Investigating the effects of traumatic white matter microbleeds on white matter microstructural integrity with modern MRI techniques

PhD Thesis

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Table of contents

Introduction

Diffuse axonal injury

Based on literature data, diffuse axonal injury (DAI) is considered the most significant of the diffuse brain lesions resulting from traumatic brain injury. It can be caused by both impact and impulsive cranial trauma, where acceleration and deceleration forces generate shear forces. These forces occur during the relative displacement of brain structures of different consistencies (such as grey matter and brainstem), which possess different kinetic energies. Changes in angular velocity during craniocerebral trauma are most pronounced at the boundary between grey and white matter and in the brainstem. Additionally, differences in kinetic energy, due to variations in densities and masses, are most pronounced in the brainstem. These areas are therefore predilection sites for the development of DAI. In these regions, diffuse (microvascular) damage to the capillaries in the white matter can lead to microscopic hemorrhages, which also hold diagnostic value.

DAI typically develops in blunt head trauma cases, especially in occupants of high-speed vehicles, but it has also been implicated in mild repetitive trauma in combat sports. Furthermore, it may have forensic medical significance in cases of "shaken baby syndrome."

Treatment of diffuse axonal injury and subsequent consequences

Currently, medication is available only for treating the neuropsychological effects that follow DAI, such as depression, anxiety, agitation, and impulsive behavior. However, due to the inherently unpredictable nature of DAI, which is more so than that of classical neuropsychological disorders, the long-term medication management of such patients necessitates particular caution. Furthermore, it has become evident that rehabilitation is most effective when initiated early. Therefore, it is crucial to diagnose the extent of traumatic brain injury (TBI) both early and accurately.

Prognosis of diffuse axonal injury

In 90% of patients with severe DAI, the persistent vegetative state may last for decades. Even if recovery from the vegetative state occurs, such patients are, with very rare exceptions, left with permanent and severe cognitive, motor, and neuropsychological deficits. Generally, improvement, where possible, is observed within 12 to 24 months post-trauma, following comprehensive rehabilitation and therapy.

Typically, DAI patients with a Glasgow Coma Scale (GCS) score of 8 or below face the worst prognosis. A score equal to or below this threshold almost certainly predicts the development of severe neurological and neuropsychological deficits. Post-traumatic amnesia (PTA) in DAI patients also serves as a reliable prognostic factor: a PTA duration of less than one week indicates a better prognosis, while PTA lasting one month or more is linked with a significantly worse outlook, including a high likelihood that the individual will never return to work.

Age plays a crucial role as a prognostic factor as well. The literature suggests that being 20 years old or younger is associated with the best outcomes, whereas older ages are considered a negative prognostic indicator.

Diagnostic difficulties of DAI , the role of MRI in the diagnosis.

The diagnosis of Diffuse Axonal Injury (DAI) poses significant challenges due to its microscopic nature, making it predominantly a diagnosis of exclusion even with current medical advances. As of now, there are no specific biomarkers available for DAI, rendering it "invisible" to conventional imaging techniques.

However, the field of imaging diagnostics is rapidly evolving, and newer MRI modalities have emerged as reliable tools for detecting DAI. Notable examples include Diffusion Weighted Imaging (DWI), Diffusion Tensor Imaging (DTI), Fluid Attenuated Inversion Recovery (FLAIR), and Susceptibility Weighted Imaging (SWI) sequences.

In our research, we utilized the Siemens Tim Trio and MAGNETOM PrismaFit 3T MRI systems at the Pécs Diagnostic Centre (PDC) to employ high-resolution T1 and T2 weighted, susceptibility weighted MRI, fluid attenuation inversion recovery (FLAIR), and diffusion tensor imaging (DTI MRI) modalities.

Susceptibility weighted MRI

The pathological component of DAI that we focus on, and which holds considerable practical importance for clinical imaging diagnostics are traumatic microbleeds TMB emanating from capillaries interspersed among axons.

At present, Susceptibility Weighted Imaging (SWI) MRI stands out as one of the most sensitive techniques for identifying these microbleeds. Remarkably, TMBs can be detected years after the initial axonal injury, indicating potential axonal damage not just in the immediate aftermath but also in the long term. In the literature, these TMB-induced hypointense lesions are generally characterized as hypointense areas measuring 2-10 mm in diameter, with shapes that may be rounded, ovoid, or resemble curved lines.

Diffusion tensor imaging

Diffusion Tensor Imaging (DTI) MRI is a sophisticated, sensitive imaging modality designed for the examination of histologically "ordered" organs and structures within the human body, such as white matter, kidneys, and heart muscle. Through advanced postprocessing, alongside mathematical and statistical methods to be elaborated on subsequently, the integrity and microstructural condition of each anatomically uniform axon bundle within the brain's white matter in the CNS can be characterized. This is achieved by employing derived diffusion parameters, which include:

Fractional Anisotropy (FA): A measure of the directional dependence of diffusion within a unit volume.

Mean Diffusivity (MD): Represents the average diffusivity within a volume unit.

Axial Diffusivity (AD): Corresponds to the principal eigenvalue (λ1), reflecting diffusivity along the axon's main axis.

Radial Diffusivity (RD): The average of the secondary eigenvalues (λ2, λ3), indicating diffusivity perpendicular to the axon's main axis.

These parameters facilitate a quantitative description of diffusion for a specified volume unit of white matter. They are captured in "diffusion maps," though solely visual assessment of these maps by radiologists in routine clinical practice is nearly unfeasible due to their complexity.

The directionality of changes in diffusion parameters, indicative of various pathologies, is somewhat understood and includes conditions such as:

-Amyotrophic Lateral Sclerosis (ALS),

-Multiple Sclerosis (MS),

-Parkinson's Disease,

-Alzheimer's Disease,

-Various types of epilepsy,

-Ischemic stroke,

-Traumatic brain injuries, including Diffuse Axonal Injury (DAI),

-Spinal cord injuries.

Problem definition and aims

Problem definition

Problem definition

Based on the results previously published by our research group, along with the heterogeneous findings in existing literature, the precise clinical significance of TMBs as an imaging marker of DAI developing in near-endemic TBI necessitates further clarification: A) The detectability of TMBs in human studies can be significantly influenced by the interval between the SWI scan and the time of cranial trauma. B) Currently, there is no clear evidence directly associating TMBs with DAI.

The application of DTI on an individual basis remains an unresolved issue. However, in our view, DTI has the potential to revolutionize the diagnosis and prognosis estimation of DAI and various other CNS lesions. It could enhance the planning and effective implementation of rehabilitation, and expedite the return to normal life, work, and professional duties for athletes, law enforcement, and military personnel.

The barriers to the routine use of DTI in individual clinical practice currently include:

1). Complex and Time-consuming DTI Postprocessing: DTI is highly sensitive to distortion effects such as kinetic motion, susceptibility artifacts, "eddy currents," and off-resonance fields. Tract-level analysis is significantly complicated by the presence of crossing fibers within a voxel. Identifying these fibers is challenging, requiring substantial computational resources and time. Notably, the DTI model is ill-suited for resolving intersections and contacts between fibers. More advanced methods exist, but their clinical application is less practical than DTI's. Our research utilizes the FSL-BEDPOSTX algorithm, which does not resolve these fiber configurations but instead propagates the uncertainty values characterizing these voxels, used by probabilistic tractography—a discussion beyond the scope of this paper.

2). Mathematical and Computational Challenges: Solutions to these complex problems are currently confined to research settings and are far from user-friendly.

3) Variance in diffusion parameters: There is considerable variance in diffusion parameters both at the individual level and within specific areas of brain white matter, making accurate, numerical assessment challenging. This variance renders statistical evaluation as difficult as, for example, measuring blood glucose levels.

4) Influencing factors on white matter diffusion scalars: Numerous biological, clinical, and sociological factors can affect white matter diffusion parameters, including age, sex, history of trauma, neurological diseases, alcohol consumption habits, and dehydration.

5) Utility of Diffusion Maps: The results of DTI examinations, or diffusion maps, are challenging to interpret independently and are currently of limited utility to radiologists in routine diagnostics.

Objectives

Based on the above, our objectives were:

Ad 1) To investigate the TMB intensity increase (proved by our research group both in rodent and human studies), "invisibility", the temporal dynamics of lesion disappearance and appearance, and the optimal time to perform SWI.

Ad 2) To investigate whether TMBs are colocalised with axonal damage, and thus whether their location may be of strategic importance for diagnosis and prognosis.

Ad 3) In order to localize DAI, -based on our previous tract-level results-, our research group aimed to develop a DTI-based neuroradiological decision support system for individual tract-level diagnostics within the framework of the Cooperative Doctoral Program.The planned steps were as follows:

1) Preparation for setting up an exact number of elements of an estimated control group
2) In a first step, the description of the normal diffusion parameters of the different brain areas as accurately as possible (as small as possible, even at rational size), measured on the Pécs Diagnostic Center Siemens MAGNETOM PrismaFit MRI machine
3) Enable individual, tract-level comparisons
4) Creation and interpretation of well-interpretable, individually assessable DTI results (in eRAD, Medview systems)
5) Increase evaluation speed, improve postprocessing manageability, improve the "user experience" of DTI evaluation

   Subtasks:
   a. Identify and set up a DTI control group by sex and age.
   b. We plan to allow the automated generation of a tract-segmented image from the raw DTI data, in which the average diffusion parameters of the tracts are determined.
   c. We also plan to automate the comparison of diffusion parameters per patient, per tract, with the pre-programmed values of our control group. Automatically indicate if there is a significant difference between patient and control values. Based on literature data, we will record the diffusion parameter change directions in the neurological pathologies best investigated with DTI, with automatic comparison with these tract-by-tract.
   d. For the sake of easier transparency and detectability, we plan to colour-code the trajectories with average diffusion parameters different from the normal range.

Methods

Methods I: Investigation of temporal signal intensity dynamics of TBI-induced TMBs in human SWI studies

Subjects

Between January 1, 2011, and October 1, 2018, 195 patients aged 18 to 60 years with no history of neurological, psychiatric, or neurotraumatological conditions and who experienced closed head trauma were enrolled for the initial phase of the study. They underwent Susceptibility Weighted Imaging (SWI) MRI at the Diagnostic Centre of Pécs within the same timeframe. A critical inclusion criterion was the precise temporal documentation of the traumatic brain injury (TBI). Additionally, the exact times of admission, CT scans, and MRI assessments were meticulously recorded. Patients were excluded if they had any co-morbidities known to cause microbleeds, such as fat embolism, chronic hypertension, cerebral amyloid angiopathy, cavernous malformations, epilepsy, Alzheimer's disease, dementia, migraine, brain tumors, or brain metastasis. A Grubbs test was applied to identify and exclude patients with outlier traumatic microbleeds (TMB). Figure 13 illustrates our inclusion algorithm, along with the criteria for inclusion and exclusion.

The cohort was ultimately narrowed to 46 cases, categorized into 6 asymptomatic, 8 mild, and 32 severe TBI patients (37 males and 9 females), according to the MAYO classification system. This study was carried out in strict adherence to the guidelines of the Declaration of Helsinki and received approval from the Regional Research Ethics Committee of the University of Pécs (No. 4525). Written informed consent for the MRI scans used in this study was obtained from all participants or their legally authorized representatives.

Clinical data and admission CT parameters

The severity of TBI was individually determined using the MAYO classification. Factors recorded included age at the time of trauma, sex, Rotterdam and Marshall CT scores (assessed from the admission CT scans), MRI field strength (either 1.5T or 3T), and all parameters identified in the literature as potentially influencing the number and detectability of TMBs, including the number of FLAIR lesions and macroscopic lesions. Additionally, we documented the approximate volume of contusions using the CT scans (MedView™) at the time of admission, applying the following formula:

$$A \times B \times C / 2$$

A = greatest hemorrhage diameter in the axial plane

B = hemorrhage diameter at 90º to A in the axial plane

C = the number of CT slices with hemorrhage multiplied by the slice thickness

MRI imaging protocol

SWI, T1-weighted MPRAGE, and FLAIR images were evaluated using Siemens MRI scanners: 1.5T (Avanto/AvantoFit) and 3T (Magnetom Trio/Prisma Fit). The interval between the trauma and the subsequent SWI imaging was measured in hours. The timing of the trauma was determined based on the admission records from either the National Ambulance Service or the Department of Emergency Medicine at UP MS. Additionally, the precise timing of the imaging sessions was documented using the DICOM data from the MRI scans.

Evaluation of haemorrhagic and non-haemorrhagic MRI lesions

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On SWI, TMBs were characterized as ellipsoidal or rounded-oblong hypointensities, measuring 1-10 mm in diameter, and predominantly situated in the white matter—especially at the white-grey matter junction, within the brainstem or corpus callosum, and the basal ganglia. To distinguish TMBs accurately, it was essential to differentiate them from other hypointense lesions that resemble TMBs but act as "mimics" on SWI MRI. These mimics include vein transections, minor accumulations of blood in a sulcus, calcifications, and artifacts arising from air-tissue interfaces, among others. Consequently, we employed a technique known as co-registration of SWI images with high-resolution T1-weighted images, utilizing the FSL Linear Registration Tool (FLIRT) from the FSL (Oxford-FMRIB) software package. This approach enabled a multimodal and anatomically precise assessment of TMBs.

Statistical analysis

Statistical analyses were conducted using MedCalc for Windows, version 19.1.1 (MedCalc Software, Ostend, Belgium), with the exception of Fisher exact tests, which were carried out using IBM SPSS Statistics for Windows, version 27.0 (Armonk, NY: IBM Corp.). Descriptive statistics summarized the clinical, CT, and MRI data. For data exhibiting a non-normal distribution, the median and interquartile range were documented, while the mean and standard deviation (SD) were reported for data following a normal distribution.

To model the temporal trends of lesions, we fitted linear, exponential, and second-order polynomial trend lines to the number of TMBs and FLAIR hyperintensities as a function of time elapsed since the TBI occurrence. Grubbs test was applied to identify and exclude outliers. The trend line with the highest R^2 value was chosen for further analysis. For both TMB and FLAIR variations, the second-order polynomial trend line exhibited the best fit ($R^0 = 0.20$). By solving the equation for this trend line for the average TMB count, we determined the precise time intervals where TMB counts fell below the average. This interval was then adjusted for clinical and practical relevance, resulting in the creation of four groups based on the time between the trauma and the earliest MRI scan: 0-24h (n=11), 24-48h (n=14), 48-72h (n=11), and >72h (n=10). The Shapiro-Wilk normality test assessed the normality of the distribution of TMB and FLAIR lesions, subjects' ages, number of contusions, and total volume distribution. Fisher exact test evaluated differences in incidence among groups for categorical variables

potentially influencing lesion counts, such as gender, MAYO classification, Rotterdam and Marshall scores, TMB localization, slice thickness, and scanner field strength. Kruskal-Wallis H-test with Conover post-hoc analysis determined differences in mean numbers of TMB and FLAIR lesions, contusion numbers, and volumes between groups. The statistical power of these comparisons was calculated using the MultNonParam-kwpower package in R statistical software (version 3.6.0; R Foundation for Statistical Computing, Vienna, Austria).

Methods II: Investigating the microstructural integrity of perilesional white matter through local DTI scalar alterations in TBI

Subjects:

In this study, 61 patients with moderate to severe TBI (45 men, 16 women; age range 21-88 years, mean age = 56 years, SD = 17.6 years) were recruited from the Department of Neurosurgery, PTE KK. Additionally, 61 healthy subjects (27 men, 34 women; age range 22-85 years, median age = 36 years, IQR = 22.5-52.5 years) with no history of neurological, psychiatric, or prior neurotraumatological disorders were included as controls. To further refine our control group, 28 patients with non-traumatic microbleeds (nTMB) of non-traumatic origin, previously identified in SWI recordings (8 men, 20 women; median=64,5 years IQR= 52.25-66.5 years), were included as internal controls. This was to ensure that the diffusion abnormalities investigated in our study were not attributed to white matter microbleeds themselves. From our initial pool of TBI, nTBI, and healthy control subjects, we formed "triplets" matched within a ±3-year age range, following DTI literature recommendations and practices, and conducted a group-level analysis.

Imaging protocol

All participants underwent MRI scans on the Siemens MAGNETOM Prisma 3T machine at PDK, adhering to a specially designed MRI protocol for both clinical and research-level detection and analysis of cranial trauma pathologies. The imaging protocol comprised sequences including MPRAGE, T2-weighted, FLAIR, DTI, and SWI.

Evaluation of MRI scans

The number, morphology, and precise locations (x, y, and z coordinates) of TMBs and nTMBs identified on SWI were meticulously recorded for each subject. Additionally, the number and precise locations of focal hyperintensities observed on FLAIR were documented to investigate white matter surrounding focal edema commonly occurring in cranial trauma. To accurately delineate microbleeds and focal edema, co-registration of SWI, FLAIR, and T1-weighted images was performed using FMRIB's Linear Image Registration Tool (FLIRT).

The perilesional diffusion parameters of white matter microbleeds (TMB and nTMB) and focal edema of different etiologies were examined as follows:

1) Processing of raw DTI images using FSL-FDT, including calculation of diffusion maps containing FA, MD, AD, RD values per voxel across the whole brain at a 222 mm resolution.
2) Reconstruction, merging, and binarization of white matter brain pathways using FSL's XTRACT module, based on a probabilistic model, creating a 3D "mask" accurately encompassing the white matter for individual diffusion parameter analysis.
3) To mitigate magnetic field distortion effects potentially influencing DTI from microbleeds: voxels with intensity beyond 1 SD (using fslstats, fslmaths) were isolated from SWI images. A 3D mask representing distortion-free voxels was then generated from the binarized image.
4) Co-registration of steps 1) and 2) was executed with FSL FLIRT.
5) Fixation of nTMB or TMB center coordinates on the original SWI recording, registered to the T1-weighted recording.
6) Translocation of this central voxel to DTI images via FSL FLIRT.
7) Definition of concentric 3D spherical shells (masks) around this voxel at a 2 mm resolution matching DTI, using the fslmaths module.
8) Combination of masks created in steps 1), 2), and 6) (via fslmaths).
9) The algorithm's output: 3D masks of undistorted voxels, confirmed as white matter, spaced every 2 mm from the microbleed center. These can be applied to diffusion maps to accurately ascertain FA, MD, AD, and RD values in the white matter surrounding the microbleeds.

This entire algorithm has been automated for user convenience. Analyses were also conducted on contralateral, apparently healthy white matter at identical locations to the microbleeds for each patient. Peri-SWI lesional and contralateral central voxels were translocated to healthy control subjects, repeating the evaluation and documenting the findings. Comparisons were made between nTMB, TMB, and control groups, and between FA, MD, AD, and RD values on opposite sides for each case. A maximum of three lesions per patient, selected via Simple Random Sampling (SPSS v27), were assessed for statistical analysis.

Statistical analysis

Statistical analysis was conducted using the RStudio statistical software package (Posit Software, PBC 2023.06.0 Build 421), leveraging an automatic algorithm/script developed and validated by the Institute of Bioanalytics at the University of Pécs Medical School. The evaluation process encompassed the following steps:

1) A minimum of one and a maximum of three lesions were analyzed per patient.
2) FA, MD, AD, RD values were calculated for each group, with a normality test conducted for each spherical shell.
3) DTI parameters for each group of spherical shells were compared based on the normality test results, with findings systematically recorded.
4) A bootstrapping procedure was employed to determine the percentages of the most typical results across all possible lesion combinations, after conducting up to 1000 iterations. The results were then presented in a bar chart and a summary table to facilitate easier interpretation.

Methods III: Development of an individual, tract-level, DTI-based neuroradiological decision support system

Subjects

To complement and expand upon the studies outlined in the introduction, which are aimed at identifying the required number of subjects/items to achieve statistical power in tract-level studies (thereby establishing the statistical foundation for individual-level DTI studies), the following actions were undertaken:

Within the framework of previously funded research by OTKA and NAP, DTI, MPRAGE, SWI, T2-weighted, and FLAIR images of patients with mild, moderate, or severe TBI, along with healthy controls free from neurotraumatological, neurological, and psychiatric diseases (61 controls and 99 TBI patients), were included. Post-anonymization in compliance with GDPR was performed for the algorithm's compilation and initial testing (licence no: 4525, approved by the PTE KK Regional Research Ethics Committee).

Our imaging protocol adheres to the one described in "Methods II: Investigation of the microstructural status of perilesional white matter through Focal DTI scalar changes."

The individual assessment comprises the following steps in DTI processing:

Diffusion Tensor Imaging:

1.1. DTI acquisition: 70 axial slices, isotropic 2x2mm resolution, 30 directions.

1.2. DTI postprocessing involves:

1.2.1. Utilization of the most widely accepted algorithm in current literature:
1.2.1.1. FMRIB FSL software package FDT toolbox "Correction algorithms":

1.2.1.1.1. TOPUP: Identifies distortions due to different magnetic susceptibilities of various tissues, movement of artificial objects, and so-called eddy currents.

1.2.1.1.2. EDDY: Implements corrections as defined by TOPUP.

1.2.1.1.3. DTIFIT: Fits the diffusion tensor and calculates FA, MD, AD, RD maps.

Tractography and evaluation algorithm:

1.3. Detailed tract definition and evaluation:

1.3.1. BEDPOSTX: Determines crossing fibers in each voxel of the white matter.

1.3.2. PROBTRACKX: Models the potential pathways of two fibers per voxel, generating probability histograms of the "most typical" fiber runs from adjacent voxels at a selected threshold to define the tract from the probabilistic model.

1.3.3. Calculation of average diffusion parameters for each tract and documentation in text files.

1.3.4. Integration of identified tracts with high-resolution T1-weighted structural images for enhanced detectability using FSL FLIRT and FNIRT.

Employing a CUDA-compatible GPU, the described evaluation algorithm operates at a clinically acceptable speed, requiring approximately 1.5 hours per patient.

Statistical analysis

The average diffusion parameters for each tract were meticulously recorded for each participant. The resulting data underwent the following statistical evaluations:

1) Outliers were excluded using the Grubbs test.
2) The distribution of the mean values of the measured diffusion parameters per tract in both the healthy and trauma groups was ascertained using the Shapiro-Wilk test.
3) Variance homogeneity among normally distributed tracts was assessed with Levene's test to determine if they were homoscedastic or heteroscedastic.
4) For tracts and white matter regions with normal distribution, the mean diffusion parameters per group were calculated; for those without normal distribution, median diffusion parameters were determined.
5) A Mann-Whitney test was utilized for between-group comparisons of median diffusion parameters for tracts with non-normal distributions.
6) Mean values of normally distributed parameters were compared using a two-tailed Student's T-test, with the variance type determined by Levene's test.

Additionally, the distribution of clinical parameters known to influence diffusion parameters was examined between the control and patient groups using the Chi-square ($\chi 2$) test. Among the parameters compared between the two groups were:

1) Age
2) Gender distribution
3) Admission Glasgow Coma Scale (GCS) scores

All clinical parameters reported in the literature as influencing DTI imaging outcomes (the detailed description and statistical analysis of which are beyond the scope of this report).

Results

Results I: Investigation of temporal signal intensity dynamics of TBI-induced TMBs in human SWI studies

According to the MAYO classification, the severity of the group of 46 patients was classified as follows: 6 asymptomatic, 8 mild, and 32 moderate. The age distribution was not normally distributed across the entire patient group (p=0.02), with a mean age at the time of trauma of 46.09 years (SD=24.39). A total of 248 TMBs (131 on 3T and 117 on 1.5T scanners) and 220 hyperintense focal FLAIR lesions were identified in the 46 patients. Acute CT scans revealed 16 contusions in 9 patients. A second-order polynomial trend line, demonstrating the highest R^2 value, was fitted to the time course of TMB counts (R^2=0.2; p=0.002; y=3.0206X^2 - 13.065X + 15.04).

The average TMB count for the entire population was 5.4. By inserting this value into the solver for second-degree equations (x1,2 = (-b ± √(b^2 - 4ac)) / 2a), we found X1=85h 55min and X2=21h 50min. The closest two recordings in our patient group to these results were 21h 11min and 79h 45min post-trauma, respectively. When plotting the focal FLAIR hyperintensities as a function of time, a clear trend line could not be identified; the best approximation was again a polynomial trend line (R^2=0.07, p=0.08, as shown in Figure 17).

The Shapiro-Wilk normality test indicated that both TMB and FLAIR lesion counts significantly deviated from a normal distribution in all time groups and the whole population (p<0.001 for both TMB and FLAIR lesion counts). The number and volume of contusions also did not follow a normal distribution (p<0.001 in all groups), with the median contusion volumes as follows: 0-24h=842.00 mm^3 (IQR 539.29-1316.00); 24-48h=331.50 mm^3 (IQR 0.00-1642.25); 48-72h=214.00 mm^3 (IQR 143.28-9480.25); >72h=129.60 mm^3. Patient age in each group did not significantly differ from a normal distribution: 0-24h: p=0.12; 24-48h: p=0.16; 48-72h: p=0.28; >72h: p=0.14. One-way ANOVA revealed no significant difference in age between groups (p=0.19), as outlined in Table 6.

Fisher's exact test showed no significant differences in MAYO classification (p=0.11), Rotterdam (p=0.09), and Marshall (p=0.73) scores, SWI field strength (p=0.77), slice thickness (p=0.59), distribution of macroscopic pathologies (p=0.79), or patient gender (p=0.72), detailed in Table 6. The median TMB count and number of FLAIR lesions in each time group are reported in Table 3. The Kruskal-Wallis test identified significant differences between groups for TMBs (p=0.01) but not for FLAIR lesions (p=0.18), number of contusions (p=0.66), or mean contusion volume (p=0.69), as presented in Tables 5-7 and Figure 18. The statistical power was 1-β>0.9 for comparisons involving TMBs, the number of FLAIR lesions, and the volume of contusions. No significant differences were observed in TMB localization between groups (p=0.68).

Results II: Investigating the microstructural integrity of perilesional white matter through local DTI scalar alterations in TBI

From our initial pool of TBI, nTBI, and control subjects, three groups of 20 subjects each were formed, allowing for a maximum age variation of ±3 years. The demographic data for these groups are presented in Table 8. In the TBI group, 99 TMBs and 137 instances of focal edema were detected, while the nTBI group had 104 nTMBs and 143 instances of focal edema. None of the lesion types were identified in the control subjects, adhering to the inclusion criteria. Isolated lesions (i.e., without any other pathological findings in their vicinity across all utilized imaging modalities) comprised 67 TMBs and 89 nTMBs, along with 137 and 143 focal edema instances in the TBI and nTBI groups, respectively. Due to their distribution and the exclusion of surrounding pathologies, a maximum of 44 TMBs and 43 nTMBs were evaluated, resulting in 37 TMBs and 36 nTMBs, along with 52 and 45 instances of focal edema of traumatic and non-traumatic origins being analyzed independently.

A lesion was deemed significant if, after False Discovery Rate (FDR) correction, at least 80% of the bootstrapping iterations yielded a p-value <0.05, indicating a mean diffusion parameter change (either increase or decrease) at the group level for each sphere:

For TMBs devoid of surrounding pathologies, significant changes were observed between the peri-TMB area and its contralateral identical white matter, as well as the control group. These changes included a decrease in FA within shells 5, 6, and 9, an increase in MD within shells 3, 8, and 9, and an increase in RD within shells 4 and 7-9. When comparing TMB-adjacent identical contralateral white matter to the control group, there was a decrease in FA in shell 6, an increase in MD in shells 6 and 7-9, and an increase in RD in shells 6 and 7-9.

For isolated nTMBs, no significant differences were detectable compared to either the control group or their contralateral counterparts.

Significant changes in the peri-lesional white matter of focal edema of traumatic origin, devoid of surrounding pathologies, included a decrease in FA in shells 7 and 9, an increase in MD in shells 7-9, and an increase in RD in shells 4-9, when compared both to contralateral identical white matter and the control group. Traumatic-origin focal edema with intact-appearing contralateral white matter showed a decrease in FA in shell 9, an increase in MD in shells 7-9, and an increase in RD in shells 4-9 compared to the control group.

In the case of non-traumatic white matter focal edema, no DTI differences were observed in either the peri-lesional white matter or the white matter with identical contralateral localization when compared to the control group.

Results III: Development of an individual, tract-level, DTI-based neuroradiological decision support system

No significant differences were observed among the clinical parameters known to influence DTI imaging across the study groups. Given the absence of established standard values in the

literature for mean diffusion parameters measured with DTI on the PDK SIEMENS Magnetom PrismaFit MRI machine under specific measurement conditions, a post hoc power analysis was conducted using G*Power 3.1 software. This analysis suggested that an average of 42 subjects per tract in both TBI and control groups would be required to detect a significant difference, with a power (1-β) exceeding 0.95.

Development of Software for Customized, Tract-level DTI Testing:

A user-friendly web-based system was developed atop the FSL framework, facilitating direct communication between users and evaluators via an HTTP server hosted on a Linux system. Upon receiving anonymized data, converted into NIfTI format in compliance with GDPR, the server processes the data individually according to the previously described algorithm. A registry of measurement results is then created, enabling later individual-level evaluation and straightforward management (listing, modifying, or deleting) of the data by users. For ease of interpretation, a "lab-like" report detailing increases or decreases in tract-level diffusion parameters, as well as a "fusion image" showcasing the affected tracts on a high-resolution T1-weighted MPRAGE image, are generated. The web server, utilizing PHP-bash execution, controls the evaluation script (initiation, termination, configuration, etc.), manages uploaded data, and systematically archives the results.

The web application, developed natively in PHP and constructed within an MVC framework, offers greater stability compared to framework-dependent sites. This approach not only enhances resistance to updates but also simplifies future modifications and maintenance.

Conclusion

Conclusion I: Investigation of temporal signal intensity dynamics of TBI-induced TMBs in human SWI studies

Our retrospective study, which explores the temporal changes in MRI signal intensity of traumatic microbleeds (TMBs), indirectly substantiates the phenomenon of short-term transient visibility loss of TMBs in humans—a finding previously documented in rodent models. The results indicate that TMB visibility diminishes between 24 and 72 hours following traumatic brain injury (TBI). Attempting to detect TMBs during this critical window using MRI may lead to false-negative results, thus contributing to the underdiagnosis of the injury's severity and an inaccurate prognosis estimation.

Conclusion II: Investigating the microstructural integrity of perilesional white matter through local DTI scalar alterations in TBI

Based on our findings and corroborative literature data, it appears that TMBs do not consistently colocalize with DAI, underscoring the necessity for further research to elucidate their precise clinical significance. The absence of microbleeds in cranial trauma does not automatically indicate that the white matter is microstructurally intact. Inverting our interpretation suggests that the development of microbleeds, both of traumatic and non-traumatic origins, is more intricately linked to the condition and susceptibility of the microvasculature rather than the vulnerability of axons or the severity of axonal injury.

This perspective, aligned with our previous findings, accentuates the criticality of scrutinizing seemingly intact white matter in cranial trauma, even down to the individual tract level. It posits that TMBs, previously deemed a significant imaging marker of DAI, might more accurately represent independent microvascular injuries that do not necessarily colocalize with DAI. Consequently, additional research is imperative to clarify the precise interplay between the formation of TMBs and the severity of DAI.

Conclusion III: Development of an individual, tract-level, DTI-based neuroradiological decision support system

In alignment with our initial research objectives, we have successfully developed a system for automated DTI evaluation. This system, with further refinement, has the potential to facilitate DTI studies at the individual level.

Original publications, scientific achievements

Publications:

MTMT ID: 10074097

Total number of original publications: 6

Total IF=27.4, number of independent citations 69 (total number of citations: 77), H-index: 4

Original publications on which the thesis is based:

Környei, Bálint S. ✉ ; Szabó, Viktor ; Perlaki, Gábor ; Balogh, Bendegúz ; Szabó Steigerwald, Dorottya K. ; Nagy, Szilvia A. ; Tóth, Luca ; Büki, András ; Dóczi, Tamás ; Bogner, Péter et al.

Cerebral Microbleeds May Be Less Detectable by Susceptibility Weighted Imaging MRI From 24 to 72 Hours After Traumatic Brain Injury

FRONTIERS IN NEUROSCIENCE 15 Paper: 711074 , 13 p. (2021)

Toth, Arnold ✉ ; Berente, Zoltán ; Bogner, Péter ; Környei, Bálint ; Balogh, Bendegúz ; Czeiter, Endre ; Amrein, Krisztina ; Dóczi, Tamás ; Buki, Andras ; Schwarcz, Attila

Cerebral microbleeds temporarily become less visible or invisible in acute susceptibility weighted magnetic resonance imaging : a rat study

JOURNAL OF NEUROTRAUMA 36 : 10 pp. 1670-1677. , 8 p. (2019)

Toth, A ✉ ; Kornyei, B ; Kovacs, N ; Rostas, T ; Buki, A ; Doczi, T ; Bogner, P ; Schwarcz, A

Both hemorrhagic and non-hemorrhagic traumatic MRI lesions are associated with the microstructural damage of the normal appearing white matter.

BEHAVIOURAL BRAIN RESEARCH 340 pp. 106-116. , 11 p. (2018)

Toth, Arnold ✉ ; Kovacs, Noemi ; Tamas, Viktoria ; Kornyei, Balint ; Nagy, Mate ; Horvath, Andrea ; Rostas, Tamas ; Bogner, Peter ; Janszky, Jozsef ; Doczi, Tamas et al.

Microbleeds may expand acutely after traumatic brain injury

NEUROSCIENCE LETTERS 617 pp. 207-212. , 6 p. (2016)

The software included in the thesis was accepted as know-how by the Innovation Committee of University of Pécs in its decision 1/2024.02.14. and decided to include it in the innovative product portfolio of University of Pécs.

Presentations related to the topic of the thesis:

Conferences:

National:

XXX Congress of the Hungarian Society of Radiology- presentation: Investigation of the correlation between white matter microbleeds and white matter microstructural status in traumatic brain injury

Congress of the Hungarian Society of Neuroradiology, Mátraháza 2019- presentation

XXIX Congress of the Hungarian Society of Radiology, Pécs 2018- presentation

Pécs Interventional Radiology Symposium 2019- presentation

Congress of the Hungarian Society of Neuroradiology, Hajdúszoboszló 2014- co-authored presentation

Congress of the Hungarian Society of Neuroradiology, Eger 2016- co-authored presentation

International

International Society for Magnetic Resonance in Medicine (ISMRM) Conference, Honolulu, HI, USA 2017- co-authorship in poster

12th Slovenian- Croatian-Hungarian-Slovakian Radiological Symposium- Ragaska Slatina

7th Pannonian Symposium on CNS Injury, Pécs 2017- co-authorship in poster

International Society for Magnetic Resonance in Medicine (ISMRM) Conference, Paris 2018- co-authorship in poster

European Congress of Radiology, Vienna 2018- co-authorship in poster

European Congress of Radiology, Vienna 2022- co-authored poster

European Congress of Radiology, Vienna 2022- co-authorship in poster

European Congress of Radiology, Vienna 2023 -last author in poster

Scientific and professional awards, prizes, scholarships:

-UP MS Outstanding Author 2022

-Pro Scientia Gold Medal 2019

-UP MS Mestyán Gyula Award

-European Congress of Radiology- European Society for Hybrid, Molecular and Translational Imaging: Best of Subspeciality Poster

-Astellas Pharma Ltd. Astellas Young Researcher Program- "Astellas Award" - 2016

-Cooperative Doctoral Program, Doctoral Student Scholarship 2020-2023

-New National Excellence Programme- National Scholarship for Excellence in Higher Education 2023/24 academic year

-New National Excellence Programme- National Scholarship for Excellence in Higher Education 2021/22 academic year

-New National Excellence Programme- National Scholarship for Excellence in Higher Education Academic Year 2020/21

-New National Excellence Programme- National Scholarship for Excellence in Higher Education 2019/20 academic year

-New National Excellence Programme- National Scholarship for Excellence in Higher Education 2018/19 academic year

-New National Excellence Programme- National Scholarship for Excellence in Higher Education 2017/18 academic year

Achievements as TDK topic supervisor:

4 TDK topics' supervisor (3 in Hungarian, one in English)

in total 9 (6 in 2023 in parallel) TDK students.

5 theses (1 of which at the University of Medicine and Pharmacy in Târgu Mures), 2 of which were also submitted as Dean's thesis at the UP MS

Târgu Mureș University of Medicine and Pharmacy Scientific Student Conference 2021- Zsolt Magos 1st place

PTE ÁOK and GyTK House TDK Conference 2022.

HMAA Füred 2022 Congress: Petneházy Zalán -Excellence in Radiology Award, Ivan Krisztinicz Award (section and conference absolute best presentation)

UP MS TDK Conference 2023: Dávid Bognár 2nd place.

UP MS TDK Conference 2023: Dávid Bognár 3rd place

UP MS TDK Conference 2023: Laár Péter 1st place

UP MS TDK Conference 2023: Petneházy Zalán 2nd place

36th National Scientific Students' Conference, Medical and Health Sciences Section: Péter Laár 2nd place

36th National Scientific Student Conference, Medical and Health Sciences Section: Dávid Bognár 1st place

36th National Scientific Student Conference, Medical and Health Sciences Section:

Zalán Petneházy 1st place

Supervisor of PTE Kriszbacher Ildikó Scholarship winner student (Dávid Bognár) 2022-2023 academic year

Supervisor of UP MS MD-PhD programme students (Dávid Bognár, Zalán Petneházy)

Supervisor of New National Excellence Programme- National Scholarship for Excellence in Higher Education winner students (Dávid Bognár, Zalán Petneházy) -2023/24 academic year

Other scientific activities:

Invited reviewer:

European Radiology (D1, IF=4.01), American Journal of Neuroradiology (Q1, IF=3.653), Neuroradiology (Q1, IF=2.8), Acta Neurologica Scandinavica (Q2, IF=3.9) Neurology Review (Q4 IF=0.4)

Scientific and social activities during PhD training:

- PTE KK Medical Imaging Clinic TDK responsible 2020-

-Student Liaison Officer 2014-, Conference Coordinator 2016-2018, Advisory Board Member: 2023-.

-PTE ÁOK Romhányi György Szakkollégium -member 2021-2023, conference organizer 2022.

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