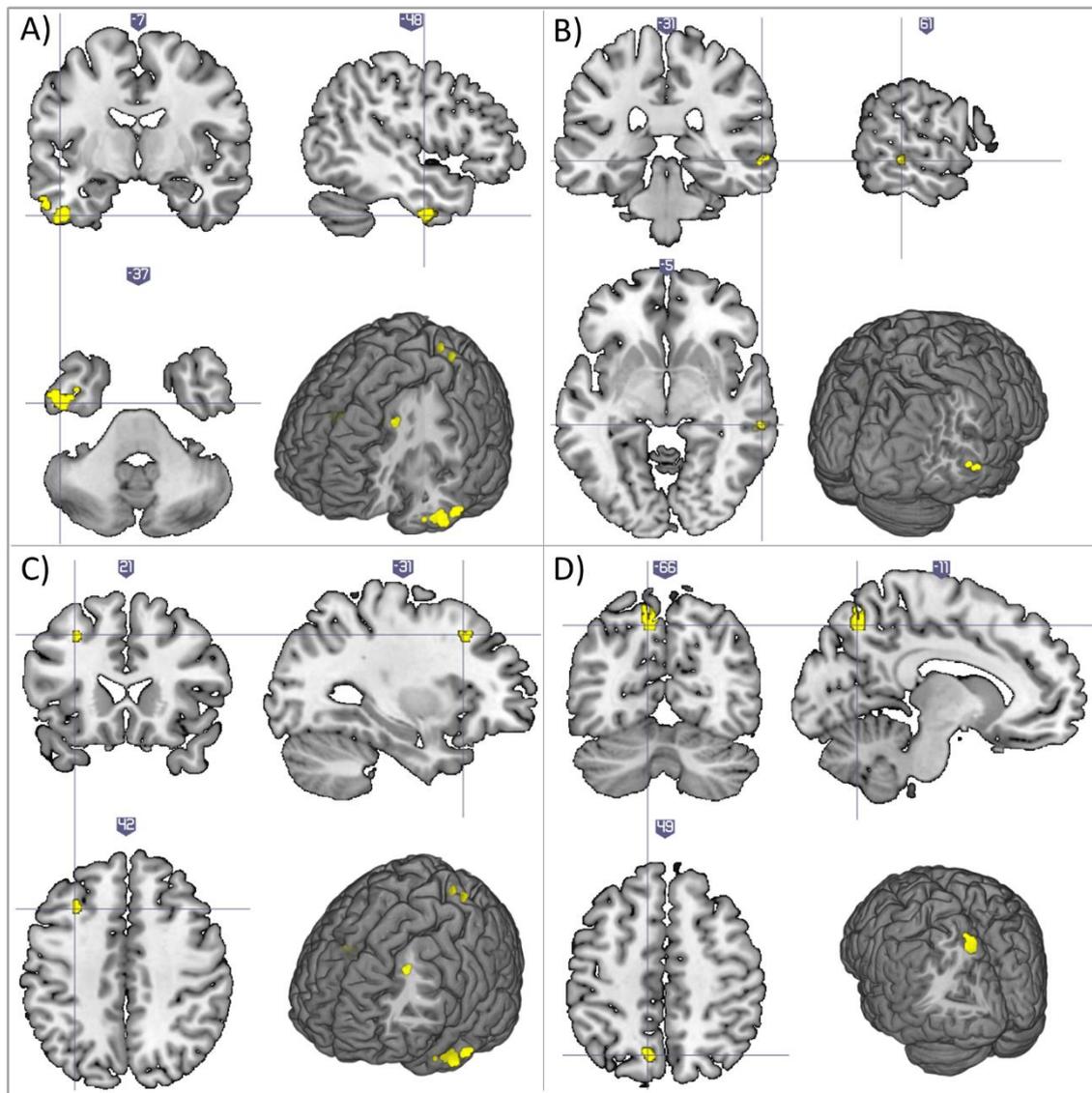
Fig 12 Significant results of the voxelwise between group analyses

Between–group, two sample *T*–tests identified regions of higher mean diffusivity (MD) in the left inferior temporal gyrus (A), the right middle temporal gyrus (B), and the left superior frontal gyrus (C) in the amnestic MCI group, and also in the left precuneus (D) in the non–amnestic MCI group, compared to healthy control subjects. Maps showing clusters with significant (FWE corrected on voxel level) differences transformed to MNI152 space and overlaid on a single subject T_1–weighted image, shown following neurological convention (left side on left). Small clusters of significant differences all emerge as peaks of larger regions with trend–like behavior; see Fig 13 for details.
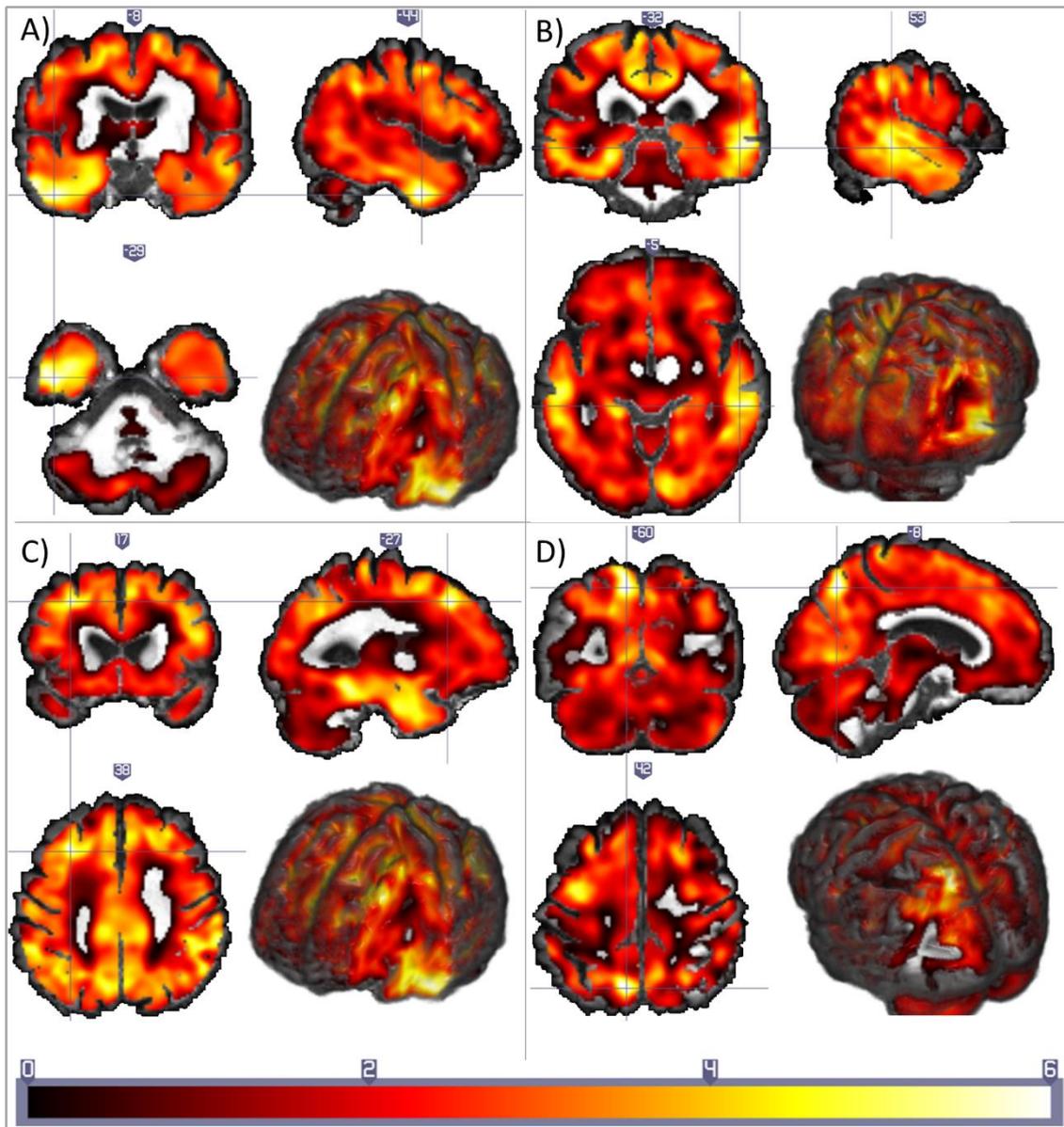
Fig 13 *T*–score 'landscape' of the voxelwise between group comparisons

Between–group, two sample *T*–tests identified regions of higher mean diffusivity (MD) values in the left inferior temporal gyrus (A), the right middle temporal gyrus (B), and the left superior frontal gyrus (C) in the amnestic MCI group, and also in the left precuneus (D) in the non–amnestic MCI group, compared to healthy control subjects. Raw *T*–score maps in the DARTEL Template space overlaid on a single subject T$_1$–weighted image (shown following neurological convention, i.e. left side on left) reveal regions of higher MD values with clear maxima in locations deemed significant.

1.2 ROI–based analyses

1.2.1 ROI–based correlations with the results of the neuropsychology tests

Both FA and MD in the left cingulum and in the left stria terminalis / left crus of the fornix correlated with the RAVLT total scores, with the total adjusted trials in the PAL test, and with the total and verbal fluency scores of the ACE. The results are summarized in Fig 14. After correction for age the correlation between RAVLT total score and MD in the left cingulum (Pearson partial $R = -0.41$ (Spearman partial $R = -0.39$), $n = 65$, $p = 0.0008$), and the correlation between the PAL test result and MD in the left stria terminalis / left crus of the fornix (Pearson partial $R = 0.51$ (Spearman partial $R = 0.47$), $n = 54$, $p = 0.0001$) remained significant. Furthermore, the correlations of the RAVLT (Pearson partial $R = 0.43$ (Spearman partial $R = 0.43$), $n = 65$, $p = 0.0004$) and the verbal fluency subscore of the ACE (Pearson partial $R = 0.40$ (Spearman partial $R = 0.48$), $n = 65$, $p = 0.001$) with FA in the left cingulum were found significant, while correlation of the ACE total score with FA in the left cingulum did not reach the level of significance (Pearson partial $R = 0.39$ (Spearman partial $R = 0.44$), $n = 65$, $p = 0.0015$).
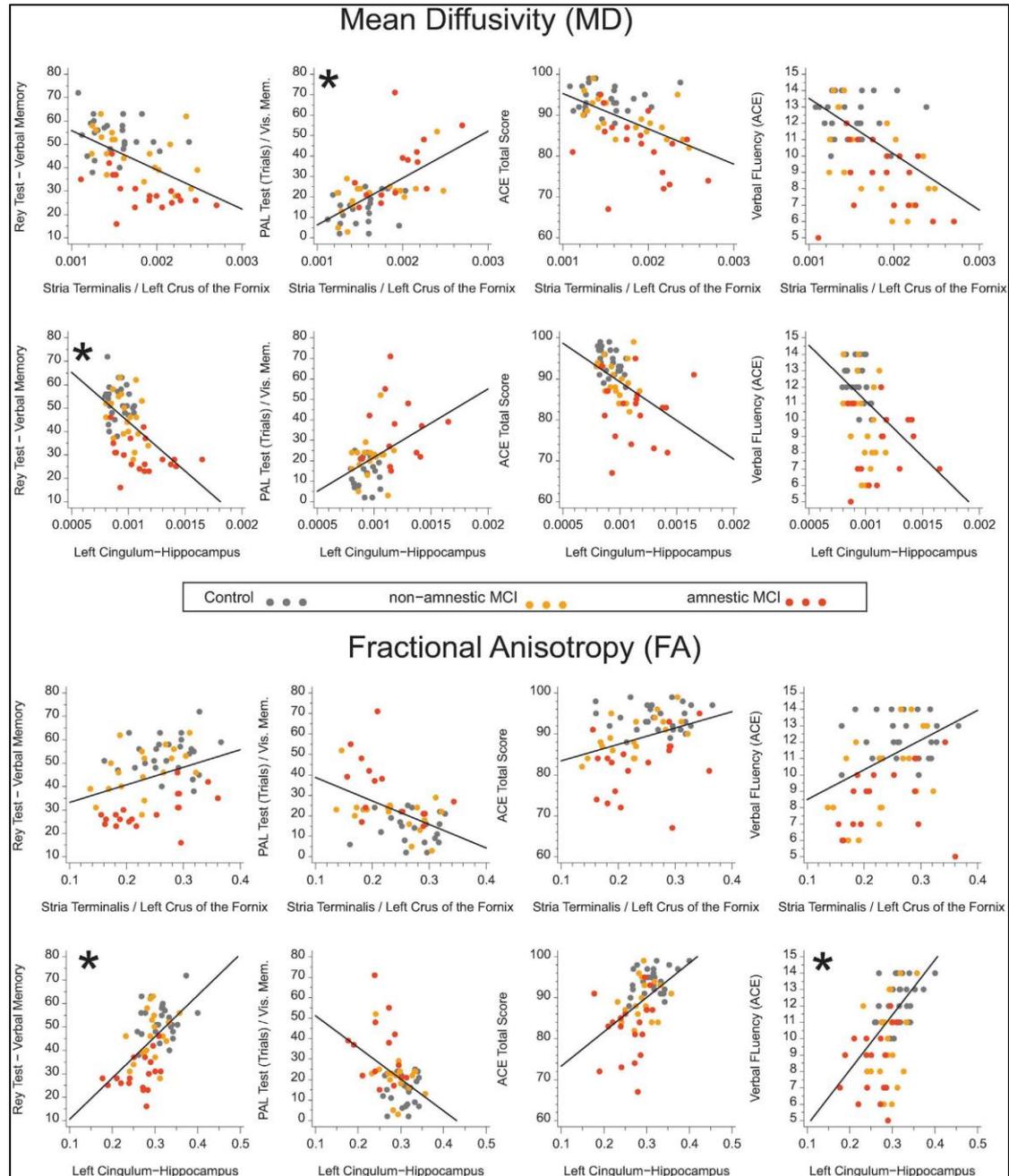
Fig 14 Results of the correlation analyses between DTI measures and neuropsychological tests

Results of the correlation analyses between the average values of mean diffusivity (MD) and fractional anisotropy (FA) in the ROIs covering the left cingulum and the left crus of the fornix, and the results of the four neuropsychological tests. (The Rey Verbal test, which measures verbal memory, the PAL – Paired Associates Learning – test, that measures visual memory, the ACE – Addenbrooke's Cognitive Examination –, a comprehensive measure of cognitive functions, and a relevant subscore of the ACE test, measuring verbal fluency). Different colors represent the three study groups. All correlations are corrected for multiple comparisons. Correlations remained significant after correction for age are marked with asterisk. Trend lines in black are fitted for the whole sample.

1.2.2 ROI–based between group differences

Fractional anisotropy of the left cingulum (hippocampal subdivision) was significantly decreased in the aMCI group relative to the control group ($F(1, 44) = 20.4$, $p < 0.0001$) and to the naMCI group ($F(1, 37) = 15.7$, $p < 0.0004$), while FA did not differ between controls and naMCI subjects ($p > 0.05$); (lower left panel of Fig 15). Mean diffusivity of the left cingulum was significantly increased in the aMCI group relative to controls ($F(1, 44) = 19.8$, $p < 0.0001$) and subjects with naMCI ($F(1, 37) = 12.5$, $p < 0.0012$). Again, controls and naMCI subjects did not differ from each other (upper left panel of Fig 15). Furthermore a tendency level difference in MD was detected between controls and aMCI patients in the left stria terminalis and the left crus of the fornix ($p = 0.0041$; upper right panel of Fig 15), with a similar but non–significant pattern of differences regarding FA (lower right panel of Fig 15).
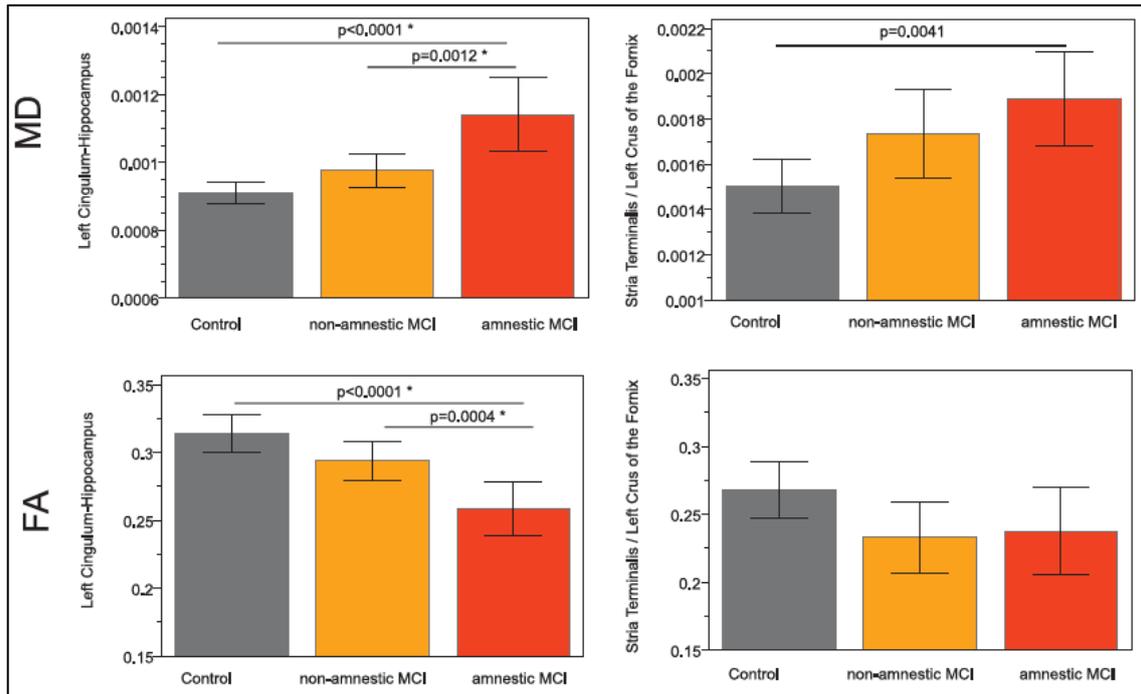
Fig 15 Between–group differences in fractional anisotropy (FA) and mean diffusivity (MD)

Mean values of fractional anisotropy (FA) and mean diffusivity (MD) in the three subject groups in two regions of interest (ROIs) show between–group differences from the post–hoc tests following the Analysis of Covariance (ANCOVA) calculations, with age and gender as covariates. The 'Left Cingulum–Hippocampus' ROI showed significant differences after Bonferroni's correction for multiple comparisons (marked with asterisks) between the amnestic mild cognitive impairment (aMCI) and control groups; while the 'Stria Terminalis/Left Crus of the Fornix' only contained nominal differences in MD and FA, not significant after Bonferroni's correction.

1.3 ROI–based logistic regression analysis: combined cortical thickness and DTI–based differentiation between study groups

In the first set of stepwise logistic regression models, only cortical thickness measurements and subcortical brain structure volumes were entered as variables. Structures with the largest discriminatory power (a Cohen's *d* of at least one, i.e. more than one SD difference between study groups) were used as input [110], namely the volume of the hippocampus, the cortical thickness of the entorhinal cortex, the fusiform gyrus, the precuneus, and the isthmus of the cingulate gyrus.

These volumetric and thickness measurements of grey matter structures were amended with the FA and MD measurements of the *36* WM ROIs (i.e. tracts) in the second and third sets of models, separately. Categorization results of each model, when

tested on the independent, albeit small test subsets are summarized in Table 5–Table 13 and detailed on the subject level in the supplementary Tables S1-S9; the following subsections contains a brief overview.

1.3.1 Differentiation between aMCI subjects and healthy controls

The volume of the left (in *8* out of the *10* training subsets) or the right (in the remaining *2* subsets) hippocampus stayed in the models after the stepwise logistic regression, based solely on volumetric measures; the former extended by the cortical thickness of the precuneus in three subsets. Overall, *78.95%* of the subjects was categorized correctly across the subsets. (Table 5)

The average FA of the aforementioned WM structures did not stay in the models after stepwise logistic regression, in any but the last subset, where the average FA of the 'stria terminalis / left crus of the fornix' was selected as a potential measure with substantial difference , however, the overall categorization performance did not change. With the second test–subgroup, the volume of the right hippocampus was replaced by the volume of the left hippocampus, once again, with no resulting effect on categorization. (Table 6)

None of the MD measurements remained in the third set of models, thus the original GM–volumetric models were not improved by including DTI this way, however, categorization of the second test–subgroup was slightly improved (one more correct decision) with the average cortical thickness of the precuneus, raising overall correct categorization to *81.58%* across subsets. (Table 7).

Table 5 Logistic regression: amnestic MCI vs. Control – only volumetry

Test set no.	Effect1	Effect2	Ratio
1	Left Hippocampus^V	Meanthickavg precuneus^T	0.75
2	Right Hippocampus^V		0.25
3	Left Hippocampus^V		1
4	Left Hippocampus^V		0.5
5	Left Hippocampus^V	Meanthickavg precuneus^T	0.75
6	Left Hippocampus^V		1
7	Left Hippocampus^V		1
8	Right Hippocampus^V		1
9	Left Hippocampus^V		1
10	Left Hippocampus^V	Meanthickavg precuneus^T	0.5

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Effect1 & 2: volumetric, or cortical thickness measurements deemed meaningful in the stepwise logistic regression; Meanthickavg: average cortical thickness; Ratio: decision performance in each subgroup. ^{V}: volumetry–based measure ^{T}: thickness–based measure

Table 6 Logistic regression: amnestic MCI vs. Control – volumetry with FA

Test set no.	Effect1	Effect2	Effect3	Ratio
1	Left Hippocampus^V	Meanthickavg precuneus^T		0.75
2	Left Hippocampus^V			0.25
3	Left Hippocampus^V			1
4	Left Hippocampus^V			0.5
5	Left Hippocampus^V	Meanthickavg precuneus^T		0.75
6	Left Hippocampus^V			1
7	Left Hippocampus^V			1
8	Right Hippocampus^V			1
9	Left Hippocampus^V			1
10	Left Hippocampus^V	Meanthickavg precuneus^T	Fornix crus Stria terminalis L^{DTI}	0.5

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10*[th], which contained the last *2* controls), the remaining *35 (37)* were used as training data; Effect1, 2 & 3: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; Meanthickavg: average cortical thickness; Ratio: decision performance in each subgroup; ^{V}: volumetry–based measure; ^{T}: thickness–based measure; DTI: DTI–based measures

Table 7 Logistic regression: amnestic MCI vs. Control – volumetry with MD

Test set no.	Effect1	Effect2	Ratio
1	Left Hippocampus^V	Meanthickavg precuneus^T	0.75
2	Left Hippocampus^V	Meanthickavg precuneus^T	0.5
3	Left Hippocampus^V		1
4	Left Hippocampus^V		0.5
5	Left Hippocampus^V	Meanthickavg precuneus^T	0.75
6	Left Hippocampus^V		1
7	Left Hippocampus^V		1
8	Right Hippocampus^V		1
9	Left Hippocampus^V		1
10	Left Hippocampus^V		0.5

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10*th, which contained the last *2* controls), the remaining *35 (37)* were used as training data.; Effect1 & 2: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; Meanthickavg: average cortical thickness; Ratio: decision performance in each subgroup; ^{V}: volumetry based measure; ^{T}: thickness based measure

1.3.2 Differentiation between naMCI subjects and healthy controls

Volumetry– and thickness–based models with each but one test–subset included the average cortical thickness of the precuneus, with the only other meaningful measure being the volume of the right hippocampus. (Table 8)

Adding the FA measures to the models resulted in having the average values measured in the fornix (body and column), the posterior thalamic radiation, the right or left external capsule, or the right superior fronto–occipital fasciculus staying in the model, separately, each of them in some of the test subsets, however, the original overall *52.63%* categorization performance was once again only slightly improved (to *55.26%*, meaning only two more correct decisions). (Table 9)

Average MD of the left cingulum (hippocampus), the left external capsule, or the fornix (body and column) was also found meaningful for few of the models, yet the overall categorization performance was only slightly improved, with *3* more correct decisions in total (*57.89%* of all subjects). (Table 10)

Table 8 Logistic regression: non–amnestic MCI vs. Control – only volumetry

Test set no.	Effect1	Effect2	Ratio
1	Meanthickavg precuneus^T		0.5
2	Right Hippocampus^V	Meanthickavg precuneus^T	0.5
3	Meanthickavg precuneus^T		0.5
4	Meanthickavg precuneus^T		0.5
5	Meanthickavg precuneus^T		0.75
6	Right Hippocampus^V	Meanthickavg precuneus^T	0.5
7	Right Hippocampus^V		0.5
8	Meanthickavg precuneus^T		0.5
9	Meanthickavg precuneus^T		0.5
10	Meanthickavg precuneus^T		0.5

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data; Effect1 & 2: volumetric or cortical thickness measurements deemed meaningful in the stepwise logistic regression; Meanthickavg: average cortical thickness; Ratio: decision performance in each subgroup; ^{V}: volumetry based measure; ^{T}: thickness based measure

Table 9 Logistic regression: non–amnestic MCI vs. Control – volumetry with FA

Test sett no.	Effect1	Effect2	Effect3	Ratio
1	Meanthickavg precuneus[T]	Fornix column & body of fornix[DTI]		0.75
2	Right Hippocampus[V]	Meanthickavg precuneus[T]		0.5
3	Meanthickavg precuneus[T]	Posterior thalamic radiation R[DTI]	External capsule R[DTI]	0.25
4	Meanthickavg precuneus[T]	External capsule_R[DTI]		0.5
5	Meanthickavg precuneus[T]	Fornix column & body of fornix[DTI]	Superior fronto occipital fasciculus R[DTI]	1
6	Cingulum hippocampus L[DTI]			0.25
7	Right Hippocampus[V]			0.5
8	Meanthickavg precuneus[T]	External capsule L[DTI]	Tapetum L[DTI]	0.5
9	Meanthickavg precuneus[T]	Fornix column & body of fornix[DTI]		0.75
10	Meanthickavg precuneus[T]	External capsule L[DTI]		0.5

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data.; Effect1, 2 & 3: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; Meanthickavg: average cortical thickness; Ratio: decision performance in each subgroup; [V]: volumetry based measure; [T]: thickness based measure; [DTI]: DTI–based measure

Table 10 Logistic regression: non–amnestic MCI vs. Control – volumetry with MD

Test set no.	Effect1	Effect2	Ratio
1	Meanthickavg precuneus^T	Cingulum hippocampus L^{DTI}	0.5
2	Right Hippocampus^V	Cingulum hippocampus L^{DTI}	0.25
3	Meanthickavg precuneus^T		0.5
4	Meanthickavg precuneus^T	Cingulum hippocampus L^{DTI}	0.75
5	Meanthickavg precuneus^T	Cingulum hippocampus L^{DTI}	0.75
6	Right Hippocampus^V	Meanthickavg precuneus^T	0.5
7	Right Hippocampus^V		0.5
8	Meanthickavg precuneus^T	External capsule L^{DTI}	0.75
9	Meanthickavg precuneus^T	Fornix column & body of fornix^{DTI}	0.75
10	Meanthickavg precuneus^T	External capsule L^{DTI}	0.5

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data; Effect1, 2 & 3: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; Meanthickavg: average cortical thickness; Ratio: decision performance in each subgroup; ^{V}: volumetry based measure; ^{T}: thickness based measure; ^{DTI}: DTI–based measure

1.3.3 Differentiation between aMCI and naMCI subjects

The same volume and cortical thickness measures were entered into the first set of models as in the former comparisons, once again followed by adding the average DTI scalar values of the same ROIs as before. (Table 11)

The first set of stepwise logistic regression calculations (only volumetric and thickness measurements) all identified the volume of the left hippocampus as the only meaningful effect, and achieved an overall *63.89%* correct categorization performance (*23* subjects out of the *36*) in the nine separate models.

After adding FA measurements of WM ROIs, the average value in the 'stria terminalis / left crus of the fornix' stayed as a relevant effect in all nine models; interestingly the volume of the left hippocampus was replaced by the volume of the right hippocampus in two of the models.

This addition of the average FA of this specific WM region improved correct categorization with all but one test subsets, resulting in an overall *86.11%* (*31* correct decisions out of *36*) categorization performance, a solid *22.22%* (*8* subjects) increase compared to the solely volumetry–based models. (Table 12)

Average MD values of the body of the corpus callosum (*8* models) or the column and body of the fornix (one model) also improved the categorization performance in the final sets of models: together with the volume of the left hippocampus, *75%* (*27* out of *36*) of subjects were categorized correctly.(Table 13)

Table 11 Logistic regression: amnestic vs non–amnestic MCI – only volumetry

Test set no.	Effect1	Ratio
1	Left Hippocampus^V	0.5
2	Left Hippocampus^V	0.5
3	Left Hippocampus^V	1
4	Left Hippocampus^V	0.5
5	Left Hippocampus^V	0.25
6	Left Hippocampus^V	1
7	Left Hippocampus^V	0.75
8	Left Hippocampus^V	0.75
9	Left Hippocampus^V	0.5

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Effect1: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; Ratio: decision performance in each subgroup; ^{V}: volumetry based measure

Table 12 Logistic regression: amnestic vs non–amnestic MCI – volumetry with FA

Test set no.	Effect1	Effect2	Ratio
1	Left Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	0.75
2	Right Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	1
3	Left Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	1
4	Left Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	0.25
5	Left Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	1
6	Left Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	1
7	Left Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	1
8	Right Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	1
9	Left Hippocampus [V]	Fornix crus Stria terminalis L [DTI]	0.75

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Effect1&2: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; Ratio: decision performance in each subgroup; [V]: volumetry based measure; [DTI]: DTI–based measure

Table 13 Logistic regression: amnestic vs non–amnestic MCI – volumetry with MD

Test set no.	Effect1	Effect2	Mean
1	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	0.5
2	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1
3	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1
4	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	0.25
5	Left Hippocampus ^{V}	Fornix column & body of fornix ^{DTI}	0.5
6	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	0.75
7	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1
8	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1
9	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	0.75

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Effect1&2: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; Ratio: decision performance in each subgroup; ^{V}: volumetry based measure; ^{DTI}: DTI–based measure

2. Mahalanobis–distance in MCD lesion detection

The squared Mahalanobis-distance (D^2) and the critical values used for inference were calculated using in-house algorithms following (Eq. 10) and (Eq. 11). The analytical derivation uses the number of observations, dimensions, and desired level of significance; the appropriate critical values were determined for each application.

The FWE–corrected, D^2 critical value, calculated from n = 46, p = 3, and $\alpha_{FWE} = \frac{0.05}{\#voxels} = \frac{0.05}{3.4054 \times 10^5} = 1.4683 \times 10^{-7}$ was **27.8324**. This value was used in simulations and subject evaluations.

As FDR correction uses the *p*–values of each statistical test and determines the critical *p* for a given set (the tests in each voxel, in our case), the FDR corrected D^2 critical values were unique for each patient image, typically in the range between *19* and *21*.

Groupwise average values and standard deviation for the whole grey and white matter of the coregistered eigenvalue maps from the controls are included in Table 14, while their spatial distributions are presented in Fig 16.

Table 14 Mean values and standard deviations of the tensor eigenvalues

	Grey Matter		White Matter	
	Mean	SD	Mean	SD
λ1	1.1295×10^{-3}	2.3623×10^{-4}	1.2117×10^{-3}	2.5012×10^{-4}
λ2	9.3691×10^{-4}	2.1694×10^{-4}	8.0431×10^{-4}	1.6876×10^{-4}
λ3	8.1112×10^{-4}	2.1290×10^{-4}	6.0377×10^{-4}	1.7571×10^{-4}

Means and standard deviations (SD) of the DTI eigenvalues, averaged over the control sample, in the whole grey and white matter, presented in units of mm^2/s.

During manual revision of the results of independent lesion detection with the MAP07 toolbox, only *11* abnormalities were identified in the example cases, thereby the remaining lesion masks were entirely hand drawn.
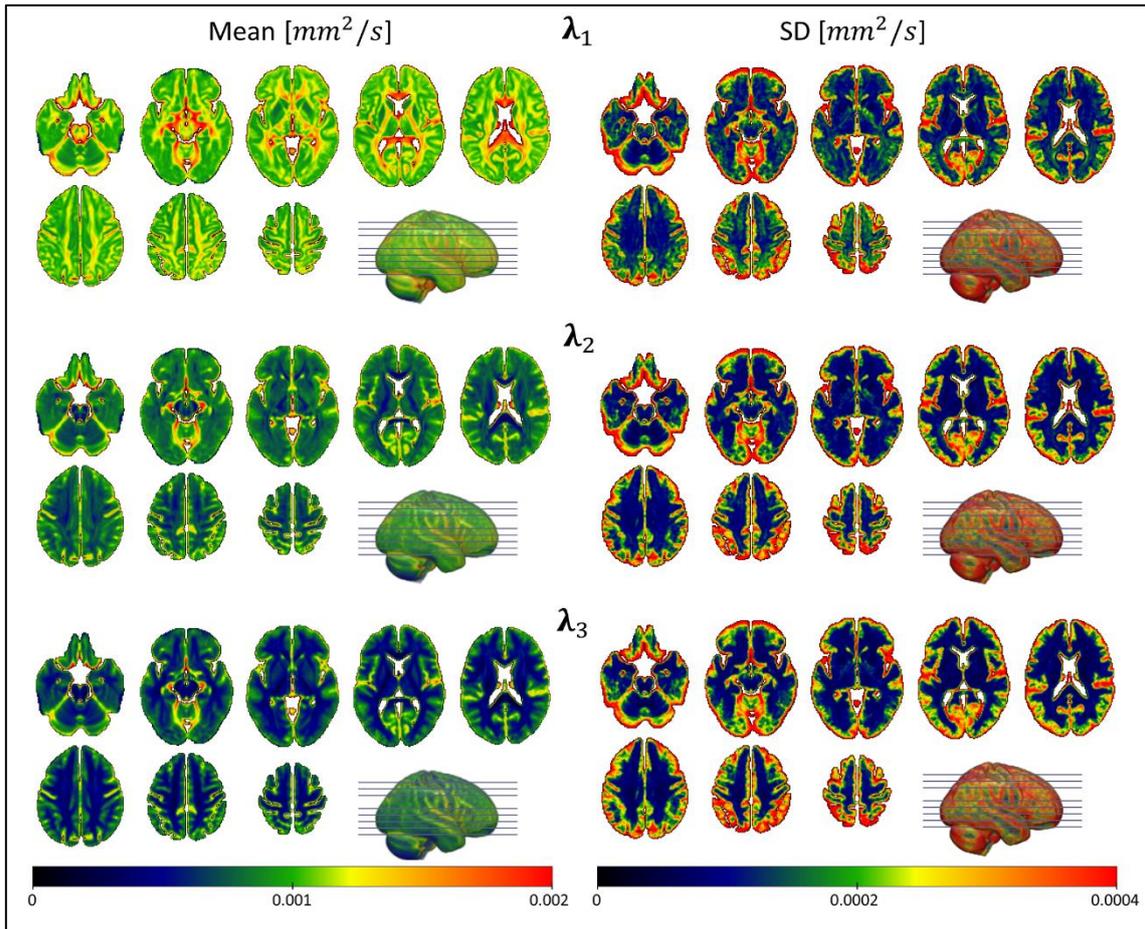
Fig 16 Spatial distribution of the sample–wise mean and standard deviation of the coregistered eigenvalue maps from the controls.

Mean values (left column) and standard deviations (right column) are presented on the same respective scales for the three diffusion tensor eigenvalues in units of mm²/s.

2.1 SMVND simulations

2.1.1 False Positives

In the simulations with SMVND data, false positives were identified in all cases when no cluster size thresholding was employed, with both FWE and FDR corrected critical values. On the contrary, no false positives were identified with thresholds larger than *4* voxels, meaning that for simulated lesions with voxel values from standard Gaussian distribution, and sizes that are reasonable to assume any true malformation would have, the method had *100%* specificity.

2.1.2 True positive rates and hit rates

AUC values, calculated for each lesion size–CNR parameter pair, with both FWE and FDR corrected critical values are summarized in Table 15 for both definitions of true positives (AFROC curves can be seen in Fig 17). As expected, with increasing CNR and lesion sizes, both the TPR and the TPRB (hit rate) increased.

Table 15 AUC value results of the simulations with SMVND data

SMVND										
					FDR					
Lesion size [vox] →	19		35		50		100		200	
CNR ↓	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary
2σ	0.000	0.000	0.000	0.004	0.000	0.003	0.000	0.005	0.001	0.011
1 FWHM	0.296	0.593	0.339	0.840	0.349	0.941	0.368	0.998	0.382	1.000
3σ	0.660	0.953	0.702	0.998	0.713	0.999	0.736	1.000	0.752	1.000
2 FWHM	0.996	1.000	0.998	1.000	0.999	1.000	0.999	1.000	0.999	1.000
					FWE					
Lesion size [vox] →	19		35		50		100		200	
CNR ↓	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary
2σ	0.000	0.000	0.000	0.004	0.000	0.003	0.000	0.005	0.000	0.011
1 FWHM	0.158	0.593	0.185	0.840	0.201	0.941	0.216	0.998	0.222	1.000
3σ	0.493	0.953	0.536	0.998	0.555	0.999	0.576	1.000	0.580	1.000
2 FWHM	0.984	1.000	0.991	1.000	0.994	1.000	0.995	1.000	0.996	1.000

Area under the curve (AUC) values resulting from the alternative free–response receiver–operator characteristics curves (AFROC) of simulations with standard multivariate normal distribution (SMVND) data, FDR and FWE corrected critical values, and following both the fractional and binary definition of true positive rate (TPR); calculated from the *[0; 0.05]* false positive rate (FPR) range.
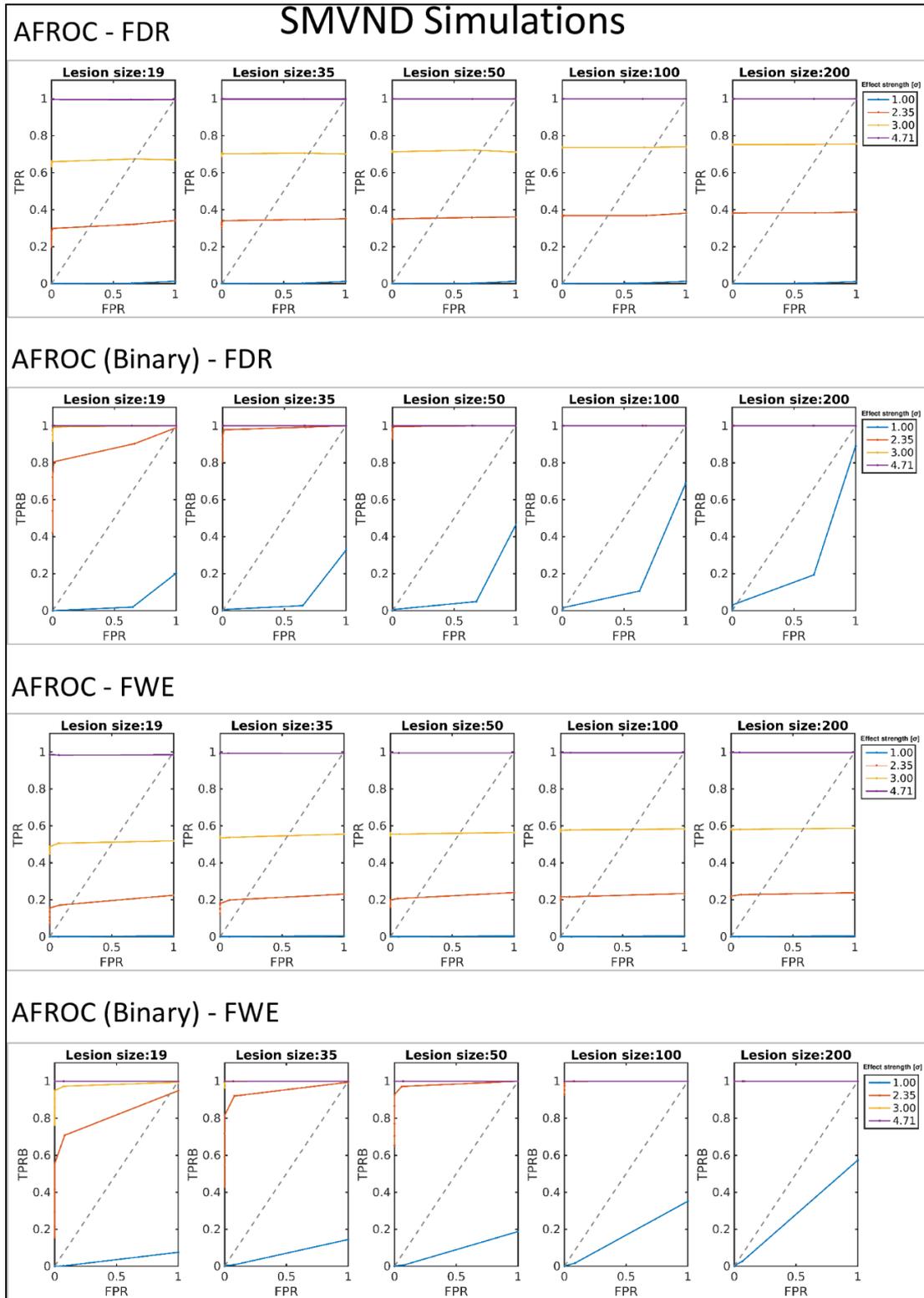
Fig 17 Alternative free–response receiver–operator characteristic (AFROC) curves of the simulations with standard multivariate normally distributed (SMVND) data.

Results with both FWE– and FDR–corrected critical values, following both definitions of true positives (fraction of positive voxels – TPR – and hit rates – TPRB), with all different values for simulated lesion size and effect strength (contrast to noise ratio) are presented.

In the *[0; 0.05]* FPR interval, all AUC values exceeded *84%* in lesion detection, with lesion sizes above *19* voxels and CNR above *1* FWHM, using either FDR or FWE–corrected critical values. More than half of the lesion voxels were identified with *CNR > 3σ*, with all lesion sizes and critical values (except for the smallest lesions and FWE correction, were the AUC was *0.493*).

2.2 Real Eigenvalue simulations

2.2.1 False Positives

Simulations based on real DTI eigenvalue data resulted in similar behavior of false positives: every case showed false positive clusters with a minimum size of one or two voxels, but with cluster size thresholds of *6* (with FWE–correction) or *7* (with FDR–correction) voxels, FPR decreased to *0.1 – 0.3%* (i.e. *1 – 3* false positives per sets of *1000* simulations).

2.2.2 True positive rates and hit rates

The resulting AUC values are summarized in Table 16; AFROC curves are presented in Fig 18.

Lesion identification performance (Binary *AUC*) was above 70% with *CNR = 1FWHM* in cases of lesions larger than *50* voxels, or with *CNR = 3σ* and at least *35* voxels, using either FDR, or FWE–corrected critical values. More than half of the lesion voxels were identified at *CNR = 2FWHM*, achieving *77.3 – 85.9%* AUC with FDR–corrected, and *75.1 – 77.8%* AUC with FWE corrected critical values.

Based on these simulation results, we expected the proposed method to identify the abnormal diffusion profile of MCDs in patients. A seven-voxel large cluster size threshold was used in subsequent analyses, first with FDR–corrected critical values, but the latter were replaced by the FWE-corrected ones, as described in 2.3.1.

Table 16 AUC value results of the simulations with Real Eigenvalue data

Real Eigenvalues										
FDR										
Lesion size [vox] →	19		35		50		100		200	
CNR ↓	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary
2σ	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.002	0.001	0.018
1 FWHM	0.161	0.299	0.228	0.533	0.229	0.596	0.248	0.702	0.272	0.863
3 σ	0.430	0.637	0.450	0.756	0.414	0.740	0.456	0.884	0.463	0.939
2 FWHM	0.773	0.858	0.843	0.940	0.859	0.960	0.822	0.920	0.818	0.920
FWE										
Lesion size [vox] →	19		35		50		100		200	
CNR ↓	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary	AUC	AUC Binary
2σ	0.000	0.000	0.000	0.000	0.000	0.001	0.000	0.001	0.000	0.001
1 FWHM	0.108	0.221	0.141	0.403	0.160	0.544	0.168	0.696	0.166	0.752
3σ	0.337	0.598	0.353	0.712	0.352	0.745	0.356	0.835	0.353	0.946
2 FWHM	0.751	0.947	0.776	0.998	0.778	0.999	0.777	1.000	0.760	0.980

Area under the curve (AUC) values resulting from the alternative fractional receiver operating characteristics curves (AFROC) of real eigenvalue simulations with FDR and FWE corrected critical values and following both the fractional and binary definition of true positive rate (TPR); calculated from the *[0; 0.05]* false positive rate (FPR) range.
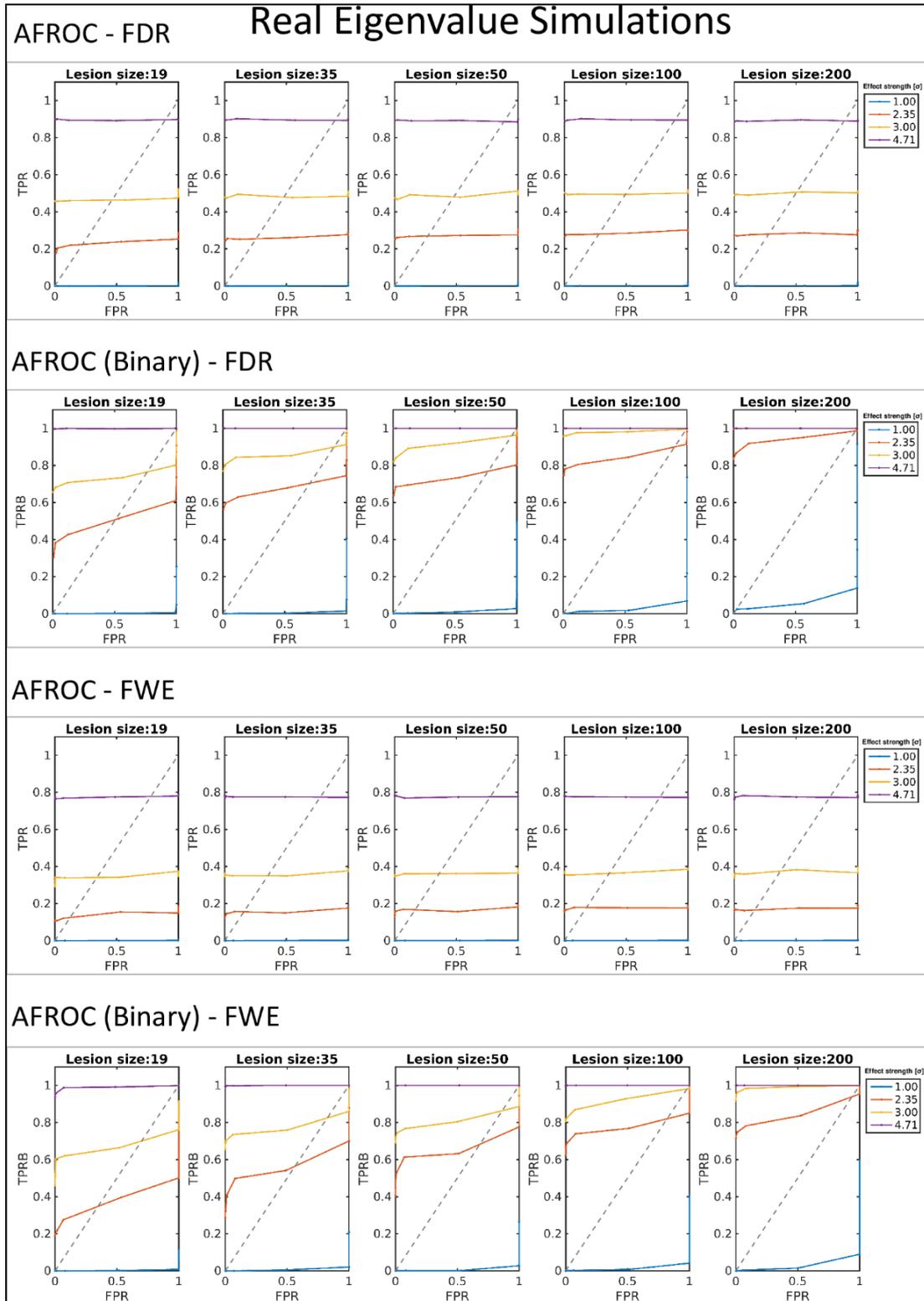
Fig 18. Alternative fractional receiver operating characteristics (AFROC) curves corresponding to the simulations based on real diffusion tensor eigenvalue data.

Results with both FWE– and FDR–corrected critical values, following both definitions of true positives (fraction of positive voxels –TPR– and hit rates –TPRB), with all different values for simulated lesion size and effect strength (contrast to noise ratio) are presented.

2.3 Real data examinations

2.3.1 Leave–one–out analysis of controls

The FDR–corrected critical values resulted in an average of *21.11 (5 – 55)* clusters/subject, while the more conservative FWE–correction yielded *4.93 (0 – 13)* clusters in average, *1.79 (0 – 5)* of those being in the WM. Based on this result, combined with the observation that the true positive clusters in subsequent patient examinations were also present with the more conservative approach (Fig 19), we decided to only use critical values aimed to control the FWE for patient examinations, decreasing the influence of inherent variability and/or coregistration inaccuracy.
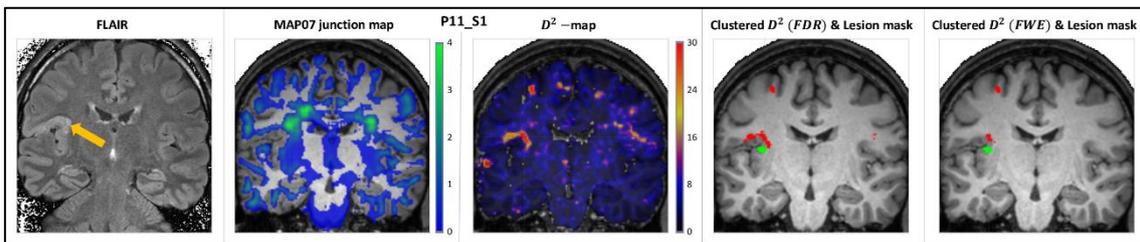
Fig 19 Comparison of the results with FDR and FWE corrected critical values.

Thresholded and clustered D^2–results overlaid on the T_1–weighted image of a 27 y.o. male patient with polymicrogyria in the basal region of the left inferior frontal gyrus (see panel D of Fig 21, as well.) Coronal slices presented in neurological orientation, i.e. left side is on the left, slices of the 2D FLAIR image were angulated perpendicular to the axes of the hippocampi.

After removing clusters based on the δ–values (those with more than half of the voxels with $\delta > 0.1$), the number of remaining clusters decreased to an average of *2.79 (0–7)* with an average size of *16.21* voxels *(7–167)*, meaning, that most of those resulting from insufficient coregistration or normal differences in gyrification patterns (mainly located in the CSF) were filtered out. Examples of the resulting few minimal cluster–masks overlaid on each control subject's T_1–weighted images are shown on Fig 20.
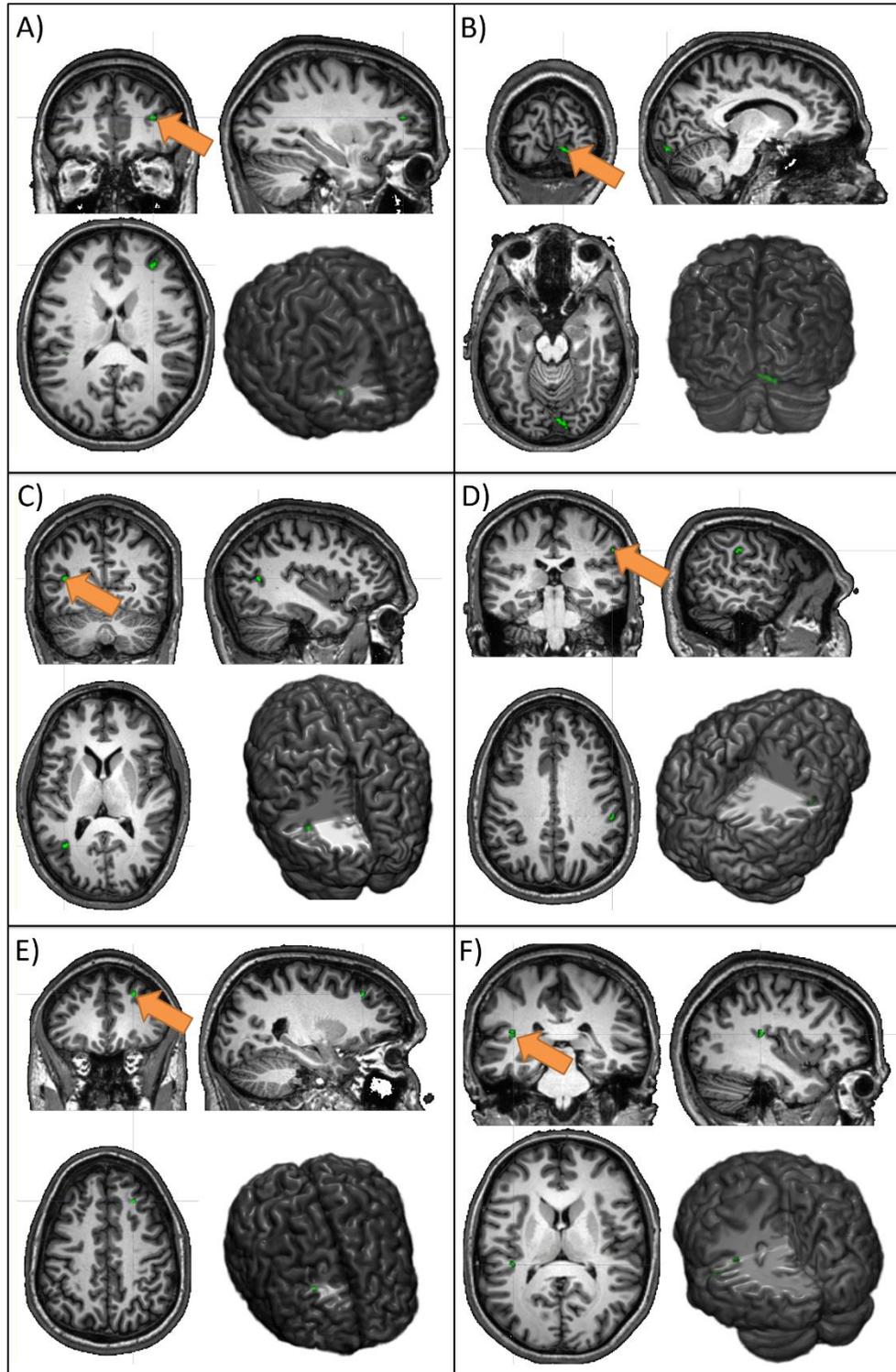
Fig 20 Examples of the observed clusters in the leave–one–out examinations of healthy control subjects, using critical values corrected for controlling the FWE rate.

Cluster masks (green with arrows) overlaid on each individual's T_1–weighted image. Typical clusters that remained after the filtering steps, emerged deep in the sulci or close to the GM–CSF boundary (A, B, C, and D) with small sizes (*16.21* voxels in average), and also in the WM in some cases (E, F). Axial and coronal slices are presented in neurological orientation, i.e. left side is on the left.

2.3.2 Patient Examination

After applying the previously detailed processing steps to the *16 D²*–images of the *13* patients, on average *59.4 (35 – 90)* clusters per subject were identified with an average size of *31.4 (7 – 680)* voxels (after removing *6* larger clusters emanating from missing cerebellar slices). The majority of these clusters were obvious artefacts, identifiable by their shape and location (e.g. in the occipital lobes, close to and following the GM–CSF boundary, independent of the underlying gyral and sulcal pattern), see Discussion. Examples of resulting clustered D^2–images are shown on the rightmost panels of Fig 21, along with coronal FLAIR images, MAP07 junction maps and the raw D^2–images overlaid on each subject's T_1–weighted image. Regions with outlying diffusion properties, corresponding to *22* (out of the *23*) MCDs and other abnormalities were identified in the patient group, in good spatial concurrence with the neuroradiological evaluation and the lesion masks. The remaining, *23rd*, an FCD–type malformation only resulted in two supra–threshold voxels, subceeding cluster size threshold; it was only identified when using the less conservative, FDR–corrected critical values. The (physical) distances between centers of masses of the resulting D^2–clusters and the lesion masks are summarized in Table 17.

Table 17 Positive clusters in select cases of MCDs

Code	P01	P02	P03	P04	P05 S1	P05 S2	P05 S3	P06
Number of positive clusters	1	3	1	1	3	3	7	2
Average distance (min max) [mm]	12.2	18.8 (12.9-25.7)	6.5	13.6	13.6 (9.44-17.2)	10.4 (5.1-17.1)	19.0 (9.5-29.2)	19.6 (3.7-35.4)

Code	P07	P08	P09	P10	P11 S1	P11 S2	P12	P13
Number of positive clusters	1	1	2	3	1	1	2	4
Average distance (min max) [mm]	13.5	11.9	12.1 (6.7-17.6)	12.1 (3.5-9.9)	7.7	7.7	4.3 (2.3-6.3)	17.6 (10.2-24.1)

Number of positive D^2–clusters, presented with the average, minimum, and maximum center-of-mass distances between the clusters and the lesion masks [mm]
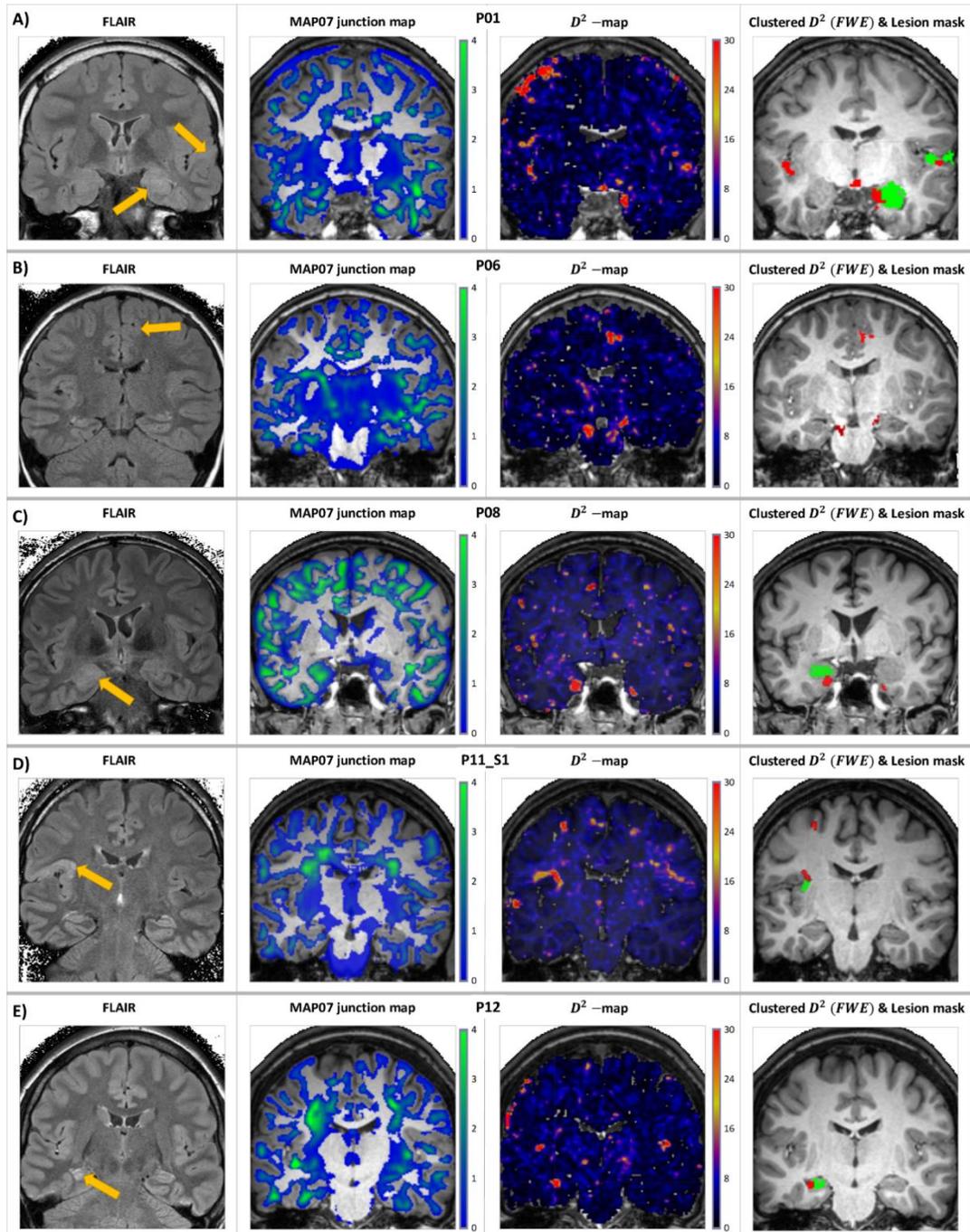
Fig 21 Example results in select cases of abnormalities

Coronal 2D FLAIR images, and MAP07 junction maps, raw, and final, clustered D^2–images (red) and lesion masks (green) overlaid on T_1–weighted images in select cases: presumed right superior temporal FCD or PMG and hippocampal sclerosis (panel A); cortical dysplasia and presumed PMG in the right medio–frontal part of the cingular gyrus (panel B); dysgenesis and partial sclerosis of the left hippocampus (panel C); presumed PMG or FCD in the basal region of the left inferior frontal gyrus and the posterior pat of the insula (panel D); and left hippocampal sclerosis (panel E). Coronal slices presented in neurological orientation, i.e. left side is on the left, coronal slices of the 2D FLAIR images were angulated perpendicular to the hippocampi.

90

V. Discussion

1. DTI and Mild Cognitive Impairment

In the first study, two independent statistical approaches were applied consecutively, in order to establish the findings, starting from the exploratory whole brain analysis on voxel–level and then identifying the strongest white matter differences on the more robust ROI–level, to be used later in differentiation between study groups by means of logistic regression. Voxelwise analysis confirmed decreased grey and white matter integrity in aMCI subjects compared to healthy controls and naMCI subjects; moreover, increased MD was found in naMCI subjects relative to controls. Decreased WM integrity (as indexed by MD and FA) was correlated with short–term memory performance and verbal fluency in the whole sample, further confirming the sufficiency of the study material in making inferences about MCI.

Based on previous evidence [118, 119], the most prominent between group differences and the strongest correlations with memory functions were expected in the cingulum and the fornix; this hypotheses was also confirmed in our ROI–based calculations, and utilized in improving differentiation between study groups in logistic regression analysis.

Use of the widely acknowledged tract based spatial statistics (TBSS) [78] method was considered for its higher statistical power, but due to its limited volume of inference and poor spatial registration performance in complex WM structures — also see section 1.3 — this option was omitted.

1.1 Functional–structural correlations

Correlations between DTI measures and memory performance in subjects with MCI and the elderly has been confirmed in previous studies. For example, in [176], a link between the ADC in the medial temporal lobe and verbal recall was identified, using rectangular, hand drawn ROIs, and a correlation between 'composite memory' and the FA of large parts of the frontal and occipital WM in a TBSS analysis was found in [177]. Similarly, our calculations confirmed that more severe cognitive impairment (indexed by

decreased performance in the neuropsychological tests) is linked to altered diffusion profile in several GM and WM regions.

Voxelwise analysis revealed negative correlation between the ACE total score (a comprehensive index of cognitive performance), and increased MD in the left parahippocampal region and in the pole of the left middle temporal gyrus, regions demonstrated to show early neuropathological changes in AD, as demonstrated by histological [178] and volumetry [179] studies. Verbal memory (indexed by the Rey test) also showed significant correlation with MD in the left parahippocampal region, while the PAL test, reflecting visual and working memory performance correlated with FA in the pars triangularis of the left inferior frontal gyrus (Brodmann area 45, a part of the ventrolateral prefrontal cortex —VLPFC, which has a role in semantic tasks and the cognitive control of working memory [180]).

Visuospatial attention as indexed by the Trail Making test (part A) correlated with MD in the angular gyrus, which is associated with orienting attention to salient features in space [181, 182]. Each of the small clusters with significant differences or correlations were identified as focal points of larger volumes with relatively high R–scores, achieving significance at exploratory thresholds (e.g. $T > 3$, or $|R| > 0.4$, $p < 0.001$) (Fig 10 and Fig 11), supporting the statement that our voxelwise results are pinpointing the key anatomical structures associated with cognitive impairment.

The voxelwise calculations identified the strongest correlation in voxels around the GM–WM boundary, mainly belonging to subcortical WM (in agreement with the aforementioned histological findings [178]), pointing towards the hypothesis that pathological changes in the fiber pathways of the temporal WM, assumed to precede the atrophy of the hippocampus or the entorhinal cortex [179, 183, 184] might be the reason behind the early evincible cognitive impairment.

The more robust ROI–level approach strengthened these findings, by identifying similar correlation between decreased average FA values (decreased WM integrity) in the left cingulum and decreased verbal memory performance (as indexed by the Rey test), and decreased verbal fluency (as indexed by the ACE subscore). The left crus of the fornix / stria terminalis also showed decreased FA, correlated to visual memory performance as

indexed by the PAL test. These results confirmed that the expected microstructural differences are present and significant in these ROIs therefore they might aid the automated differentiation between subject groups.

1.2 Impairments in aMCI patients compared to naMCI patients and healthy controls

As described e.g. in [145], the cingulum, the fornix and the stria terminalis are C–shaped WM bundles, connecting the hippocampus to other parts of the limbic system, such as the amygdala, mammillary bodies, septal area, and hypothalamus. The cingulum also connects the hippocampus to the occipital, parietal, and frontal cortex, while the fornix and the stria terminalis connects the amygdala to the cortex, and the former also projects to the medial prefrontal cortex [185].

Similarly to how the structure of the fornix is affected in MCI [186], a disruption in these WM tracts (increased MD and decreased FA) was detected in our study in patients with aMCI, compared to healthy controls or patients with naMCI, in the ROI based analysis. Meanwhile, voxelwise analysis confirmed these findings by showing increased MD in the left and right temporal regions in aMCI patients relative to controls.

These results are also in line with previous investigations showing that "early Alzheimer disease is underpinned by the damage of inter–connected network, which predominantly involves degeneration of the tracts connecting the circuit of Papez (limbic system)" as stated in [166]. However, it is yet unclear if these disruptions in WM connectivity are consequences or causes of disease progression. Changes in metabolism and atrophy of the precuneus are also shown to be associated in Alzheimer's disease and MCI [187]. Similarly, our voxelwise analysis also confirmed its involvement, as increased MD in left precuneal regions in aMCI patients. Additionally, MD was also increased in the left frontal cortex of aMCI patients, where axon density was shown to decrease in AD [188], but no significant differences were identified between the two MCI groups.

In summary, both methods showed impairments in the temporal regions of patients of the aMCI group, which is in line with results of numerous previous studies [118, 119,

189-191], while the voxelwise approach also found differences in the left frontal and precuneal regions: differences also revealed by previous investigations [187, 188, 192].

1.3 Impairments in naMCI patients compared to control subjects

Voxelwise analysis showed increased MD in the left precuneus and in the left temporal region in naMCI subjects, relative to controls. The precuneus is an important hub of the default mode network, which is linked to several executive functions declined in dementia [193]. These results are supported by previous DTI, brain metabolism (FDG–PET) and fMRI studies [124, 194, 195], however our ROI based analysis did not confirm this difference, possibly because the ROI–based analysis was limited to WM tracts (based on an atlas [63, 145]), while the voxelwise analysis covered the GM as well.

1.4 Differentiation between study groups by logistic regression

Average FA and MD values, measured in the 'cingulum (hippocampus)' and the 'stria terminalis / left crus of the fornix' ROIs, were identified to be correlated with cognitive performance and to differ significantly between the study groups, thereby they were hypothesized to be potential candidates to improve the volumetry–based models' differentiation performance when comparing study groups. A K–fold cross–validation approach was used to test the discriminative models on small test samples, independent from the data they were constructed on. The features selected by the logistic regression in the separate models were mostly consistent; chance level discriminative performance was exceeded in all cases.

Like previous investigations (e.g. in [196]) claiming that combined DTI and volumetric/cortical thickness measurements can improve categorizations between subjects with aMCI and controls, three sets of logistic regression models were compared in our work. Without including DTI scalars, one or two volumetry- or thickness–based measures (the volume of the left hippocampus and the cortical thickness of the precuneus) stayed as relevant effects in the final models. Incorporating ROI–wise, average MD did not change the overall outcome; indeed, all MD measures were excluded in the stepwise regression. On the same token, FA measures were also excluded from all but one final models. Thereby the introduction of DTI measures in the discriminative models did not

improve the approximately *80%* categorization performance of volumetry and thickness based models for discrimination between aMCI patients and healthy controls.

Similarly, three sets of logistic regression models were compared to test discrimination performance between naMCI and controls. Only the cortical thickness of the precuneus stayed in all of the models without DTI measures, yielding a low discriminatory power. No further volumetric or DTI–based measures could significantly improve categorization, possibly because of the heterogeneous nature of the non–amnestic MCI subtype. A larger sample and the separation of the wide range of underlying pathologies to meaningful subgroups seem to be necessary for stronger inference.

Despite the lack of improvement of categorization performance in patient versus control comparisons, introducing DTI measures had substantial benefit when discriminating between the two MCI subtypes. Especially the FA of the left crus of the fornix improved the models, raising correct categorization performance by *22.22%*; in the same token, the MD of the body of the corpus callosum resulted in *11.11%* improvement compared to volumetry–derived models discriminating based on the volume of the left hippocampus. Moreover, these two white matter regions were stable in the K–fold cross validation, further supporting their importance for future discriminative models, as well.

Note, that our strategy of transforming the predefined ROIs to each subject's anatomical space, is less susceptible to registration artefacts compared to similar studies using coregistration to a common template space (e.g. MNI), therefore it can be considered more precise, and if implemented properly, the improved categorization performance may even be achievable for general clinical applications.

1.5 On the value of DTI measurements in MCI and AD

Here, we presented a series of results that represent different levels of description from the voxel–level, through ROI–level to model–level. Even though the results may seem fragmented by the analysis methods there is a consistent pattern of WM involvement that is present through all levels of description. Voxel–level calculations demonstrated both strong correlations between the performance in neuropsychology tests and MD

95

values and significant between–group differences in MD values in GM areas that are usually affected in Alzheimer's disease in general, signaled by atrophy [115, 179, 184, 187]. These findings proved that the early involvement of these structures (most prominently the hippocampus) was present in our sample and was readily detectable through the altered diffusion profile.

Abnormal tissue microstructure in the hippocampal areas is likely to be accompanied by measurable changes in the corresponding WM fiber pathways, as well [119, 170]. Although no meaningful clusters were identified in the white matter on the voxel level, presumably due to the weaker sensitivity resulting from the highly conservative thresholding (for proper voxel–level correction for multiple comparisons), the expected significant correlation with cognitive performance and between–group differences were demonstrated on the ROI–wise average values in the cingulum (hippocampal subdivision) and the stria terminalis / crus of the fornix ROIs in the left hemisphere.

ROI–wise average FA and MD values of these two well–defined, atlas–based WM regions were relatively simple to calculate in a straightforward manner. Moreover, as DTI is most sensitive in the WM, these ROIs also exhibited stable and substantial differences in between–group comparisons. Furthermore, the average FA of the stria terminalis / crus of the fornix also proved to be a relevant effect in the logistic regression analysis when creating models for discrimination between aMCI and naMCI study groups, with the MD of the body of the corpus callosum having similar relevance in improving discrimination performance. Although the FA of the left cingulum was also found significantly decreased in aMCI patients compared to controls, it was deemed to be irrelevant by logistic regression, as left hippocampal volumetry proved to contain sufficient information for correct categorization in itself.

1.6 Limitations of the study

While our results demonstrate the usefulness of DTI measures in improving categorization between study groups, especially between aMCI and naMCI, the relatively low sample sizes of the study may limit the generalizability of the findings. Nevertheless, even the limited size of the study groups allowed the logistic regression analysis to be performed on separate training and testing datasets using a K–fold approach that clearly

showed stably increased categorization performance with the inclusion of DTI–metrics, despite the expected high variability with such low sample sizes. Further studies with larger sample sizes would be beneficial to corroborate our results.

The cross–sectional nature of the study can also be considered a major limitation, but that can also be overcome with further (especially follow–up) examinations that would also allow for investigating the negative predictive value of including the DTI measures in the discriminative models, providing additional means for confirming the presented results.

2. Mahalanobis–distance in MCD lesion detection

2.1 Multidimensional approaches

When selecting a multidimensional approach to combine different modalities, the research question determines the level at which information is pooled, from group–level, through individuals, down to voxel–based methods. Examining more general processes, like response to stimulation in fMRI calls for 'cohort level' statistical methods, like combining p–value maps with pooling approaches in [81], or using the conjunction method, testing a simultaneous null hypothesis [80].

Higher level information pooling has also been proven efficient in examining systemic disorders of the CNS, e.g. for Alzheimer's disease in [82], combining T–score maps from univariate parametric tests on GM density and perfusion data; or in amyotrophic lateral sclerosis, with multivariate linear regression on spectroscopy findings of different metabolites [84]. The superiority of multivariate models compared to combined univariate models was demonstrated in [83], examining simultaneous changes in FA, cortical thickness, and perfusion also in AD, and logistic regression was shown to improve categorization of patients with different subtypes of mild cognitive impairment in the first study of the present thesis [85] by combining ROI–level DTI, volumetry, and cortical thickness data at the subject level.

On the other hand, when searching for unique abnormalities (like injuries or MCDs) in individuals, inference is made below the subject level: combining data from independent modalities into multivariate distributions and performing statistical

evaluation in this high dimensional space enables the pooling of information on the lowest level, only preceded by necessary spatial coregistration. An example for the resulting increased sensitivity was in [86], where the combination of voxelwise MD and volumetry data (using Hotelling's T^2–test, a two–sample equivalent of the Mahalanobis–distance) outlined the effects of traumatic brain injury (TBI), even in cases where none of the individual modalities alone yielded significant results.

Recent studies also demonstrated the utility of machine–learning based approaches for epileptic lesion detection. Surface–based methodology formed the basis of the work in [88] and [89] using morphologic and intensity–based features (such as cortical thickness, sulcal depth, curvature of the surface, and gradient of intensity; all calculated from T_1 or T_2–weighted images on the vertex–level), with similar performance as our approach. In [88], higher specificity was achieved in detecting FCD type lesions.

Similarly to the present study, outlier–detection approach was used in [87], identifying epilepsy–related malformations, using a voxel–based, one–class support vector machine classifier. By working on feature maps computed from T_1–weighted data, comparable sensitivity and less false positives were achieved than with our approach, partially due to a far more conservative cluster size threshold (*82* voxels, compared to *7* in our work).

Such machine–learning based methods are expected to lead the analysis of multidimensional neuroimaging data; however, our study drew merit from several advantages. The straightforward and easy–to–use application of the multidimensional statistics with moderate computation times (only a few seconds per subject on a commercial PC, after preprocessing and registration) aided the accessibility of the method, while the use of DTI data opened the scope of research to disruptions in tissue microstructure.

2.2 On information sources and dimensionality considerations

Theoretically, there is no limitation to the number of examined dimensions in the multivariate distribution examined with the Mahalanobis–distance (as long as the number of subjects exceeds the number of dimensions). Therefore, in order to circumvent the

limitations of the diffusion tensor representation, any diffusion processing model (e.g. diffusion kurtosis imaging [140, 141], spherical deconvolution [197, 198], etc.), or even raw diffusion weighted data could be evaluated in the same straightforward manner.

On the other hand, since L^2–type distance metrics tend to show decreasing performance with higher number of dimensions [199], known as the effect of distance concentration, and, as was demonstrated in [104], the calculation of the Mahalanobis–distance may induce a bias, dependent on sample size, that becomes substantial with higher ($P > 10$) number of dimensions, simply pooling together every available source of information would not necessarily increase statistical power. Other types of distance metrics, particularly an L^P–norm should be a viable choice in such higher dimensional examinations [200], however, such avenues of research were out of the scope of the current study.

Another intriguing possibility for MRI–based lesion detection using the Mahalanobis–distance is including voxel–level data from other modalities, such as T_1 or T_2–weighted images, tissue probability maps, MRI or Positron Emission Tomography (PET) based perfusion measurements, etc., as long as proper spatial coregistration is achievable [86]. Since data in any given dimension is rescaled and cleared of correlations, any meaningful modality could be incorporated to the analysis framework, also including more complex measures from related processing pipelines, such as cortical parcellation, volumetry or morphometry results [85, 88, 89], once again, with distance concentration kept in mind.

Feature selection based on the analysis of meaningful components in such an extended parameter space may be the aim of future investigations. Quantitative imaging, a feat currently under intensive research [201], may also benefit from the use of multidimensional distance–metrics in statistical evaluation.

2.3 Simulation results

Simulations with standard multivariate Gaussian data were used to demonstrate the numerical stability and lesion detection performance of the calculations based on the Mahalanobis–distance. AUC values calculated from the *[0; 0.05]* FPR range indicated

that above *1 FWHM* mean difference, the method is sufficiently sensitive to even the smallest artificial lesions, using critical values aimed to control either the family–wise error rate or the rate of false discoveries. This is the level of sensitivity typically aimed for in image processing or spectroscopy as the resolution (i.e. the minimal distance between two peaks required to separate them) is generally defined as *1 FWHM*.

The use of eigenvalue maps of the control population yielded similar performance: for effect strengths and lesion sizes expected in MCDs (i.e. *50* voxels, corresponding to *168.75 mm³* volume, around *5 – 7 mm* in diameter, [87]) the proposed method effectively identifies regions of abnormal diffusion profile. This performance is on pair with that e.g. [174] achieved in simulations introducing the threshold–free cluster enhancement (TFCE) method. Although the distribution of the tensor eigenvalues was not exactly Gaussian, this only resulted in a small reduction of observed sensitivity, which did not cause any substantial reduction in lesion detection performance.

False positives were completely eliminated in simulations on Gaussian random data, with cluster size thresholds of *4* voxels, but a *7* voxel threshold was needed to reduce the FPR to *0.1 – 0.3%* in simulations based on the resampling of real eigenvalue maps, with both FWE and FDR corrected critical values. Additional exploratory analysis (not included in the thesis) using larger thresholds – *19*, *27*, and *50* voxels – confirmed the complete elimination of false positives, at the cost of reduced sensitivity (reduced true positive rates) to smaller lesions.

Based on these findings we concluded that a cluster size threshold of *7* voxels (i.e. one voxel and its nearest neighbors) should be an optimal choice for lesion detection, when no spatial smoothing is performed on the diffusion tensor eigenvalue images. Only this value was used in the subsequent examinations of healthy controls and patients with MCDs.

Outlier values emanating from measurement errors or numerical instability usually affect single voxels, thereby false positives of such origin could effectively be eliminated with the cluster size threshold of seven voxels. For applications with statistical inference performed on images with substantially different resolution from that of the acquisition (e.g. if the eigenvalue images are resampled to a much smaller voxel size during the

processing), an adjusted cluster size threshold (covering roughly the same volume as *7* voxels of the acquisition voxel size) should achieve similar robustness to such effects. Similar consideration should go for applications where spatial smoothing is performed at some point during data processing.

2.4 Leave–one–out examination of controls

Use of the more conservative FWE–corrected critical D^2–values and the TPM–based cluster–evaluation method (δ–values) limited the number of false positives to an acceptable level. Examination of the control subjects demonstrated that even with the high performance DARTEL–coregistration, clusters of voxels with outlying diffusion profile tend to emerge in (supposedly true negative) control subjects. Most of these clusters proved to be indeed artefactual, being outside the brain parenchyma, however, in average *1.79* clusters per subject were identified in the WM as well. At this level there is no discrimination between clusters emanating from individual anatomical variability and insufficient registration or noise; this problem is usually addressed (reduced) by spatial smoothing in most voxel–level studies [202], which we omitted to retain sensitivity for smaller lesions.

2.5 Patient examinations

Apart from one case, all of the MCDs and other abnormalities in all patients were identified on the processed D^2–images, demonstrating the sensitivity of our diffusion–tensor based approach for detecting minute structural abnormalities. The remaining one FCD–type malformation was identifiable only in results obtained with the more liberal, FDR–corrected critical values. This observation demonstrates that the conservative approach with strict critical values can result in false negatives, thereby decreased sensitivity, in brain regions where the DTI eigenvalues in the control group showed higher sample variance.

Raw D^2–'heat maps', MAP07 'junction maps', and the final D^2–clusters were reviewed with an expert neuroradiologist and compared to the ground truth lesion masks. As the MCDs under consideration are mainly localized around the WM–GM boundary (MAP07 also compares voxels from T_1 images focused on this compartment) and DTI is

expected to be more sensitive in the WM, in most cases, D^2–clusters did only partially overlap with the lesion masks; hence concurrence was ascertained by spatial adjacency. The physical distance between the lesion masks and the D^2–clusters' centers of masses was also recorded; in clusters deemed positive, the average distance was *12.07 mm*, in agreement with results from literature [138].

Patient data was registered to the study specific DARTEL–template, created from only the controls. With this approach, the template was well defined with relatively low sample variance in diffusion tensor eigenvalue distributions, nevertheless artefactual clusters were commonly observed, but they were present mainly in the CSF or around the GM–CSF boundary. The δ–value–based method, evaluating clusters based on tissue probability maps was efficient in filtering out the more evident ones, however, several cases showed obvious artefacts identifiable by their shape and location (e.g. in the occipital lobes, close to and following the GM–CSF boundary, independent of the underlying gyral and sulcal pattern) escaping elimination. Additional automatic classification of artefactual clusters based on spatial distribution properties similar to those implemented in SOCK [203] and FIX [204] would further aid the evaluation of results. Since the focus of the present study was on the statistical approach for examining tissue microstructure and the surviving artefactual clusters were easily discernable among the results, thus did not severely obstruct patient evaluation, we chose to favor generality and did not penalize the examined volume any further. Although utilizing any or a combination of the above mentioned filtering or labeling approaches would possibly have increase lesion detection specificity, the detailed evaluation of cluster features was outside the scope the study, but may be investigated in the future.

In most patients, smaller clusters (typically under *50* voxels) further away from the actual lesions were also identified in the WM. Apart from the ones in the terminal WM, found in several of the adolescent patients, likely reflecting age–related differences in myelination; based on previous studies [138, 139], such extended WM–abnormalities are to be expected in epileptic patients [127]: they most likely reflect either the underlying pathological networks or compensatory effects or elicited by them [205]. Exploratory analysis of DTI tractography data in select cases demonstrated that most of these

additional WM clusters are indeed located in or close to the fiber pathways passing through the primary lesion volumes (Fig 22).
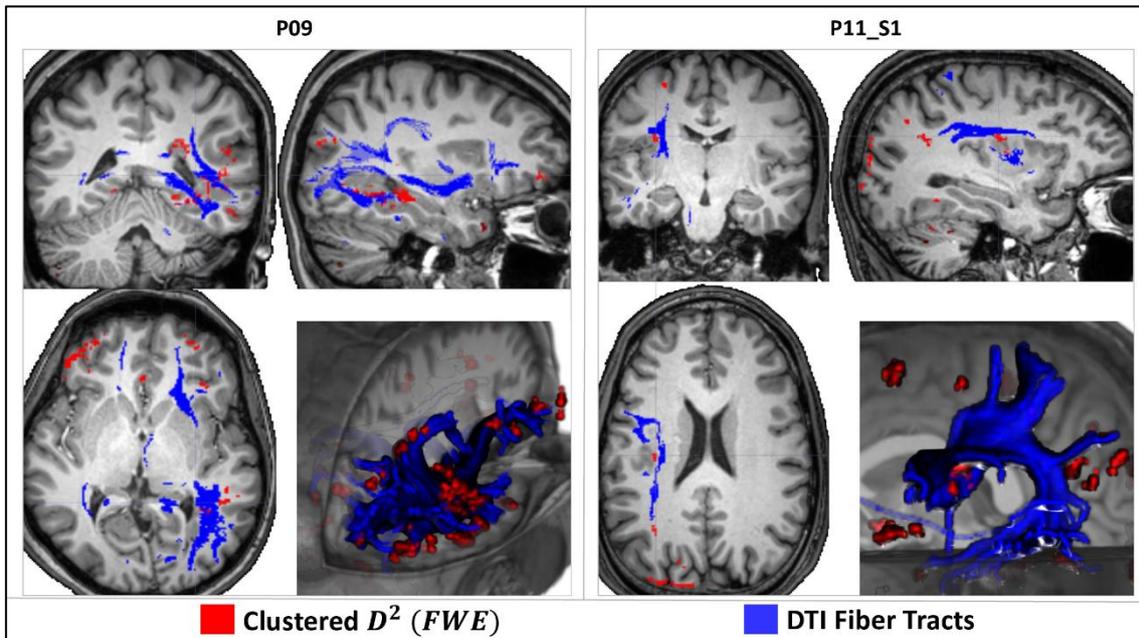
Fig 22 Comparing the location of distant WM clusters to tractography

Deterministic DTI tractography (performed in ExploreDTI) revealed, that several of the distant WM clusters are connected to the primary lesions, for example in a 33 y.o. female patient with multiplex right temporal closed–loop schizencephaly and subependymal heterotopia (left), and in a 27 y.o. male patient with presumed polymicrogyria or FCD in the left inferior frontal gyrus and the posterior third of the left insula (right). Axial and coronal slices presented in neurological orientation, i.e. left side is on the left.

Such clusters suggest that microstructural changes reflected in the DTI data is not specific to the malformations themselves, but also to the disruptions that the actual MCDs inflict on the corresponding WM pathways. In qualitative evaluation, they may be of clinical importance shedding light on the extent and/or organization of the epileptic networks themselves. Nevertheless, including other sources of information (e.g. relaxometry, susceptibility, perfusion, or morphometry measurements) in the proposed multidimensional statistical framework is likely to improve lesion detection specificity. Following this avenue of research was, once again, outside the scope of the study, but is the evident direction to go for the future.

As the mean age of our control group was *25.2*, the method performed better with adults. In two younger patients (age < *10*) more additional clusters were identified, most

likely resulting from differences in myelination and erroneous registration due to more pronounced anatomical (i.e. head and brain size) differences.

As the method proved to be sensitive to a wide range of malformations and even to more pronounced physiological variations, more carefully selected control group(s) of matching age would increase specificity (Fig 21) and thus would yield better characterization of abnormal tissue microstructure. Nevertheless, since MCDs associated with the epileptic seizures were identified in all but one cases, even with approximately *17* years of age difference, it was established that detecting disrupted tissue microstructure using tensor eigenvalues based on the Mahalanobis–distance is indeed feasible and may aid in single subject evaluations. Additional case studies, not included in the thesis, demonstrated that the effects of large anatomical abnormalities, higher level of subject motion, or differences in scan parameters (even with a robust dMRI processing pipeline with thorough motion correction and high performance spatial registration) lead to more severe artefact contamination of the results, therefore age difference, seems to be a less pronounced limiting factor.

With clusters observed partially outside the brain parenchyma (typically in the sulci) or evidently following the GM–CSF boundary, regardless of the underlying tissue macrostructure, registration performance may also be a major effect; potentially causing a high number of artefactual clusters, not all of which could be filtered out with the TPM–based cluster–evaluation method. Fortunately, such clusters are easily identifiable as obvious artefacts, and so are the results of possible missing slices, postoperative resection sites, large anatomical variations (e.g. agenesis of the corpus callosum), or large–scale shifts, rotations, or shears.

Papers in the field of automated lesion detection usually examine single types of pathologies, for example patients with FCDs [88, 89, 133, 206], benefiting from the more specific research question. On the other hand, as clinical practice suggests that different types of MCDs tend to develop together, our patient group of individuals with mixed pathologies more faithfully represents typical cases of drug resistant epilepsies [127]. The multidimensional approach proved to be sensitive to the different types of malformations, which is a satisfying result for a potential lesion detection method, however, if the

framework is to be extended with data from other modalities in future studies, feature selection analysis would benefit from selecting cases with single types of MCDs.

The altered diffusion profile (potentially resulting from several aforementioned normal, pathological, or compensational processes – that could also be varying across individuals), can only be detected, not characterized by the distance metric. Therefore, the generalization of findings would benefit from group–based measures of the pathology–related alterations. For such an endeavor the identified regions of disrupted microstructure could be subjected to subsequent conventional testing, for example, exploring whether FA is increased or decreased in the region, or assessing abnormal connectivity through tractography by using the clusters as seed regions [207]. In future studies, such subsequent examinations, potentially including group–based measures derived from patients with similar pathologies, could help discerning between direct and compensatory effects, explaining some of the observed distant WM clusters.

The proposed method proved successful in combining separate eigenvalue maps, benefiting from the advantages of the multidimensional approach, and achieved sufficient sensitivity in detecting abnormal diffusion profile. The straightforward application of analytically–derived critical values [102] allowed making strong inferences, although specificity was limited due to registration artefacts and normal or pathological variations: effects inherent to all single subject examinations [208].

2.6 Limitations

The wide range of pathologies and the technical impediments may constrain the generalization of findings, nevertheless, as the major goal of the present study was to introduce a new method of statistical evaluation, these predicaments may prove useful in assessing the flexibility of the method.

Using study specific templates, e.g. the DARTEL approach in the present study may be considered a limitation, especially when evaluating possible diagnostic tools, nevertheless, the aim of the current paper was to demonstrate the value of the Mahalanobis–distance based approach in single patient vs control group comparisons. Further analyses using multi–center multi–scanner data may further warrant the

evaluation of the diagnostic potential of a Mahalanobis–distance based lesion detection tool.

During additional patient examinations, not presented in the thesis, we found that a system upgrade also affected the outcome of the statistical analyses, leading to apparent alterations in almost the entire WM, this effect may also most probably stem from the rather homogeneously collected control data. A multi–center, multi–scanner investigation, like mentioned above, may prove to be useful in overcoming such limitations.

VI. Conclusions

1. DTI and Mild Cognitive Impairment

The findings of the first study supported the hypothesis, that impairments of white matter integrity appear as early signs of pathological cognitive decline in both amnestic and non–amnestic clinical manifestations of MCI. DTI measurements in the fornix, the stria terminalis and the cingulum can add valuable information to analyses based on grey matter volumetry and thus can help detect Alzheimer Disease in an early, preclinical stage.

Future medications in AD are expected to be effective in such early stages, therefore extending volumetric analyses with DTI–derived metrics may help the early identification of the disease well within the possible therapeutic window of these proposed medications to help preventing further decline.

Aside from the prospective advantages of the proposed methods, differentiation between MCI patient groups was also demonstrated to be improved after extending GM volumetry–based models with DTI measurements, yielding an immediate utility of the addition of DTI–based metrics in the evaluation of MCI.

Furthermore, the utility of the approach may not be limited to MCI and AD, as based on our results, it seems that DTI measurements can also help detecting non–Alzheimer type dementias in early stage, however, these findings must be confirmed by further studies with larger sample sizes.

2. Mahalanobis–distance in MCD lesion detection

Investigating other aspects of the utility of DTI–based microstructural evaluations, the Mahalanobis–distance based method, proposed in the second study, efficiently combined information from maps of the three diffusion tensor eigenvalues on the voxel–level. Altered diffusion profiles corresponding to malformations of cortical development in single subject vs. control group examinations were detected as outlier values in the voxelwise multidimensional distributions, based on but not necessarily limited to DTI data.

Searching for pathological brain regions of individuals as outliers, using the Mahalanobis–distance in evaluation of diffusion weighted imaging data (even with more sophisticated models for processing, if necessary) seems to be a viable approach, and as the calculations could easily cover data from other modalities, this evaluation method may substantially advance the field of quantitative MRI in general.

3. General conclusions

Multidimensional and multi–modal approaches in the processing and evaluation of brain MR images proved to be efficient in detecting the disease–related alterations of tissue microstructure based on DTI data, both when characterizing impairments associated with cognitive decline and when searching for malformations related to drug resistant epilepsies.

The application of state–of–the–art data processing methods, thorough image correction and using anatomical scans as targets for registration and "up–sampling", combined with the volume–based creation of study–specific templates using the DARTEL method (originally developed for volumetry) was efficient in treating voxel–level dMRI data.

Resulting sample distributions had low observed variance and good spatial congruency between control subjects, which facilitated strong inferences, even when considering the high number of simultaneously performed statistical tests. Voxel–level correlation analyses and between–group comparisons pinpointed the key structures affected through cognitive impairment; these findings subserved the application of multi–modal logistic regression on the region–level and the multidimensional statistics in single subject evaluation.

The combined information resulted in high sensitivity, yielding improved accuracy in the detection of abnormal tissue microstructure, originating from MCI–related changes or epilepsy–related malformations, suggesting the clinical utility of such evaluation methods.

VII. Summary

Diffusion magnetic resonance imaging (dMRI) refers to a rapidly developing group of methods capable of probing tissue microstructure non–invasively, with proven unique sensitivity to various diseases, thus making them essential in research protocols and everyday clinical practice. With the increasing amount and complexity of MRI data, efficient processing methods and the combination of information from different sources are necessary when searching for biomarkers to detect and characterize abnormalities. The present thesis describes two separate research projects with state–of–the–art dMRI processing methods and the use of multidimensional–multimodal statistics to search for disease–specific alterations of tissue microstructure using diffusion tensor imaging (DTI) data in the brain.

In the first project, the potential role of DTI in the differential diagnosis of mild cognitive impairment (MCI) was investigated. A study–specific template using anatomical information proved to be efficient for registering whole brain voxel–level data, facilitating strong inference, both when comparing groups of healthy subjects and patients with amnestic and non-amnestic subtypes of MCI, or when examining correlation between neuropsychology and tissue microstructure. Robust effects were confirmed with region–level logistic regression analyses in the white matter, showing substantially improved discrimination between MCI subtypes, by using a combination of DTI and volumetry data.

The second part of the thesis describes a novel approach for single subject lesion localization, employing outlier detection at the voxel level using the multidimensional squared Mahalanobis-distance on DTI–eigenvalue data. Potential sensitivity and specificity were evaluated through simulations and clinical utility was demonstrated on data of epilepsy patients with malformations of cortical development and other abnormalities. Altogether 15 of the 16 example lesions were detected, whilst false positives resulting from registration inaccuracies were also marked alongside distant regions suggesting potential network–level abnormalities.

Advanced dMRI processing combined with multimodal strategies aids the detection of altered tissue microstructure, yielding potential diagnostic biomarkers in the brain.

VIII. Összefoglalás

A diffúziós mágneses rezonancia képalkotás (dMRI) olyan eljárásokat jelöl, melyekkel a szöveti mikrostruktúra egyedülálló érzékenységgel vizsgálható, nem invazív módon; így kutatási projektek és a mindennapi klinikai gyakorlat alapvető részét képezik. A nagy mennyiségű, komplex MR képanyag értékelését, új biomarkerek azonosítását, és összetett eltérések jellemzését segítheti hatékony adatfeldolgozó eljárások, illetve a több forrásból származó információt egységesen kezelni képes megközelítések alkalmazása. Jelen disszertáció két tudományos munkát mutat be, melyekben betegségspecifikus eltérések azonosításához a legmodernebb dMRI feldolgozást többdimenziós és multimodális statisztikai eljárásokkal kombináltuk, agyi diffúziós tenzor (DTI) adatok értékelésére.

Az első projektben a DTI adatok lehetséges differenciáldiagnosztikai jelentőségét vizsgáltuk enyhe kognitív zavarban (mild cognitive impairment–MCI). Az egyéni anatómiai felvételekből vizsgálatspecifikus közös koordinátarendszert képezve javítottuk a voxel-szintű adatok illesztését. Ennek köszönhetően javult a statisztikai tesztek ereje, mind az amnesztikus és nem-amnesztikus betegcsoportok illetve egészséges kontroll alanyok összehasonlításakor, mind a szöveti mikrostruktúra kognitív teljesítménnyel mutatott korrelációjának vizsgálatában. Fehérállományi területek régió szintű vizsgálatával erős hatásokat igazoltunk, majd logisztikus regressziós eljárás segítségével a DTI adatokat volumetriai számítások eredményével kombináltuk, szignifikánsan javítva az MCI alcsoportok elkülönítését.

A dolgozat második része egyedi páciensek lézióinak voxelszintű detekciójára alkalmazható új eljárást mutat be, az eltéréseket Mahalanobis-távolság segítségével kiszóró pontokként azonosítva a DTI-sajátértékek terében. Az elérhető szenzitivitást és specificitást szimulációkkal vizsgáltuk, majd, kérgi fejlődési rendellenességek példáján, klinikai adaton is demonstráltuk. Összesen 15 léziót sikerült azonosítani a 16-ból, bár az értékelést illesztési pontatlanságok nehezítették A primer lézióktól távolabb lézióként jelölt területek hálózati szintű eltérésekre utalhatnak.

A fejlett dMRI adatfeldolgozás és a multimodális stratégiák kombinációja elősegíti a mikrostrukturális elváltozások azonosítását és új diagnosztikus biomarkerek fejlesztését.

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List of publications

1. Articles related to the thesis

Gyebnar G, Szabo A, Siraly E, Fodor Z, Sakovics A, Salacz P, Hidasi Z, Csibri E, Rudas G, Kozak LR, Csukly G (2018) What can DTI tell about early cognitive impairment? - Differentiation between MCI subtypes and healthy controls by diffusion tensor imaging. Psychiatry Res Neuroimaging, 272: 46-57.

https://doi.org/10.1016/j.pscychresns.2017.10.007
IF: 2.270

Gyebnar G, Klimaj Z, Entz L, Fabo D, Rudas G, Barsi P,Kozak LR (2019) Personalized microstructural evaluation using a Mahalanobis-distance based outlier detection strategy on epilepsy patients' DTI data - Theory, simulations and example cases. PLoS One: 14(9):e0222720.

https://doi.org/10.1371/journal.pone.0222720
IF: 2.740

2. Other articles

Lakatos A, Kolossvary M, Szabo M, Jermendy A, Barta H, Gyebnar G, Rudas G, Kozak LR (2019) Neurodevelopmental effect of intracranial hemorrhage observed in hypoxic ischemic brain injury in hypothermia-treated asphyxiated neonates - an MRI study. BMC Pediatr,19(1):430.

https://doi.org/10.1186/s12887-019-1777-z
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Csukly G, Szabó Á, Polgár P, Farkas K, Gyebnár G, Kozák LR, Stefanics G (2020). Fronto-thalamic structural and effective connectivity and delusions in schizophrenia: A combined DTI/DCM study. Psychological Medicine, 1-11.

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Reprints of publications related to the thesis

Supplementary material

Table S1 Logistic regression: amnestic MCI vs. Control – only volumetry

Test set no.	Subject ID	From: group	Into: group	Effect1	Effect2	Correct	Mean
1	15	Control	Control			1	
	16	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T	1	0.75
	49	a-MCI	Control			0	
	56	a-MCI	a-MCI			1	
2	24	Control	a-MCI			0	
	31	Control	a-MCI	Right Hippocampus^V		0	0.25
	60	a-MCI	Control			0	
	67	a-MCI	a-MCI			1	
3	33	Control	Control			1	
	34	Control	Control	Left Hippocampus^V		1	1
	77	a-MCI	a-MCI			1	
	81	a-MCI	a-MCI			1	
4	37	Control	Control			1	
	39	Control	Control	Left Hippocampus^V		1	0.5
	89	a-MCI	Control			0	
	301	a-MCI	Control			0	
5	40	Control	Control			1	
	42	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T	1	0.75
	364	a-MCI	a-MCI			1	
	879	a-MCI	Control			0	
6	48	Control	Control			1	
	75	Control	Control	Left Hippocampus^V		1	1
	30971	a-MCI	a-MCI			1	
	34845	a-MCI	a-MCI			1	
7	76	Control	Control			1	
	193	Control	Control	Left Hippocampus^V		1	1
	60294	a-MCI	a-MCI			1	
	69355	a-MCI	a-MCI			1	
8	198	Control	Control			1	
	200	Control	Control	Right Hippocampus^V		1	1
	69359	a-MCI	a-MCI			1	
	69367	a-MCI	a-MCI			1	
9	332	Control	Control			1	
	631	Control	Control	Left Hippocampus^V		1	1
	69371	a-MCI	a-MCI			1	
	69376	a-MCI	a-MCI			1	
10	23074	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T	1	0.5
	60293	Control	a-MCI			0	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: subject identifiers used in the study, Form: group: subject category, as determined by the Petersen criteria ('truth'); Into: group: subject category determined by the models ('test decision'); Effect1 & 2: volumetric, or cortical thickness measurements deemed meaningful in the stepwise logistic regression; a–MCI: amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup. ^{V}: volumetry–based measure ^{T}: thickness–based measure

Table S2 Logistic regression: amnestic MCI vs. Control – volumetry with FA

Test se no.	Subject ID	From: group	Into: group	Effect1	Effect2	Effect3	Correct	Mean
1	15	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T		1	0.75
	16	Control	Control				1	
	49	a-MCI	Control				0	
	56	a-MCI	a-MCI				1	
2	24	Control	a-MCI	Left Hippocampus^V			0	0.25
	31	Control	a-MCI				0	
	60	a-MCI	Control				0	
	67	a-MCI	a-MCI				1	
3	33	Control	Control	Left Hippocampus^V			1	1
	34	Control	Control				1	
	77	a-MCI	a-MCI				1	
	81	a-MCI	a-MCI				1	
4	37	Control	Control	Left Hippocampus^V			1	0.5
	39	Control	Control				1	
	89	a-MCI	Control				0	
	301	a-MCI	Control				0	
5	40	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T		1	0.75
	42	Control	Control				1	
	364	a-MCI	a-MCI				1	
	879	a-MCI	Control				0	
6	48	Control	Control	Left Hippocampus^V			1	1
	75	Control	Control				1	
	30971	a-MCI	a-MCI				1	
	34845	a-MCI	a-MCI				1	
7	76	Control	Control	Left Hippocampus^V			1	1
	193	Control	Control				1	
	60294	a-MCI	a-MCI				1	
	69355	a-MCI	a-MCI				1	
8	198	Control	Control	Right Hippocampus^V			1	1
	200	Control	Control				1	
	69359	a-MCI	a-MCI				1	
	69367	a-MCI	a-MCI				1	
9	332	Control	Control	Left Hippocampus^V			1	1
	631	Control	Control				1	
	69371	a-MCI	a-MCI				1	
	69376	a-MCI	a-MCI				1	
10	23074	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T	Fornix crus Stria terminalis L^{DTI}	1	0.5
	60293	Control	a-MCI				0	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10*th, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: subject identifiers used in the study, Form: group: subject category, as determined by the Petersen criteria ('truth'); Into: group: subject category determined by the models ('test decision'); Effect1, 2 & 3: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; a–MCI: amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; ^{V}: volumetry–based measure; ^{T}: thickness–based measure; DTI: DTI–based measure

Table S3 Logistic regression: amnestic MCI vs. Control – volumetry with MD

Test set no.	Subject ID	From: group	Into: group	Effect1	Effect2	Correct	Mean
1	15	Control	Control			1	0.75
	16	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T	1	
	49	a-MCI	Control			0	
	56	a-MCI	a-MCI			1	
2	24	Control	a-MCI			0	0.5
	31	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T	1	
	60	a-MCI	Control			0	
	67	a-MCI	a-MCI			1	
3	33	Control	Control			1	1
	34	Control	Control	Left Hippocampus^V		1	
	77	a-MCI	a-MCI			1	
	81	a-MCI	a-MCI			1	
4	37	Control	Control			1	0.5
	39	Control	Control	Left Hippocampus^V		1	
	89	a-MCI	Control			0	
	301	a-MCI	Control			0	
5	40	Control	Control			1	0.75
	42	Control	Control	Left Hippocampus^V	meanthickavg precuneus^T	1	
	364	a-MCI	a-MCI			1	
	879	a-MCI	Control			0	
6	48	Control	Control			1	1
	75	Control	Control	Left Hippocampus^V		1	
	30971	a-MCI	a-MCI			1	
	34845	a-MCI	a-MCI			1	
7	76	Control	Control			1	1
	193	Control	Control	Left Hippocampus^V		1	
	60294	a-MCI	a-MCI			1	
	69355	a-MCI	a-MCI			1	
8	198	Control	Control			1	1
	200	Control	Control	Right Hippocampus^V		1	
	69359	a-MCI	a-MCI			1	
	69367	a-MCI	a-MCI			1	
9	332	Control	Control			1	1
	631	Control	Control	Left Hippocampus^V		1	
	69371	a-MCI	a-MCI			1	
	69376	a-MCI	a-MCI			1	
10	23074	Control	Control	Left Hippocampus^V		1	0.5
	60293	Control	a-MCI			0	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10*th, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: subject identifiers used in the study, Form: group: subject category, as determined by the Petersen criteria ('truth'); Into: group: subject category determined by the models ('test decision'); Effect1 & 2: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; a–MCI: amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; ^{V}: volumetry based measure; ^{T}: thickness based measure

Table S4 Logistic regression: non–amnestic MCI vs. Control – only volumetry

Test set no.	Subject ID	From: group	Into: group	Effect1	Effect2	Correct	Mean
1	15	Control	Control			1	
	16	Control	na-MCI	meanthickavg precuneus^T		0	0.5
	25	na-MCI	na-MCI			1	
	26	na-MCI	Control			0	
2	24	Control	na-MCI			0	
	31	Control	Control	Right Hippocampus^V	meanthickavg precuneus^T	1	0.5
	36	na-MCI	Control			0	
	38	na-MCI	na-MCI			1	
3	33	Control	na-MCI			0	
	34	Control	Control	meanthickavg precuneus^T		1	0.5
	44	na-MCI	Control			0	
	58	na-MCI	na-MCI			1	
4	37	Control	na-MCI			0	
	39	Control	Control	meanthickavg precuneus^T		1	0.5
	59	na-MCI	na-MCI			1	
	63	na-MCI	Control			0	
5	40	Control	Control			1	
	42	Control	Control	meanthickavg precuneus^T		1	0.75
	74	na-MCI	Control			0	
	216	na-MCI	na-MCI			1	
6	48	Control	Control			1	
	75	Control	Control	Right Hippocampus^V	meanthickavg precuneus^T	1	0.5
	69357	na-MCI	Control			0	
	69360	na-MCI	Control			0	
7	76	Control	Control			1	
	193	Control	Control	Right Hippocampus^V		1	0.5
	69361	na-MCI	Control			0	
	69364	na-MCI	Control			0	
8	198	Control	Control			1	
	200	Control	na-MCI	meanthickavg precuneus^T		0	0.5
	69372	na-MCI	na-MCI			1	
	69403	na-MCI	Control			0	
9	332	Control	na-MCI			0	
	631	Control	Control	meanthickavg precuneus^T		1	0.5
	69404	na-MCI	Control			0	
	69412	na-MCI	na-MCI			1	
10	23074	Control	Control	meanthickavg precuneus^T		1	0.5
	60293	Control	na-MCI			0	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: identifiers used in the study, Form: group: category, as determined by the Petersen criteria ('truth'); Into: group: category determined by the models ('test decision'); Effect1 & 2: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; na–MCI: non–amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; ^{V}: volumetry based measure; ^{T}: thickness based measure

Table S5 Logistic regression: non–amnestic MCI vs. Control – volumetry with FA

Test set no.	Subject II	From: group	Into: group	Effect1	Effect2	Effect3	Correct	Mean
1	15	Control	Control				1	
	16	Control	na-MCI	meanthickavg precuneus^T	Fornix column & body of fornix^{DTI}		0	0.75
	25	na-MCI	na-MCI				1	
	26	na-MCI	na-MCI				1	
2	24	Control	na-MCI				0	
	31	Control	Control	Right Hippocampus^V	meanthickavg precuneus^T		1	0.5
	36	na-MCI	Control				0	
	38	na-MCI	na-MCI				1	
3	33	Control	na-MCI				0	
	34	Control	Control	meanthickavg precuneus^T	Posterior thalamic radiation R^{DTI}	External capsule R^{DTI}	1	0.25
	44	na-MCI	Control				0	
	58	na-MCI	Control				0	
4	37	Control	na-MCI				0	
	39	Control	Control	meanthickavg precuneus^T	External_ capsule_R^{DTI}		1	0.5
	59	na-MCI	na-MCI				1	
	63	na-MCI	Control				0	
5	40	Control	Control			Superior fronto occipital fasciculus R^{DTI}	1	
	42	Control	Control	meanthickavg precuneus^T	Fornix column & body of fornix^{DTI}		1	1
	74	na-MCI	na-MCI				1	
	216	na-MCI	na-MCI				1	
6	48	Control	Control	Cingulum hippocampus L^{DTI}			1	
	75	Control	na-MCI				0	0.25
	69357	na-MCI	Control				0	
	69360	na-MCI	Control				0	
7	76	Control	Control				1	
	193	Control	Control	Right Hippocampus^V			1	0.5
	69361	na-MCI	Control				0	
	69364	na-MCI	Control				0	
8	198	Control	Control				1	
	200	Control	na-MCI	meanthickavg precuneus^T	External capsule L^{DTI}	Tapetum L^{DT}	0	0.5
	69372	na-MCI	na-MCI				1	
	69403	na-MCI	Control				0	
9	332	Control	Control				1	
	631	Control	Control	meanthickavg precuneus^T	Fornix column & body of fornix^{DTI}		1	0.75
	69404	na-MCI	Control				0	
	69412	na-MCI	na-MCI				1	
10	23074	Control	na-MCI	meanthickavg precuneus^T	External capsule L^{DTI}		0	0.5
	60293	Control	Control				1	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: identifiers used in the study, Form: group: category, as determined by the Petersen criteria ('truth'); Into: group: category determined by the models ('test decision'); Effect1, 2 & 3: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; na–MCI: non–amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; ^{V}: volumetry based measure; ^{T}: thickness based measure; ^{DTI}: DTI–based measure

Table S6 Logistic regression: non–amnestic MCI vs. Control – volumetry with MD

Test set no.	Subject ID	From: group	Into: group	Effect1	Effect2	Correct	Mean
1	15	Control	Control			1	
	16	Control	na-MCI	meanthickavg precuneus^T	Cingulum hippocampus L^{DTI}	0	0.5
	25	na-MCI	Control			0	
	26	na-MCI	na-MCI			1	
2	24	Control	na-MCI			0	
	31	Control	na-MCI	Right Hippocampus^V	Cingulum hippocampus L^{DTI}	0	0.25
	36	na-MCI	Control			0	
	38	na-MCI	na-MCI			1	
3	33	Control	na-MCI			0	
	34	Control	Control	meanthickavg precuneus^T		1	0.5
	44	na-MCI	Control			0	
	58	na-MCI	na-MCI			1	
4	37	Control	Control			1	
	39	Control	Control	meanthickavg precuneus^T	Cingulum hippocampus L^{DTI}	1	0.75
	59	na-MCI	na-MCI			1	
	63	na-MCI	Control			0	
5	40	Control	Control			1	
	42	Control	Control	meanthickavg precuneus^T	Cingulum hippocampus L^{DTI}	1	0.75
	74	na-MCI	Control			0	
	216	na-MCI	na-MCI			1	
6	48	Control	Control			1	
	75	Control	Control	Right Hippocampus^V	meanthickavg precuneus^T	1	0.5
	69357	na-MCI	Control			0	
	69360	na-MCI	Control			0	
7	76	Control	Control			1	
	193	Control	Control	Right Hippocampus^V		1	0.5
	69361	na-MCI	Control			0	
	69364	na-MCI	Control			0	
8	198	Control	Control			1	
	200	Control	Control	meanthickavg precuneus^T	External capsule L^{DTI}	1	0.75
	69372	na-MCI	na-MCI			1	
	69403	na-MCI	Control			0	
9	332	Control	Control			1	
	631	Control	Control	meanthickavg precuneus^T	Fornix column & body of fornix^{DTI}	1	0.75
	69404	na-MCI	Control			0	
	69412	na-MCI	na-MCI			1	
10	23074	Control	na-MCI	meanthickavg precuneus^T	External capsule L^{DTI}	0	0.5
	60293	Control	Control			1	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10ᵗʰ*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: subject identifiers used in the study, Form: group: subject category, as determined by the Petersen criteria ('truth'); Into: group: subject category determined by the models ('test decision'); Effect1, 2 & 3: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; na–MCI: non–amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; ^{V}: volumetry based measure; ^{T}: thickness based measure; ^{DTI}: DTI–based measure

Table S7 Logistic regression: amnestic vs non–amnestic MCI – only volumetry

Test set no.	Subject ID	From: group	Into: group	Effect1	Correct	Mean
1	25	na-MCI	na-MCI		1	
	26	na-MCI	a-MCI	Left Hippocampus^V	0	0.5
	49	a-MCI	na-MCI		0	
	56	a-MCI	a-MCI		1	
2	36	na-MCI	na-MCI		1	
	38	na-MCI	a-MCI	Left Hippocampus^V	0	0.5
	60	a-MCI	na-MCI		0	
	67	a-MCI	a-MCI		1	
3	44	na-MCI	na-MCI		1	
	58	na-MCI	na-MCI	Left Hippocampus^V	1	1
	77	a-MCI	a-MCI		1	
	81	a-MCI	a-MCI		1	
4	59	na-MCI	na-MCI		1	
	63	na-MCI	na-MCI	Left Hippocampus^V	1	0.5
	89	a-MCI	na-MCI		0	
	301	a-MCI	na-MCI		0	
5	74	na-MCI	a-MCI		0	
	216	na-MCI	a-MCI	Left Hippocampus^V	0	0.25
	364	a-MCI	a-MCI		1	
	879	a-MCI	na-MCI		0	
6	69357	na-MCI	na-MCI		1	
	69360	na-MCI	na-MCI	Left Hippocampus^V	1	1
	30971	a-MCI	a-MCI		1	
	34845	a-MCI	a-MCI		1	
7	69361	na-MCI	na-MCI		1	
	69364	na-MCI	a-MCI	Left Hippocampus^V	0	0.75
	60294	a-MCI	a-MCI		1	
	69355	a-MCI	a-MCI		1	
8	69372	na-MCI	a-MCI		0	
	69403	na-MCI	na-MCI	Left Hippocampus^V	1	0.75
	69359	a-MCI	a-MCI		1	
	69367	a-MCI	a-MCI		1	
9	69404	na-MCI	na-MCI		1	
	69412	na-MCI	a-MCI	Left Hippocampus^V	0	0.5
	69371	a-MCI	a-MCI		1	
	69376	a-MCI	na-MCI		0	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: subject identifiers used in the study, Form: group: subject category, as determined by the Petersen criteria ('truth'); Into: group: subject category determined by the models ('test decision'); Effect1: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; a–MCI: amnestic mild cognitive impairment; na–MCI: non–amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; *V*: volumetry based measure

Table S8 Logistic regression: amnestic vs non–amnestic MCI – volumetry with FA

Test set no.	Subject ID	From: group	Into: group	Effect1	Effect2	Correct	Mean
1	25	na-MCI	na-MCI			1	
	26	na-MCI	na-MCI	Left Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	1	0.75
	49	a-MCI	a-MCI			1	
	56	a-MCI	na-MCI			0	
2	36	na-MCI	na-MCI			1	
	38	na-MCI	na-MCI	Right Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	1	1
	60	a-MCI	a-MCI			1	
	67	a-MCI	a-MCI			1	
3	44	na-MCI	na-MCI			1	
	58	na-MCI	na-MCI	Left Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	1	1
	77	a-MCI	a-MCI			1	
	81	a-MCI	a-MCI			1	
4	59	na-MCI	na-MCI			1	
	63	na-MCI	a-MCI	Left Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	0	0.25
	89	a-MCI	na-MCI			0	
	301	a-MCI	na-MCI			0	
5	74	na-MCI	na-MCI			1	
	216	na-MCI	na-MCI	Left Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	1	1
	364	a-MCI	a-MCI			1	
	879	a-MCI	a-MCI			1	
6	69357	na-MCI	na-MCI			1	
	69360	na-MCI	na-MCI	Left Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	1	1
	30971	a-MCI	a-MCI			1	
	34845	a-MCI	a-MCI			1	
7	69361	na-MCI	na-MCI			1	
	69364	na-MCI	na-MCI	Left Hippocampus ^{V}	Fornix cru Stria terminalis L ^{DTI}	1	1
	60294	a-MCI	a-MCI			1	
	69355	a-MCI	a-MCI			1	
8	69372	na-MCI	na-MCI			1	
	69403	na-MCI	na-MCI	Right Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	1	1
	69359	a-MCI	a-MCI			1	
	69367	a-MCI	a-MCI			1	
9	69404	na-MCI	na-MCI			1	
	69412	na-MCI	a-MCI	Left Hippocampus ^{V}	Fornix crus Stria terminalis L ^{DTI}	0	0.75
	69371	a-MCI	a-MCI			1	
	69376	a-MCI	a-MCI			1	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: subject identifiers used in the study, Form: group: subject category, as determined by the Petersen criteria ('truth'); Into: group: subject category determined by the models ('test decision'); Effect1: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; a–MCI: amnestic mild cognitive impairment; na–MCI: non–amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; ^{V}: volumetry based measure; ^{DTI}: DTI–based measure

Table S9 Logistic regression: amnestic vs non–amnestic MCI – volumetry with MD

Test set no.	Subject ID	From: group	Into: group	Effect1	Effect2	Correct	Mean
1	25	na-MCI	na-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1	0.5
	26	na-MCI	na-MCI			1	
	49	a-MCI	na-MCI			0	
	56	a-MCI	na-MCI			0	
2	36	na-MCI	na-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1	1
	38	na-MCI	na-MCI			1	
	60	a-MCI	a-MCI			1	
	67	a-MCI	a-MCI			1	
3	44	na-MCI	na-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1	1
	58	na-MCI	na-MCI			1	
	77	a-MCI	a-MCI			1	
	81	a-MCI	a-MCI			1	
4	59	na-MCI	a-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	0	0.25
	63	na-MCI	na-MCI			1	
	89	a-MCI	na-MCI			0	
	301	a-MCI	na-MCI			0	
5	74	na-MCI	na-MCI	Left Hippocampus ^{V}	Fornix column & body of fornix ^{DTI}	1	0.5
	216	na-MCI	a-MCI			0	
	364	a-MCI	a-MCI			1	
	879	a-MCI	na-MCI			0	
6	69357	na-MCI	na-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1	0.75
	69360	na-MCI	a-MCI			0	
	30971	a-MCI	a-MCI			1	
	34845	a-MCI	a-MCI			1	
7	69361	na-MCI	na-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1	1
	69364	na-MCI	na-MCI			1	
	60294	a-MCI	a-MCI			1	
	69355	a-MCI	a-MCI			1	
8	69372	na-MCI	na-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1	1
	69403	na-MCI	na-MCI			1	
	69359	a-MCI	a-MCI			1	
	69367	a-MCI	a-MCI			1	
9	69404	na-MCI	na-MCI	Left Hippocampus ^{V}	Body of corpus callosum ^{DTI}	1	0.75
	69412	na-MCI	a-MCI			0	
	69371	a-MCI	a-MCI			1	
	69376	a-MCI	a-MCI			1	

Test set no.: number of the test subset. Each test subset consisted of *4* subjects (*2* from each group, apart from the *10th*, which contained the last *2* controls), the remaining *35 (37)* were used as training data. Subject ID: subject identifiers used in the study, Form: group: subject category, as determined by the Petersen criteria ('truth'); Into: group: subject category determined by the models ('test decision'); Effect1: volumetric, cortical thickness, or DTI measurements deemed meaningful in the stepwise logistic regression; a–MCI: amnestic mild cognitive impairment; na–MCI: non–amnestic mild cognitive impairment; meanthickavg: average cortical thickness; Correct: indicator signaling correct test decision; Mean: decision performance in each subgroup; ^{V}: volumetry based measure; ^{DTI}: DTI–based measure

Table S10: Patient details, description of the separate malformations, and comparative evaluation of the results

Code	Sex	Age	Location	Neuroradiology assessment	MAP07	Raw D^2 images	Thresholded and clustered D^2
			Right superior temporal gyrus	Presumed FCD or PMG; subsequent histology ruled out tumor or dysgenesis	Positive in a small cluster	Clear positivity with high distance values	Positive
			Right amygdala, uncus, and hippocampus	More voluminous on T_1w, with higher intensity on FLAIR images; presumable hippocampal sclerosis	The surrounding WM is marked positive	High D^2 values in the hippocampus, reaching significance in the medial aspect	Positive on the medial aspect
P01	m	14	Right insula	Thicker, but iso-intense GM on T_1w and FLAIR images, MCD can not be ruled out	Small positive cluster in the vicinity of signal disturbances	Large area of positivity with several medium-sized clusters of significant distance values	Positive
			Fronto-basal regions, occipital and left temporal lobes, and the cerebellum	No sign of abnormalities	Several, pronounced positivities distant to the above-listed lesions	Clusters of probable artefacts; neuroradiologically confirmed MCDs are distinguishable by a halo of voxels with higher yet non-significant D^2 that surrounds the significant regions	Large fronto-basal, cerebellar, and occipital artefacts, with smaller clusters in the left temporal lobe contralateral to the neuroradiologically confirmed pathologies on the right side
			Left and right cella media of the lateral ventricle and the border of the right occipital WM	Small lesions on the ventricular wall consistent with subependymal heterotopia	Negative	High, albeit not significant D^2 values in the WM surrounding the MCDs in the ventricular walls	The paraventricular MCDs are positive with clusters smaller than the lesions
P02	f	14	Bilateral frontal WM	Bilateral frontal WM signal alterations with presumably ischemic origin	Positive	Large positivities in the frontal WM and in the corpus callosum	Large positive clusters consistent with the bilateral frontal ischemic WM-lesions and a cluster in the corpus callosum
			Terminal WM	Possibly due to incomplete myelination (age difference between patient and controls)	Positive	High D^2 values in the terminal WM, significant regions surrounded by non significant voxels	Several medium-sized positive clusters in the terminal WM

Table S10 (Continued)

Code	Sex	Age	Location	Neuroradiology assessment	MAP07	Raw D^2 images	Thresholded and clustered D^2
			Right parieto-occipital sulcus	Stable FLAIR signal intensity alterations on multiple follow-ups in the right parieto-occipital sulcus consistent with cortical dysgenesis	Negative	Positive voxels clustered around the neuroradiologically confirmed MCD, a halo of voxels with higher yet non-significant D^2 surrounds the significant regions	The location of the MCD is pointed out by small clusters of significant D^2 in the adjacent WM
P03	m	16	Right occipital and bilateral frontal regions, right superior temporal WM	No sign of abnormalities	Several positive clusters	Clusters with high D^2 values in the right occipital, and bilateral frontal regions representing obvious registration artefacts; a positive region in the right superior temporal WM contralateral to the neuroradiologically confirmed lesion; clusters with higher D^2 values in the genu and splenium of the corpus callosum	There are significant voxels in the regions observed on the raw D^2 map in a distribution consistent with registration artifacts
P04	f	17	Right temporo-occipital region	Clearly visualized FCD, (presumably type IIB) on T_1w and FLAIR images	Positive	Region of voxels with high, but non-significant D^2 values around the MCD, with several voxels above the FDR-corrected threshold of significance, but only two voxels surviving FWE correction	Negative with FWE, but positive with FDR-correction
P05_S1		16			Positive		
P05_S2	m	18	Left amygdala, uncus, and hippocampus	Histology confirmed focal gliosis. The increasing involvement of the contralateral structures in the subsequent examinations (2, and 6 years later) may be resulting from damaged WM caused by the seizures originating from the left hemisphere, propagating through the interconnecting fibers.	Positive, right side shows higher D^2 values than on previous examinations	Raw D^2 values increased with time demonstrating expanding involvement of the left and right amygdala, uncus and hippocampus.	Clear positive results, subsequent examinations showed contralateral regions of abnormal diffusion; results of the last examination seemed to be more localized, with smaller clusters than previously
P05_S3		22			Positive in the left focal gliosis, but there are positive clusters in the contralateral side		

Table S10 (Continued)

Code	Sex	Age	Location	Neuroradiology assessment	MAP07	Raw D^2 images	Thresholded and clustered D^2
P06	f	8	Right medio-frontal part of the cingulate gyrus	Apparent Cortical dysplasia and mild WM glial surplus; bilateral frontal-medial cortical disgenesis with right hemisphere predominance, presumably polymicrogyria	The neuroradiologically confirmed lesion is clearly positive alongside several other clusters including fronto-basal areas and the genu of corpus callosum	Most of the neuroradiologically confirmed lesion site clearly shows high D^2 values just below the threshold of significance ($D^2 \approx 20$), there are several clusters with high D^2 including fronto-basal areas and the genu of corpus callosum	Only the posterior right frontal-cingular part of the neuroradiologically confirmed lesion is significant; there are several small clusters in the bilateral frontal WM and the genu of the corpus callosum
P07	f	15	Left temporo-basal	Confirmed DNT in the left temporo-basal region. A subsequent lesionectomy was incomplete and did not affect the hippocampus, seizure-freedom was not achieved	Widespread positive clusters throughout the brain, with the left hippocampus and left Heschl's gyrus also marked positive	Large clusters of high D^2-values in the left temporo-basal region and the left temporal pole, most pronounced around the neuroradiologically confirmed lesions	Clear positive result in the left temporo-basal areas, with several positive clusters in the left temporal lobe
			Left hippocampus	Apparent hippocampal sclerosis, dysgenesis cannot be ruled out			The left hippocampus is evidently marked
			Heschl's gyrus	Questionable signal alteration that proved to be negative on subsequent examinations		Left superior temporal gyrus and the Heschl's gyrus are marked by high D^2 values	One significant cluster is observed in the left Heschl's gyrus
P08	m	46	Left amygdala and hippocampus	Dysgenesis, and partial hippocampal sclerosis	Surrounding tissue around the left hippocampus is marked positive, along with most of the temporal and occipital WM-GM boundary, the right cingulum, the right occipital WM, and the left occipital pole	Both hippocampi (with evident left predominance) are positive	The head of the left hippocampus and a smaller part of the right is positive
			Posterior-superior part of the Sylvian fissure	Most likely pulsation artefact resulting from anatomical variation of arteries in the vicinity		Small cluster is observed with high D^2 values	One small cluster of high D^2 values above the threshold of significance
			Occipital WM	No clear sign of abnormalities		Several regions of high D^2-values	Several small-medium sized clusters in the occipital WM

Table S10 (Continued)

Code	Sex	Age	Location	Neuroradiology assessment	MAP07	Raw D^2 images	Thresholded and clustered D^2
P09	f	33	Right temporal lobe	Multiplex right temporal closed-loop schizencephaly and subependymal heterotopia, the latter also present in the peritrigonal region, connected to the cortex of the Sylvian fissure. Postictal, or dysgenetic changes in the right amygdala and hippocampus	Most of the right temporal lobe is positive, along with parts of the occipital and frontal areas	Large areas of the right temporal and occipital lobes and clusters in both frontal lobes are positive with high D^2 values	Large positive clusters in and around the neuradiologically confirmed lesions in the right temporal lobe. The connection between the frontal and occipital clusters and the primary lesions are verified by DTI-tractography
			Left middle frontal gyrus	Presumed focal cortical dysplasia in the left middle frontal gyrus	The left medial frontal gyrus is clearly positive	A larger cluster of high D^2 values around the neuroradiologically confirmed lesion and contralateral to it (the latter below the level of significance).	The neuroradiologically confirmed lesion in the left medial frontal gyrus is clearly positive
P10	m	7	Left hippocampus	Malrotation of the left hippocampus	Large areas positive in the temporal lobes bilaterally	High D^2 values in the temporal lobes bilaterally, with some significant voxels in the left hippocampus	The left hippocampus is positive
			Cingulum, terminal and occipital WM	Possibly due to incomplete myelination (age difference between patient and controls)	Large areas positive in the cingulum, and the terminal WM with smaller clusters at the occipital GM-WM boundary	Small clusters with few voxels above the level of significance and several with medium-high D^2 values	Two significant clusters in the left cingulum, and few smaller clusters in the terminal and occipital WM

Table S10 (Continued)

Code	Sex	Age	Location	Neuroradiology assessment	MAP07	Raw D^2 images	Thresholded and clustered D^2
			Basal region of the left inferior frontal gyrus and the posterior third of the left insula	Malformation of cortical development, presumably polymicrogyria or FCD	Positive	Medium-sized area with high D^2 values in and around the neuroradiologically confirmed lesion	Positive
P11_S1	m	27	Left frontal, bilateral occipital and temporal WM	No clear sign of abnormalities	Positivities in parts of the left frontal, and bilateral temporal and occipital lobes and in most of the corona radiata bilaterally	Several high D^2 clusters, with some voxels above the significance threshold	Clusters in the left frontal, the bilateral occipital, and the left terminal WM, the latter is evidently connected to the primary lesion, verified by DTI tractography. Occipital registration artefacts are easy to identify by their configuration
			Basal region of the left inferior frontal gyrus and the posterior third of the left insula	Malformation of cortical development, presumably polymicrogyria or FCD	Positive	Medium-sized area with high D^2 values in and around the neuroradiologically confirmed lesion	Positive
P11_S2	m	27	Left frontal, bilateral occipital and temporal WM	No clear sign of abnormalities	Positivities in parts of the left frontal, and bilateral temporal and occipital lobes and in most of the corona radiata bilaterally	Several high D^2 clusters, with some voxels above the significance threshold. The right insula, contralateral to the neuroradiologically confirmed lesion contains higher D^2 values in a larger volume than previously	Most WM clusters further apart from the neuroradiologically confirmed lesion are still present. Fewer artefacts than previously

149

Table S10 (Continued)

Code	Sex	Age	Location	Neuroradiology assessment	MAP07	Raw D^2 images	Thresholded and clustered D^2
			Left hippocampus	Left hippocampal sclerosis	Negative	Significantly high D^2 values in the left hippocampus, with high values in the surrounding WM	Positive
P12	m	14	Left temporal pole	Malformation of cortical development (FCD-IIIa) in the left temporal pole	Most of the left temporal lobe is marked positive	High D^2 values in the WM of the left temporal pole, most voxels below the threshold of significance	One small positive cluster in the WM close to the left temporal pole
			Right temporal pole	Gliotic cyst with approx. 2mm size in the right temporal pole	Most of the right temporal lobe is marked positive	Significantly high D^2 values in the volume of the cyst, high D^2 values in the surrounding tissue	Positive
			WM in the posterior part of the left and right superior frontal gyri	WM FLAIR signal alterations in the right superior frontal gyrus	Clusters in the superior corona radiata are marked positive bilaterally	High D^2 values in the superior frontal WM of both hemispheres with right predominance	One cluster in either hemispheres in the posterior parts of the superior frontal gyri
			Right temporal lobe	Right temporal closed-loop schizencephaly and subependymal heterotopia	Most of the temporal lobes and the superior corona radiata are marked positive bilaterally	The right temporal lobe contains the most voxels with high D^2-values clearly centered around the neuroradiologically confirmed lesion	Large significant clusters in the right temporal lobe and the hippocampus clearly mark the pathology
P13	m	35	Right occipital pole	Several WM signal alterations in the occipital poles bilaterally with right predominance. May be due to circulatory disturbance(s) during the 2nd trimester (the same cause may be behind the schizencephaly, as well).	Positive, but with smaller clusters and weaker effect size	Frontal and occipital lobes contain regions of high D^2 values bilaterally with right predominance	Several small clusters in the occipital lobes bilaterally with right predominance
			Frontal lobes bilaterally and the anterior part of the right internal capsule	No clear sign of abnormalities	The frontal WM is marked positive bilaterally	Small clusters of higher D^2-values with a few voxels above the level of significance	Few clusters in the frontal lobes and one in the anterior part of the right internal capsule

Results of independent lesion detection (MAP07) and the proposed Mahalanobis-distance based method were evaluated with the expert neuroradiologist (PB); apart from three cases, the diagnoses of MCD subtypes were based on imaging.