Memory impairment associated with Papez circuit lesions in patients with severe traumatic brain injury assessed by diffuse tensor imaging and volumetric MRI analysis.

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Research Article

Keywords: traumatic brain injury, magnetic resonance imaging, papez circuit, memory impairment, outcome, neurodegeneration

Posted Date: May 12th, 2022

DOI: https://doi.org/10.21203/rs.3.rs-1647147/v1

TITLE PAGE

RESEARCH ARTICLE:

Title: Memory impairment associated with Papez circuit lesions in patients with severe traumatic brain injury assessed by diffuse tensor imaging and volumetric MRI analysis.

Character count title: 134/150

Word count abstract: 400/400

Word count manuscript: 2839/3000

Number of references: 46/50

Number of Tables and Figures: 5/5

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Short Title: Papez circuit lesion and memory impairment after TBI

Issue Section: Research / Original investigation

KEY POINTS

Question: Is episodic memory impairment associated with lesions in Papez circuit in severe traumatic brain injury patients?

Findings: In this cohort study, 100 patients with severe traumatic brain injury did undergo neuropsychological assessment and multiparametric brain MRI five years after the trauma. Episodic memory impairment was specifically associated with diffusion tensor imaging abnormalities of the Papez circuit.

Meaning: MRI measurements of the Papez circuit provide relevant information to refine the diagnostic of episodic memory impairment in severe TBI.

ABSTRACT

IMPORTANCE: Papez circuit is composed of deep structures of the limbic system which supports episodic memory. Biomechanical modelling suggests that this circuit is particularly exposed to shear forces during traumatic brain injury (TBI). Recent studies showed the relevance of MRI-derived measures for improving diagnosis and adapt care of TBI patients. However, the relationship between MRI measures in this specific circuit and memory disorders resulting from TBI remains poorly documented.

OBJECTIVE: To relate MRI measurements of the Papez circuit to episodic memory impairment (EMI) in TBI patients, and to assess the relevance of MRI to diagnose EMI consecutive to TBI.

DESIGN, SETTING AND PARTICIPANTS: This is a prospective observational study with severe TBI patients enrolled (2006-2012) who did receive neuropsychological assessment and multiparametric brain MRI at distance from the trauma. Patients were classified by neuropsychologist into two groups: those showing an episodic memory impairment (EMI+) and those without impairment (EMI-). We defined an anatomical delineation of the Papez circuit and its sub regions. We extracted MRI measurements in each of these regions and compared statistically between EMI+ and EMI- patients. The same methodology was applied to a control group of 50 healthy controls (HC) to compare with normative values.

MAIN OUTCOMES AND MEASURES: Normalized fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were derived from diffusion tensor imaging (DTI) data. The volume of the Papez circuit was extracted from anatomical MRI.

RESULTS: Over the study period (2009-2016), 100 patients received an MRI and a neuropsychological assessment 63±22 months after the initial TBI. Patients EMI+ had significantly lower FA and higher MD, RD and AD values than the EMI- and HC in the Papez circuit. Volume

measurements showed no difference between EMI+ and EMI-. We also reported abnormalities pattern across sub regions of this circuit between EMI+ and EMI-. The potential of MRI measures in Papez circuit to help diagnosis of EMI in severe TBI patients was confirmed by a multivariate model combining clinical data at baseline and MRI features.

CONCLUSIONS AND RELEVANCE: Our study shows a high incidence of damage to the Papez circuit following severe TBI associated with episodic memory impairments. MRI measures of the Papez circuit constitute relevant information for the diagnosis of EMI in severe TBI patients.

Trial registration: ClinicalTrials.gov, NCT00577954. Registered on October 2006.

Key words: traumatic brain injury; magnetic resonance imaging; papez circuit; memory impairment; outcome; neurodegeneration.

TEXT

Introduction

Traumatic brain injury (TBI) is the most common cause of death and disability in Western countries[1]. Up to 80%[2] of severe TBI patients will present physical, cognitive and psychological disability.[2] Predominant cognitive disorders on executive functions, mood, memory and attention severely handicap these patients and seriously compromise social, family and professional reintegration with an underestimated socio-economic impact[3].
Diffusion Tensor Imaging (DTI) is an MRI technique that allows to detect abnormal white matter microstructure resulting from TBI which could allow to understand the pathophysiological mechanisms. Some works showed that DTI could refine the prognosis as in prognostication for cardiocirculatory arrest.[4] Some studies evaluated the occurrence of brain atrophy in moderate to severe TBI.[5–14] Biomechanical modeling suggested that deep circuits are particularly exposed to shear forces during TBI.[15]
The Papez circuit is a portion of the limbic system particularly involved in episodic memory function. [16,17,18]The objective of this prospective observational study was to characterize the integrity of the Papez circuit with DTI and volumetry using MRI in severe TBI with episodic memory impairment.

Materials and methods

Study population

Severe TBI patients were enrolled in this study between October 2006 and April 2013. Neuropsychological features were assessed at the university hospital Pitié-Salpêtrière

between April 2014 and September 2016. This was a prospective observational study conducted as part of a larger trial named MRI-COMA (*assessing outcome with multimodal MRI of comatose patients of various origin*; NCT00577954). TBI patients were eligible for inclusion if they were unconscious at day 7 after the initial injury (defined as the inability to obey verbal commands not attributed to sedation or aphasia). Inclusion criteria are detailed in supplementary materials. If patients were unable to respond, their relatives were contacted by phone to provide consent to patient participation. A Glasgow Outcome Scale Extended (GOSE)[19] score of at least 3 was required for inclusion. In addition, TBI patients with no family consent for follow-up, with drug or alcohol abuse, a history of TBI, prior administration of sedatives, medications, psychotropic drugs or antiepileptics, history of psychiatric, psychological, or neurological illness were excluded from the study. HC were enrolled at the same period as TBI patients.

Clinical parameters

Classical demographic data age, gender, handedness, and socio-economic level (SEL) were collected for TBI patients and HC. For TBI patients, the following additional data was collected prospectively: score relating to injury, initial Glasgow severity score, initial seizures, lowest Glasgow score, sedation duration, mechanical ventilation duration, coma duration and post-traumatic amnesia. Follow-up assessment included rehabilitation occurrence on discharge, psychiatric or psychological follow-up, epilepsy at discharge, return to professional activity, driving ability, as well as quality of life scores for patients and relatives.

Neuropsychological evaluation

Patients and relatives were contacted by telephone after intensive care unit (ICU) discharge for the follow-up evaluation phase. Trained neuropsychologist blind to the clinical data

classified patients during a structured interview into two groups: presence of an episodic memory impairment (EMI+) or absence (EMI-) with a cut-off on the z-score computed from anterograde memory neuropsychological assessment at -1.5. Participants were also assessed for physical or psychological disabilities, and level of rehabilitation or required assistance.

MRI data acquisition

MRI scanning followed the neuropsychological evaluation. In order to improve image acquisition reproducibility across participants, all of them were carefully placed in the same position. The following four conventional MRI sequences were performed: A high-resolution T1-weighted structural image with an IR-FSPGR (inversion recovery fast spoiled gradient recalled echo) 3-dimensional protocol (3DT1; 1-mm isotropic voxel); an axial T2-weighted fluid-attenuated inversion recovery (FLAIR); an axial T2*-weighted gradient-recalled echo or weighted angiography; and a DTI sequence. The precise parameters of each sequence according to the scanner are listed in the supplementary table 1 and 2. All the images underwent visual, standardized quality check (by PS and LV) to ensure that they did not suffer from MRI artefacts or movement before analysis.

Papez circuit anatomical delineation

Image processing was performed on a computer cluster (NVIDIA® DGX™ Station, Nvidia, Santa Clara (CA), USA). All 3DT1 images from all individuals were denoised using the Spatially Adaptive Non-Local Means filter from the CAT12 toolbox of SPM software (https://www.fil.ion.ucl.ac.uk/spm/software; version 12.r7240).

As no atlases exist for Papez circuit, we created a specific 3D mask by combining 5 regions of interest (ROI) from John Hopkins University atlas[20] (fornix, left and right mamillo-thalamic tracts

and cingulo-hippocampal tracts), 12 ROI from FreeSurfer (left and right hippocampi, caudal anterior cingulate, isthmus cingulate, posterior cingulate, rostral anterior cingulate and white entorhinal substance) and 2 ROI from Oxford Thalamic atlas [21] (left and right anterior thalamus) (supplementary figure 1).

DTI analysis

White matter integrity was assessed from diffusion-weighted data preprocessed with FSL software (https://fsl.fmrib.ox.ac.uk/fsl; version 5.0.6), including motion and eddy current correction on images.[35] Fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) maps were computed in each voxel using the diffusion tensor model with the FSL DTIFIT algorithm.[22] After subsequent linear and nonlinear registration on the 3DT1 with the NiftySEG tool (http://cmictig.cs.ucl.ac.uk/wiki/index.php/NiftySeg; version 1.3.9.), DTI parameters were averaged within the whole Papez circuit and in each sub-region. In addition, we computed the same parameters in a mask covering the whole white matter (supratentorial white matter mask from freesurfer) to assess the specificity of our results on the Papez circuit. To reduce inter-scanner variability [13] and allow direct comparison across scanners, DTI parameters for each participant were normalized with the mean of values acquired from HC on the same scanner and under the same DTI sequence (Supplementary table 2). The results are expressed as a percentage of the value of HC.[4]

Volumetric MRI measurements

Volumetric assessment was performed in the whole white mater, the whole Papez circuit mask and sub-regions. A visual quality check was performed at the end of the pipeline. The estimated total intracranial volume (eTIV from freesurfer) computed as the determinant of the transform

matrix used to align the image participant with the atlas[23] was included as a regressor factor in statistical analysis.

Study endpoints

The main endpoints are the MRI measures. Volume measures were expressed in cm^3 or in mm^3 when appropriate. DTI analyses were expressed as percentage of the value of HC for normalized FA, MD, RD and AD.

Statistical analysis

Continuous variables were tested for normality (Shapiro-Wilk test) and presented as mean ± standard deviation (SD) or median (interquartile range [IQR]) when appropriate. Categorical variables were presented as percentage of the population. Comparisons between the three groups according to outcome at follow-up were performed using Tukey HSD test. In the sub-regions, we further assessed the difference between EMI+ and EMI- using t-test. Significance was defined as a *P*-value <0.05. The influence of potential confounding factors was assessed in a second step: we did confirm the persistence of the differences across the groups in DTI measures when including regression factors of age, gender and SEL; for volume measures we regressed by age, gender, SEL and eTIV as in previous literature.[24,25] Multivariate analysis was performed with simple linear regression. The statistical analysis was performed using python (Panda 0.24) and multivariate analysis was performed with JMP 13.

MRI-based prediction of episodic memory impairment

A multivariate analysis was performed to assess the relevance of MRI-derived measures for diagnostic without any data exploited from neuropsychological assessment. We included in the

model the clinical data at the admission that were statistically different between EMI- and EMI+ patients and MRI-derived measures from the different modalities. The clinical scores at admission included were the initial Glasgow Coma Score, lower Glasgow Coma Score during hospital stay, duration of coma and presence of post-traumatic amnesia, in addition to gender.

Results

Population characteristics

Among severe TBI patients who were screened during the inclusion period, 217 patients were eligible for inclusion in the study. Overall, 100 severe TBI patients (33.6 ± 15.5 yrs) were included in the analysis (supplementary figure 2), with a median follow-up delay of 63 ± 22 months after injury; 51 (51%) had EMI+ and 49 (49%) had EMI-. At admission in ICU, there was a significant difference between patients with presence or absence of EMI regarding gender with more males (94% vs 76.5%; *P* = .014), lower initial Glasgow Coma Score (6[3–10] vs 10[7–13]; *P* = .001), a lower Glasgow Coma Score during hospital stay (6[3–8] vs 8 [7–11]; *P* = .0002) and a longer duration of coma (23.7±21.8 vs 14.6 ± 13.2 days; *P* = .03) in EMI+ patients (table 1). At follow-up, EMI+ patients had a statistically significant higher occurrence of post-traumatic amnesia than EMI- (37% vs 12%; *P* = .003), more ergotherapist follow-up (85% vs 50%; *P* = .001), less professional activity (51 vs 86%; *P* = .01) and were less able to drive (30% vs 54%; *P* = .015). Patients and caregiver's quality of life were also degraded in EMI+ patients (table 2). Neuropsychological assessment showed statistically significant differences between EMI+ and EMI- patients regarding all components of memory, attention, and executive functions (Supplementary table 3).

Demographics data of the 50 HC are provided as supplementary material, including the comparison with TBI patients.

Diffuse MRI assessment

The analysis of the Papez circuit revealed a statistically significant decrease in normalized FA (0.85 [0.09] vs 0.91 [0.07]; *P* < .001) associated with significant increase in normalized MD (1.20 [0.15] vs 1.12 [0.10]; *P* < .001), RD (1.28 [0.20] vs 1.16 [0.13]; *P* < .001) and AD (1.12 [0.10] vs 1.07 [0.07]; *P* = .002) in EMI+ patients than EMI- (Table 2). In contrast, no differences was observed between EMI+ patients and EMI- in the whole white matter in any of these measures. The analysis of the sub-regions of the Papez circuit showed statistically significant difference that were consistent with the results on the entire Papez circuit (Figure 1).

Volumetric assessment

As expected, we observed a greater volume in HC than in TBI patients in the whole white matter (498.6 [76.6] vs 455.1 [70.1] cm^3; *P* = .07) and in the Papez circuit (49.3 [7.0] vs 46.4 [6.1]; *P* = .012). The difference between EMI+ and EMI- patients was not significant for whole white matter volume (446.6 [78.3] vs 464.0 [59.6] cm^3; *P* > .05) as well as for the Papez circuit (45.0 [6.1] vs 47.8 [5.7] cm^3; *P* = .024) (Table 2). A slight reduction in the volume was observed in some sub-regions (Supplementary figure 3).

MRI-based prediction

As described in the material and methods part, we used clinical data with gender, initial Glasgow Coma Score at admission, lower Glasgow Coma Score during hospital stay, duration of coma and

presence of post-traumatic amnesia to compute this model with normalized FA, MD, AD and RD. The ROC_{AUC} was 0.88 (95% CI, 0.78 – 0.94) with 72.7% sensitivity (95% CI, 54.5 – 86.7) and 86.1% specificity (95% CI, 70.5 – 95.3) in this model to predict EMI+ or EMI- in severe TBI patients without including any data from neuropsychological assessment used classically for diagnostic (Figure 2).

Discussion

Our MRI measures revealed that the EMI+ had significantly lower FA and higher MD, RD and AD values than the EMI- in the Papez circuit, but no statistically significant volume change. Analyses in Papez circuit sub-regions characterized the pattern of pronounced differences in the DTI measures but limited variations in volume between the two groups. A multivariate predictive model combining clinical data at baseline and MRI features at follow-up showed good prognosis performance to predict EMI in severe TBI patients.

Beyond the acute phase, TBI is associated with chronicity with a socio-economic burden. Cognitive symptoms are common in participants with mild and severe chronic traumatic encephalopathy, with symptoms occurring in 85% of mild and 95% of severe cases. Impairments in memory, executive function, and attention symptoms are greater in severe patients.[26] Problems with memory are the most frequent subjective complaints reported by TBI patients and their relatives occurring in nearly 67.5% of these TBI patients.[27]

In terms of volume, we observed no volumetric change in the entire Papez circuit between EMI- and EMI+ patients. Association between EMI emergence and history of TBI has been shown with moderate to severe TBI[28–30] and mild TBI, demonstrating that these individuals also had smaller bilateral hippocampi.[31] Other works showed also that the volume of the hippocampus, the lateral prefrontal cortex, the thalamus, and several subregions of the cingulate cortex could predict

memory rehabilitation outcome in TBI patients.[32] Interestingly, it is important to note that all these structures are constitutive parts of the Papez circuit. We can find some of these differences in Papez circuit sub-regions, but the effect was much more pronounced in DTI measures analysis.

In our study, we found much lower normalized FA, and higher MD, AD and RD in TBI patients than HC control.[33,34] There is extensive work about DTI analysis in the literature[35–37], but the specific study of the Papez circuit is however poorly explored in the literature. Two studies on the Papez circuit using DTI were performed by Jang and colleagues. The first study was conducted in a patient with memory impairment following a hypoxic-ischemic injury. Fornix interruption was observed on DTI in both hemispheres and thinning of the thalamo-cingular tract was observed in the right hemisphere.[17]The authors suggested that analysis of the Papez circuit using DTI could provide useful information for detecting a lesion that cannot be detected by conventional MRI. The second study was conducted on a patient who showed severe episodic memory impairment and confabulation following subarachnoid hemorrhage. The DTI was performed after 3 months of the incident and the volume and DTI characteristics were analyzed. FA was significantly decreased in both the thalamo-cingulate tracts and fornix compared to normal control subjects. MD in the right thalamo-cingulate tract and fornix was increased compared to normal controls. The left cingulum and thalamic mamillo-thalamic tract showed a significant volumet decrease compared to control subjects. The authors related the extensive and multiple neural lesions of the Papez circuit in the patients to confabulation as well as to severe memory impairment that were clinically observed.[18]

Many TBI studies reported a transfer of stress and shear forces mainly in the central part of the brain, particularly in the corpus callosum and the brainstem.[15,38–41] It is noticeable

that these axial stresses impact directly the Papez circuit located in the depth of the white matter, which could explain its specific impairment in TBI patients.[42]

It is also important to note that EMI+ present clinically more severe symptoms than EMI- at admission with lower Glasgow score and longer PTA in this study. It suggests that the lesions are already established at the initial stage and are not the manifestation of secondary degeneration.

Literature reviews suggest that most sub-regions of the Papez circuit have a functional role in memory processes, with noticeable vulnerability in TBI patients with episodic memory impairment. In their review, Paterno et al.[43] precise how physiological disturbances in the circuits of the hippocampus, including the dentate gyrus, CA3 and CA1 regions, can be related to the disruption of episodic memory after TBI, including spatial memory, based mostly on studies on animals model.[44] Vann et al.[45] showed also that mammary bodies can effectively support spatial memory even in the absence of hippocampal afferents, highlighting the importance of other afferents in maintaining mammary body function. As well, a DTI study by Kinnunen et al.[46] showed that the DTI measures of the fornices were correlated with associative learning and memory across in TBI patients : fractional anisotropy within the fornix was positively correlated with memory, showing that individuals with more anisotropic white matter within the fornix had better performance. Palacios et al.[47] also reported a positive correlation between memory performance and FA measure in the fornix and corpus callosum. Moreover, Strangman et al.[32] demonstrated that the rehabilitation memory outcome can be predicted by the volume of the hippocampi, the lateral prefrontal cortex, the thalami, and several subregions of the cingulate cortex in TBI patients. Our results further confirm that considering the Papez circuit in its entirety allows a more accurate approach of memory impairment assessment.

Our findings should be interpreted considering the following potential limitations. First, this cross-sectional study has a prospective clinical setting but do not bring longitudinal radiological follow-up as no baseline MRI were underwent : maybe a longitudinal study would be more suitable to properly asses volumetric change. Second, Papez circuit is also known to have an implication in the control and management of feelings. This cognitive feature was not assessed as emotion's evaluation is still difficult to standardize and more suitable to functional MRI exploration. Third, the prognostic model we provide is based on this cohort requires an external validation cohort to truly assess the reliability of the diagnosis provided by the DTI data.

In conclusion, this prospective study evaluated Papez circuit injuries following severe TBI and relates the occurrence of memory impairment in these patientswith MRI abnormalities. The present report provides a better understanding of the early and late pathophysiology and radiological assesment in severe TBI patients with memory disorders. These results may contribute to the early identification of patients with memory disorders and their rehabilitation.

List of abbreviations: 3DT1 = three-dimensional T1-weighted imaging; **AD** = axial diffusivity; **AUC** = area under the curve; **DTI** = diffusion tensor imaging; **eTIV** = estimating total intracranial volumes; **FA** = fractional anisotropy; **FLAIR** = fluid-attenuated inversion recovery; **GOSE** = Glasgow outcome scale extended; **HC** = healthy controls; **ICU** = intensive care unit; **IQR** = interquartile range; **JHU** = Johns Hopkins University; **MRI** = magnetic resonance imaging; **MD** = mean diffusivity; **RD** = radial diffusivity; **SD** = standard deviation; **SEL** = socio-economical level; **TBI** = traumatic brain injury; **VBM** = voxel-based morphometry.

DECLARATIONS

Standard protocol approvals, registrations, and patients consents

We obtained approval from the local Ethical committee (comité de protection des personnes, CPP XI; authorization number: 1934708). In accordance with French law, patients and their relatives were informed of their initial inclusion in the database, and informed consent of participants or their legal representatives was obtained prior to follow-up assessments.

Consent for publication

Not applicable

Availability of data and materials

Anonymized data are available to qualified investigators on request for the purposes of replicating procedures or results by contacting the corresponding author.

Competiting interests

VP is the CEO of BrainTale SAS. The other authors declare that they have no competing interests.

Funding

There was no industry-sponsored funding. The MRI-COMA trial was funded by independent research grants from non-profit or governmental agencies: the French Ministry of Health, Paris, France (Programme Hospitalier de Recherche Clinique 2005 #051061), and the French National Agency for Research (ANR) for the program "Investissements d'avenir" ANR-10-IAIHU-06 (to the Brain and Spine Institute); Fondation des "gueules cassées".

Acknowledgements

We would like to thank the patients, relatives, and clinical and research staff.

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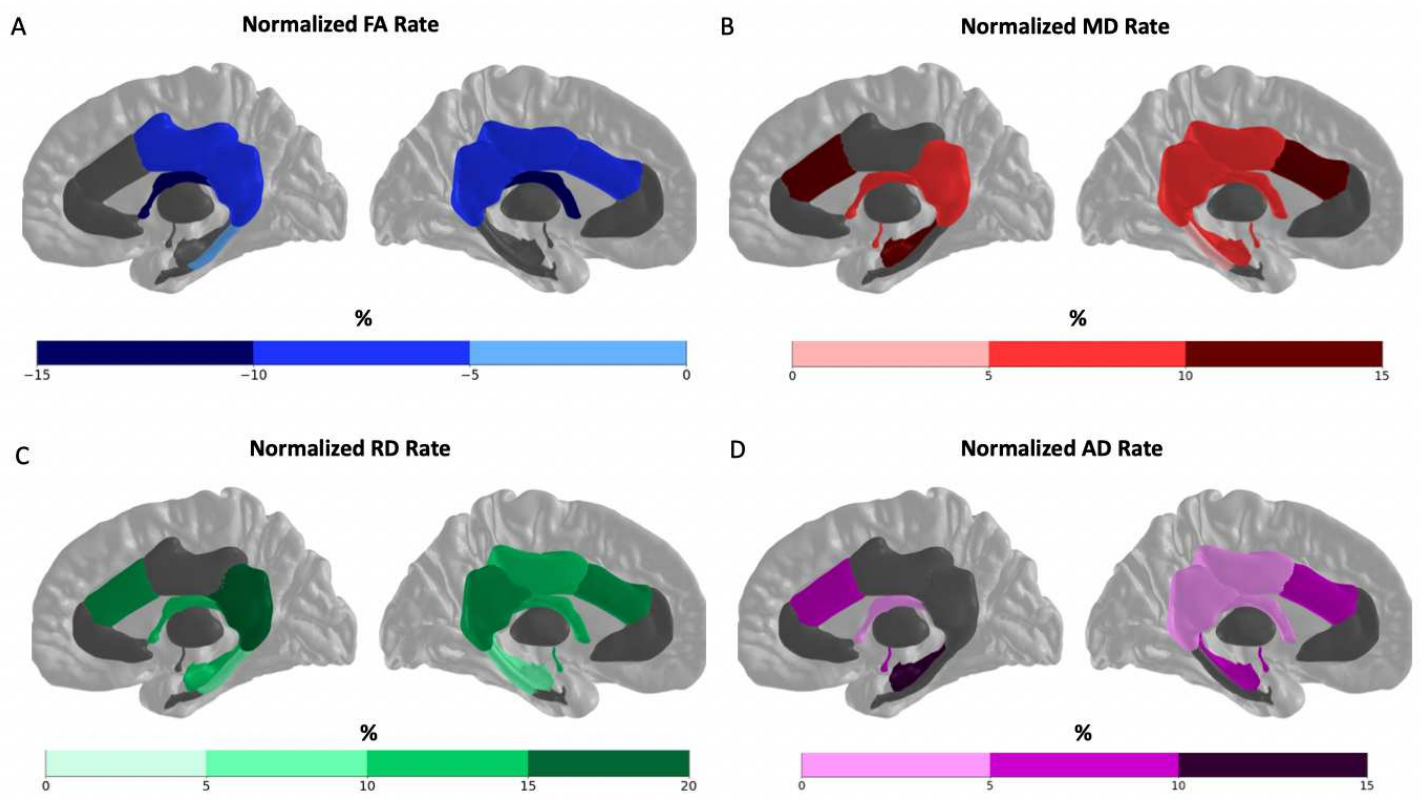
FIGURE LEGENDS

Figure 1. Papez circuit maps of volumetry and normalized DTI index analysis. Percentage of difference regarding volumetry (**A**), normalized fractional anisotropy, (**B**) mean diffusivity (**C**), axial diffusivity (**D**) and radial diffusivity (**E**) in Papez circuit between EMI+ and EMI- patients. All images are showing right brain hemisphere at the left side of the image and left hemisphere at the right side of the image.

Figure 2. Receiver-Operating-Characteristic (ROC) curve generated from multivariate model. Area Under the Curve (AUC) generated from clinical data with gender, initial Glasgow Coma Score at admission, lower Glasgow Coma Score during hospital stay, duration of coma and occurrence of post-traumatic amnesia were computed in this model with volumetric and normalized FA, MD, AD and RD.

Figure 1. Papez circuit maps of normalized DTI index analysis. Percentage of difference regarding fractional anisotropy, (**A**) mean diffusivity (**B**), radial diffusivity (**C**) and axial diffusivity (**D**) in Papez circuit between EMI+ and EMI- patients. All images are showing right brain hemisphere at the left side of the image and left hemisphere at the right side of the image.



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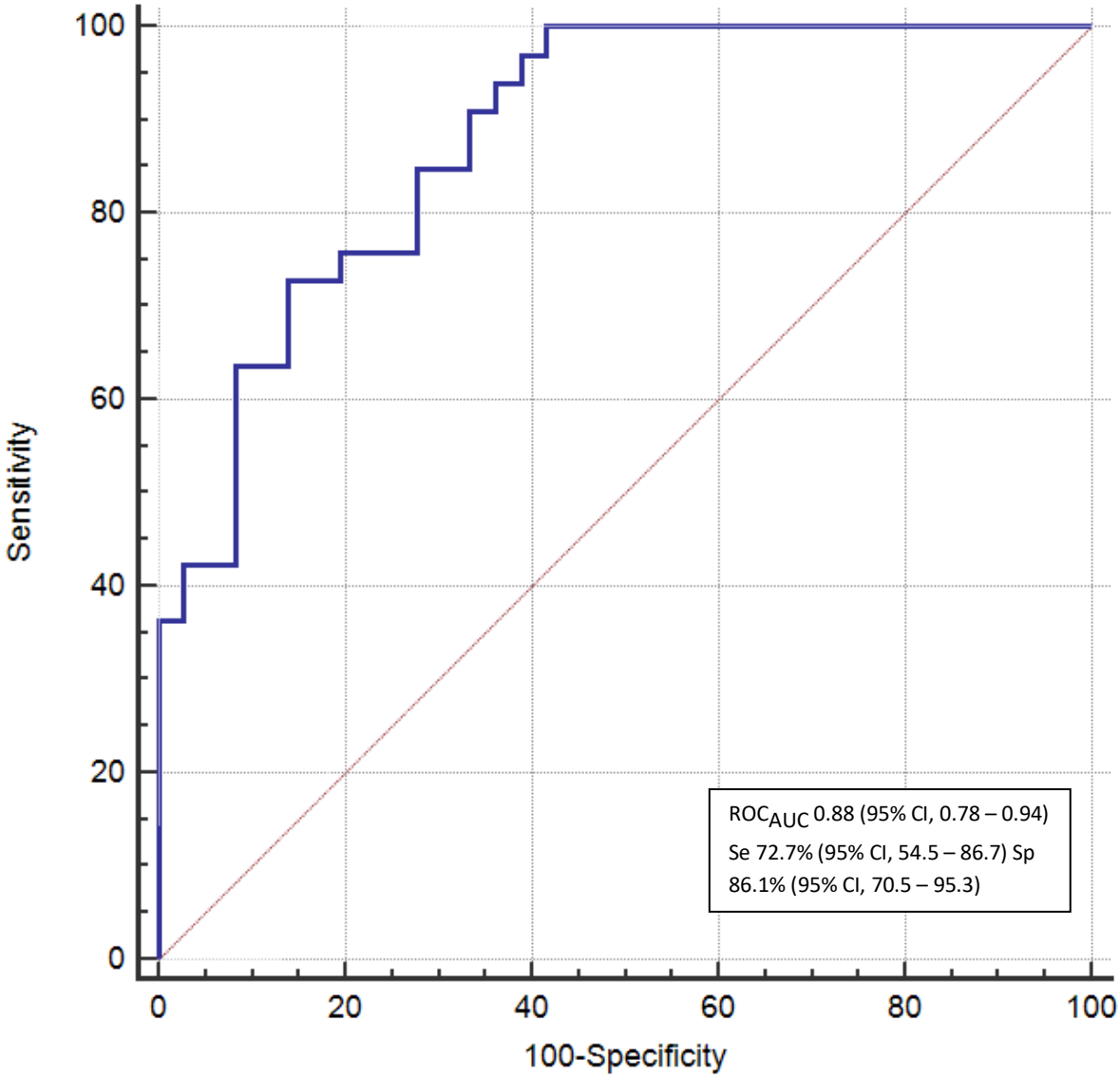

Table 1. Cohort demographic, clinical and radiographic characteristics during intensive care unit stay.

Parameters	All patients (*n* = 100)	Presence of EMI (EMI+) (*n* = 51)	Absence of EMI (EMI-) (*n* = 49)	*P*-values[a]
Demographic and clinical presentation				
Male gender*, No.* (%)	85 (85)	46 (94)	39 (76)	**.015**
Age, mean (SD), y	33.6 (15.5)	35 (16)	32 (14)	.43
Right-handed*, No.* (%)	84 (84)	40 (47)	44 (52)	.41
Education status – High school diploma	24 (24)	8 (16)	16 (31)	.075
Cause of TBI*, No.* (%)				
Assault	22 (22)	12 (23)	10 (20)	1
Motor vehicle accidents	59 (59)	30 (59)	29 (59)	1
Fall	15 (15)	5 (10)	10 (20)	1
GCS[b] at admission, median (IQR)	8 (6–12)	6 (3–10)	10 (7–13)	**.001**
Day with sedation, mean (SD)	10.5 (7.5)	12 (7)	10 (8)	.28
Duration of coma, mean (SD), d	19 (18)	24 (22)	15 (13)	**.03**
Seizures during hospital stay, *No.* (%)	11 (11)	7 (14)	4 (8)	.30
Initial CT scan				
Marshall grade initial CT scan, median (IQR)	2 (2–3)	2 (2–3)	2 (2–3)	.54

Data are expressed as mean (SD), median (IQR) or No. (%) when appropriate.
CT denotes computed tomography.
GCS denotes Glasgow Coma Score.
[a] *P*-value for patients with a presence of EMI (EMI+) versus those with absence of EMI (EMI-)
[b] Scores on the Glasgow Coma Scale range from 3 to 15, with lower scores indicating reduced levels of consciousness.

Table 2. Volumetric and normalized DTI index analysis in the entire Papez Circuit.

Parameters	Healthy Controls (HC) (*n* = 50)	Absence of EMI (EMI-) (*n* = 49)	Presence of EMI (EMI+) (*n* = 51)	*P*-values
Volumetry	493.0 (70.7)	478.5 (57.0)	450.5 (61.7)	[a]
Fractional anisotropy (FA)	1.00 (15.5)	0.91 (0.06)	0.85 (0.09)	[a,b,c]
Mean diffusivity (MD)	0.97 (0.05)	1.11 (0.09)	1.20 (0.15)	[a,b,c]
Radial diffusivity (AD)	0.97 (0.04)	1.07 (0.06)	1.12 (0.10)	[a,b,c]
Axial diffusivity (RD)	0.97 (0.05)	1.16 (0.13)	1.29 (0.21)	[a,b,c]

Data are expressed as mean (SD).
[a] Tukey HSD *P*-value<0.05 between HC and EMI+.
[b] Tukey HSD *P*-value<0.05 between HC and EMI-.
[c] Tukey HSD *P*-value<0.05 between EMI+ and EMI-.

Table 3. Cohort clinical presentation at follow-up.

Parameters	All patients (*n* = 100)	Presence of EMI (EMI+) (*n* = 51)	Absence of EMI (EMI-) (*n* = 49)	*P*-values[a]
Reeducation at discharge, No. (%)	15 (15)	8 (15.7)	7 (14.3)	.84
Current reeducation, No. (%)	70 (70)	39 (78)	31 (63)	.10
Psychiatric/psychological follow-up, No. (%)	51 (51)	27 (53)	24 (49)	.69
Post-traumatic amnesia more than 60 days, No. (%)	25 (25)	19 (37)	6 (12)	**.003**
Epilepsy at discharge, No. (%)	17 (17)	7 (14)	10 (20)	.37
Current headache, No. (%)	57 (57)	32 (64)	25 (54)	.33
Current Speech-Language Pathologist, No. (%)	81 (81)	43 (88)	38 (77)	.18
Current Ergotherapist, No. (%)	78 (78)	42 (85)	26 (50)	**.001**
Professional activity before, No. (%)	96 (96)	47 (92)	49 (100)	.89
Current professional activity, No. (%)	69 (69)	44 (86)	25 (51)	**.01**
Ability to drive before TBI, No. (%)	28 (28)	14 (28)	14 (29)	.89
Current ability to drive, No. (%)	41 (41)	15 (30)	26 (54)	**.015**
Caregivers in the home, No. (%)	21 (21)	13 (30)	8 (18)	.18
Patient quality of life, mean (SD)	6.3 (2.1)	7 (2)	5.7 (2)	**.005**
Quality of life for caregivers, mean (SD)	5.7 (2.3)	6.3 (2.5)	5.3 (1.9)	.09
Patient Complaints, mean (SD)	11.3 (6)	9.8 (5.4)	12.9 (6.1)	**.012**
Caregiver Complaints, mean (SD)	13.8 (6.3)	12.2 (6.5)	15.2 (5.5)	**.047**
Patient DEX, mean (SD)	25.5 (14.5)	21.5 (14.6)	29.6 (13)	**.008**
Caregivers' DEX, mean (SD)	29.1 (18)	24.5 (17.5)	33.2 (17.3)	.041

Data are expressed as mean (SD), median (IQR) or No. (%) when appropriate.
CT denotes computed tomography; GOSE, extended Glasgow outcome scale and MRI, magnetic resonance imaging.
[a] *P*-value for patients with a presence of EMI (EMI+) versus those with absence of EMI (EMI-)

Supplementary Files

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- 2SupplementaryV5.pdf