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SCIENTIFIC LETTER

Evaluation of functional brain damage using resting-state functional magnetic resonance imaging in patients with diffuse axonal injury admitted to the ICU

Evaluación del daño funcional cerebral mediante RM funcional en reposo en pacientes con lesión axonal difusa ingresados en UCI

Dear Editor:

Most deaths following acute brain injury in the intensive care unit (ICU) occur after a joint decision of withdraw life-support therapies (LSTW) taken by the family and medical team. This is a common process in the neuro-ICU, despite the known imprecision of available diagnostic and prognostic scales.[1]

Specifically, patients with traumatic brain injury (TBI) presenting with diffuse axonal injury (DAI) are at high risk of severe disability and therefore, potentially receive LSTW. DAI is the shearing of the brain's axons that occurs when the brain is injured as it shifts and rotates inside the skull. DAI typically causes coma and widespread brain injury. Magnetic resonance imaging (MRI) can reveal structural damage in the form of hemosiderin and ferritin deposits, which represent microbleeds, commonly located in both cerebral hemispheres, corpus callosum, and the brainstem. However, while estructural secuences are useful for identifying these lesions, they do not provide information about brain function.[2,3]

In recent years, the role of resting-state functional magnetic resonance imaging (rs-fMRI) has become increasingly important to study the function of the brain. It allows assessing brain activity without requiring a behavioral response, thereby identifying preserved brain connections. This technique can identify preserved functional connections in patients whose level of consciousness is not identified by routine neurological examinations performed in the neuro-ICU, thus it could potentially provide essential information for neuroprognostication and decision-making in the complex environment of the neuro-ICU.[4,5]

Our objective was to analyze the role of rs-fMRI in assessing brain connections in patients with TBI and DAI.

The study was approved by the IRB (CEI-IB: IB 5124/23 PI). TBI participants were recruited from the neuro-ICU at Son Espases University Hospital and the MRI was performed as part of the routine diagnosis for DAI. The rs-fMRI was added to the conventional MRI sequences upon informed consent from closest relative. Healthy voluntary participants for control purposes were recruited from the University of Balearic Islands. The neuroimaging data from healthy participants were used in a previous study.[6]

All participants underwent rs-fMRI scan using a GE 3 T scanner (General Electric Signa HDx, GE Healthcare, Milwaukee, WI). All TBI patients were without sedation at the time of the MRI but 40 mgr of propofol were administered to all TBI patients during the MRI for the transport and mechanical ventilation.

During a 10-minute resting-state period with eyes closed, 240 whole-brain echo-planar images were acquired for each participant in the control group but not in TBI patients (36 transversal slices per volume; 3-mm slice thickness; 90° flip angle; repetition time: 2500 ms; echo time: 35 ms; 64×64 matrix dimensions; 240-mm field of view; $3.75 \times 3.75 \times 3$-mm voxel size).

Structural imaging data consisted of T1-weighted images acquired with the following parameters: 220 slices per volume; repetition time: 7.9 s; echo time: 3 ms; matrix dimensions: 256×256; 256-mm field of view; 1-mm slice thickness; 12° flip angle; 10-minute duration.

Connectivity analyses were conducted using the CONN-fMRI FC toolbox v18a[2] and SPM 12 (Wellcome Department of Imaging Neuroscience, London, UK). Preprocessing of structural and functional sequences followed CONN's default pipeline for volume-based analysis, including: resampling to $2 \times 2 \times 2$-mm voxels and unwarping, centering, slice time correction, normalization to the Montreal Neurological Institute (MNI) template, outlier detection (artifact-based scrubbing) and smoothing to an 8-mm Gaussian kernel. Motion parameters (translations in the x, y, and z directions) were included as multiple regressors, and images with motion exceeding 2.0 mm were removed from the time course. Data quality was ensured by excluding any participant with more than 20% of scans removed (no participants were excluded, mean % of invalid scans = 3.42 ± 3.46; maximum % invalid scans = 12.12; minimum % invalid scans = .83). BOLD data underwent a denoising process that included the regression of white matter and cerebrospinal fluid signals

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using the CompCor method in a single linear regression step. A band-pass filter (.01−.09 Hz) was applied to reduce noise effects and low-frequency drift.

To investigate functional connectivity changes across several key networks, ROI-to-ROI analyses were performed. The Default-mode Network (DMN), Sensory-Motor Network (SMN), Salience Network (SN), Dorsal-Attention Network (DAN), and Fronto-Parietal Network (FPN) were examined, with their main regions provided by the CONN toolbox, originally derived from independent component analyses (ICA) based on the Human Connectome Project dataset (497 subjects).[7] The specific regions included in each network are displayed in electronic supplementary material (ESM1). Then, Individual correlation maps were generated by extracting the mean resting-state BOLD time course from all ROIs and calculating correlation coefficients between each pair of ROIs. Correlations were obtained through the general linear model and bivariate correlation analysis, weighted for hemodynamic response function, and used as resting-state functional connectivity (rsFC) measures.

Finally, group differences in rsFC measures were examined using one-way analysis of variance (ANOVAs) with the second-level analysis module of the CONN toolbox ($P < .05$, false-discovery rate-corrected).

Six TBI patients with DAI and six age- and sex-matched healthy control participants were included. Basal characteristics are presented in electronic supplementary material (ESM2). rsFC analyses of the key networks (Table 1) showed decreased connectivity in the comatose patients compared with healthy controls within several main regions of all the analyzed networks. Specifically, a clear reduction in interhemispheric connectivity between the nodes of the SN, SMN, DAN, and FPN was observed in comatose participants compared to healthy ones (Fig. 1, panels A, B, C and D). On the other hand, a reduction in fronto-parietal connectivity between the nodes of the DMN was found in comatose participants (Fig. 1, panel E). In no case we observed an increase in connectivity within these networks in the comatose group compared to the control group.

Table 1 Group differences in functional connectivity within major networks. Reported statistics include the t-value with degrees of freedom [T(df)], uncorrected p-values (p-unc), and false discovery rate (FDR) corrected two-sided p-values (p-FDR, 2-sided).

DAI < CONTROL	T(10)	p-unc	p-FDR (2-sided)
DMN			
LP R - LP L	−4.13	0.0020	0.0032
LP R - MPFC	−4.10	0.0022	0.0032
LP L - MPFC	−2.68	0.0233	0.0349
MPFC - PCC	−2.60	0.0267	0.0267
SMN			
PreC L - PreC R	−3.52	0.0055	0.0110
SN			
aINS R - aINS L	−5.43	0.0003	0.0017
aINS R - rPFC R	−3.65	0.0045	0.0134
aINS R - rPFC L	−3.22	0.0092	0.0185
aINS R - SMG R	−2.69	0.0227	0.0341
SMG L - SMG R	−5.01	0.0005	0.0032
aINS L - SMG R	−3.73	0.0039	0.0116
aINS L - ACC	−3.03	0.0127	0.0255
aINS L - rPFC R	−2.68	0.0229	0.0335
aINS L - rPFC L	−2.57	0.0279	0.0335
rPFC R - rPFC L	−2.73	0.0210	0.0458
DAN			
IPS L - IPS R	−2.91	0.0157	0.0470
FPN			
lPFC L - lPFC R	−3.38	0.0070	0.0211

DAI: Diffuse Axonal Injury; DMN: Default-mode Network; LP: Lateral Parietal; R: Right; L: Left; MPFC: medial Prefrontal Cortex; PCC: Posterior Cingulate Cortex; SMN: Sensory-Motor Network; PreC: Precentral gurys; SN: Salience Network; aINS: Anterior Insula; rPFC: rostral Prefrontal Cortex, SMG: Supramarginal Gyrus; ACC: Anterior Cingulate Cortex; DAN: Dorsal-Attention Network; IPS: Intraparietal Sulcus; FPN: Fronto-Parietal Network, LP; lPFC: lateral prefrontal cortex.

Rs-fMRI has emerged in recent years as a promising tool in the assessment of the function of the brain. This could be especially relevant for TBI patients with DAI, as it allows us to analyze different functional networks. Furthermore, since it does not require any active behavioral response from the patient, it is especially attractive for using during the subacute phase of TBI, while the patient remains in coma and is still admitted to the neuro-ICU. The results of this study confirm that patients with severe TBI and DAI have significantly decreased connectivity in critical neuronal networks, affecting both interhemispheric connectivity across all the networks examined, as well as fronto-parietal connections within the DMN, a neuronal network associated with the level of consciousness and self-reference. This suggests a global functional impairment that compromises the capacity for integration and connection between different brain regions, confirming the role of rs-fMRI as a useful complementary tool to assess the functional damage in the neuro-ICU. This functional evaluation could potentially contribute to improve our neuroprognostic ability and provide appropriate counselling before LSTW. Of course, research with larger samples and longer-term follow-up could validate the definitive role of rs-fMRI within the neuro-ICU environment, where improving neuroprognostic accuracy and detecting covert consciousness could be of paramount importance.

This study has several limitations: first, this is a small convenience sample of patients. Second, TBI patients received intravenous sedation that can affect the rs-fMRI analysis. Third, the patients presented a different DAI grade that could also affect the analysis.

In conclusion, in this convenience sample of TBI patients with DAI, rs-MRI allows us to evaluate how different areas of the brain communicate, giving us insights into the functional impact of trauma. Rs-MRI can complement basic MRI sequences that detect structural damage. In the future,

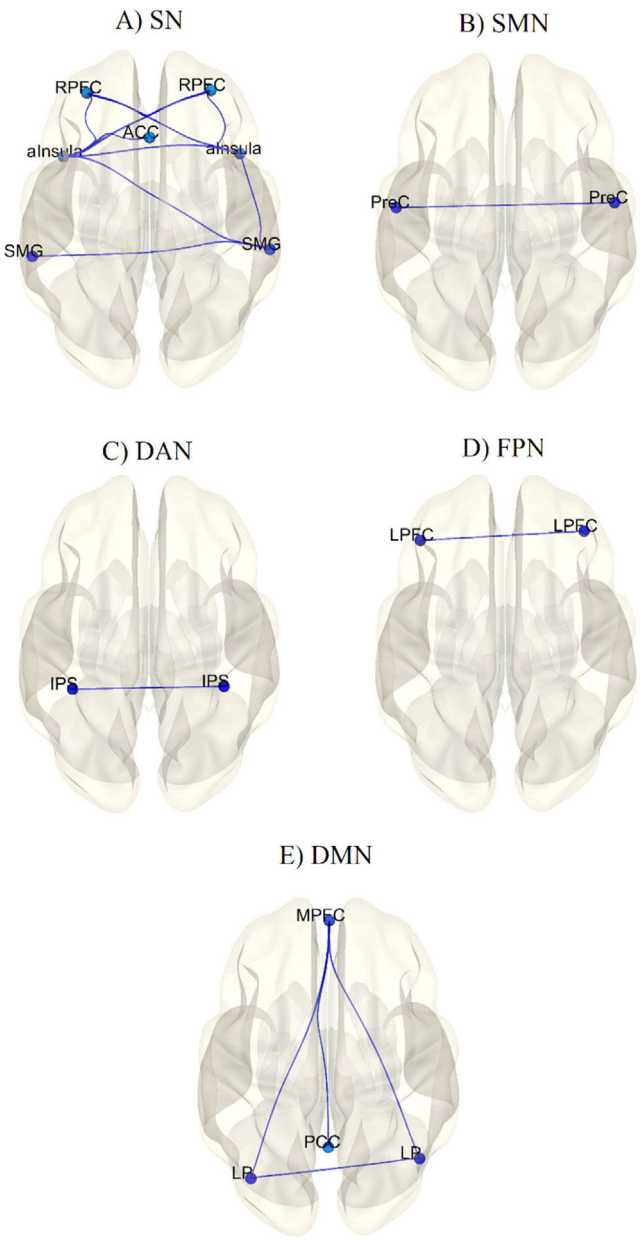

Figure 1 Representation of the decreased connectivity between regions of comatose patients compared to healthy controls. The regions are part of the Salience Network (A), SensoriMotor Network (B), Dorsal Attention Network (C), FrontoParietal Network (D), and Default-mode Network (E).

this technique could help us to improve our neuroprognostic accuracy and making-decision in the neuro-ICU.

CRediT authorship contribution statement

PSL collected data, wrote the preliminary draft and approved the final version. JALLP critically reviewed the manuscript and approved the final version. AMGR and JLTN performed the resting-state functional MRI analyses, wrote the specific technical text and approved the final version. AMS performed the conventional MRI analyses and approved the final version. JPB conceived the study, coordinated the project and wrote the final draft.

Declaration of Generative AI and AI-assisted technologies in the writing process

The authors declare that no form of Artificial Intelligence has been used to write this manuscript.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.medin.2025.502260.

Declaration of competing interest

All authors declare no conflict of interest.

References

1. McMillan T, Wilson L, Ponsford J, Levin H, Teasdale G, Bond M. The Glasgow Outcome Scale - 40 years of application and refinement. Nat Rev Neurol. 2016;12:477–85, http://dx.doi.org/10.1038/nrneurol.2016.89.
2. Adams JH, Doyle D, Ford I, Gennarelli TA, Graham DI, McLellan DR. Diffuse axonal injury in head injury: definition, diagnosis and grading. Histopathology. 1989;15:49–59, http://dx.doi.org/10.1111/j.1365-2559.1989.tb03040.x.
3. Johnson-Black PH, Carlson JM, Vespa PM. Traumatic brain injury and disorders of consciousness. Handb Clin Neurol. 2025;207:75–96, http://dx.doi.org/10.1016/B978-0-443-13408-1.00014-2.
4. Palacios EM, Sala-Llonch R, Junque C, Roig T, Tormos JM, Bargallo N, et al. Resting-state functional magnetic resonance imaging activity and connectivity and cognitive outcome in traumatic brain injury. JAMA Neurol. 2013;70:845–51, http://dx.doi.org/10.1001/jamaneurol.2013.38.
5. Lv H, Wang Z, Tong E, Williams LM, Zaharchuk G, Zeineh M, et al. Resting-state functional MRI: everything that nonexperts have always wanted to know. AJNR Am J Neuroradiol. 2018;39:1390–9, http://dx.doi.org/10.3174/ajnr.A5527.
6. Dorado A, Terrasa JL, van der Meulen M, Montoya P, González-Roldán AM. Altered endogenous pain-inhibitory function in older adults with chronic pain is associated with disruptions in functional connectivity during resting state. J Pain. 2024;25:104641, http://dx.doi.org/10.1016/j.jpain.2024.104641.

7. Whitfield-Gabrieli S, Nieto-Castanon A. Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. Brain Connect. 2012;2:125–41, http://dx.doi.org/10.1089/brain.2012.0073.

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