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Perioperative research into memory (PRiMe), part 2: Adult burns intensive care patients show altered structure and function of the default mode network

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ABSTRACT

Background: Long-term cognitive impairment (LTCI) is experienced by up to two thirds of patients discharged from Burns Intensive Care Units (BICU), however little is known about its neurobiological basis. This study investigated if patients previously admitted to BICU showed structural and functional MRI changes of the Default Mode Network (DMN).

Methods: Fifteen patients previously admitted to BICU with a significant burns injury, and 15 matched volunteers, underwent structural and functional MRI scans. Functional connectivity, fractional anisotropy and cortical thickness of the main DMN subdivisions (anterior DMN (aDMN), posterior DMN (pDMN) and right (rTPJ) and left (lTPJ) temporo-parietal junctions) were compared between patients and volunteers, with differences correlated against cognitive performance.

Results: Functional connectivity between rTPJ and pDMN ($t = 2.91$, $p = 0.011$) and between rTPJ and lTPJ ($t = 3.18$, $p = 0.008$) was lower in patients compared to volunteers. Functional connectivity between rTPJ and pDMN correlated with cognitive performance ($r^2 = 0.33$, $p < 0.001$). Mean fractional anisotropy of rTPJ ($t = 2.70$, $p = 0.008$) and lTPJ ($T = 2.39$, $p = 0.015$) was lower in patients but there was no difference in cortical thickness.

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Conclusions: Patients previously admitted to BICU show structural and functional disruption of the DMN. Since functional changes correlate with cognitive performance, this should direct further research into intensive care related cognitive impairment.

1. Introduction

As the survival rates of patients admitted to the intensive care unit (ICU) continue to improve [1,2], the cognitive deficits experienced by these patients after discharge has taken on increasing clinical importance [3]. ICU related long-term cognitive impairment (IR-LTCI) occurs in up to two thirds of intensive care patients [4] and has a significant impact on patients' subsequent quality of life [5]. Identification of neurobiological changes associated with IR-LTCI is crucial in isolating the primary causative factors and identifying potential protective measures. Currently very little is known about its pathophysiology although development of delirium during acute illness seems to be a significant risk factor [3]. There are a myriad of other potential causative factors, including, but not limited to, the inflammatory response to critical illness or surgery [6] and protracted administration of opioids and sedative agents [3]. Understanding its aetiology is further complicated by the heterogeneity of pathologies for which patients are admitted to ICU, alongside the patients' age and high comorbidity load, which alter the way they respond to critical illness and to treatment. Patients treated in a burns intensive care unit represent an ideal population to understand IR-LTCI as both the primary pathology and treatment are comparatively homogenous, whilst most patients are young and have relatively little comorbidity.

The interrogation of the structure and function of the healthy and pathological brain using MRI is an expanding area of research. Functional magnetic resonance imaging (fMRI) has been extensively used to assess the activity of the living human brain, whilst diffusion tensor imaging (DTI) has become a popular method of assessing the microstructure within cerebral white matter.

Several robust networks have been identified using fMRI in the resting brain. Of these so-called resting state networks (RSNs), one of the most reliably identified and well-studied is the Default Mode Network (DMN), which primarily comprises parts of the Medial Prefrontal Cortex, Posterior Cingulate Cortex (PCC) / Precuneus, Right Temporoparietal Junction (RTPJ) and Left Temporoparietal Junction (LTPJ) [7]. The precise functions of this network are an area of ongoing research but it is known that its components are highly active at rest with activity declining during volitional activity [8]. Dysfunction of the DMN has been shown to be associated with cognitive deficits resulting from a plethora of different pathologies, including Alzheimer's disease [9,10], Parkinson's disease [11], Traumatic Brain Injury [12] and Hepatic encephalopathy [13]. The integrity of these RSNs can be assessed by the functional connectivity (FC) between its subunits, that is the synchrony of low frequency Blood Oxygenation Level Dependent (BOLD) signals between different regions of the network. To date, no studies have investigated the association between dysfunction in RSNs and IR-LTCI.

The primary aim of this exploratory study is to identify whether FC changes between the four main subunits of the DMN associate with IR-LTCI when comparing patients discharged from BICU and matched healthy volunteers. A secondary aim of the study is to identify whether any functional changes identified correlate with white matter changes as assessed by fractional anisotropy (FA) from diffusion tensor imaging or grey matter changes assessed by cortical thickness (CT) on T1 structural MRI imaging.

2. Materials and methods

2.1. *Ethical approval*

The study was approved by the Surrey Borders Research Ethics Committee (Date 30/01/14, Reference 14/LO/0049) and was prospectively registered (ClinicalTrials.gov ID: NCT03242395). Informed written consent was obtained from all participants in accordance with the EU General Data Protection Regulation and the work was carried out in accordance with The Code of Ethics of the World Medical Association for experiments involving humans.

2.2. *Participants*

Fifteen patients and 15 age and sex matched volunteers took part in this exploratory study. This was in line with our power calculation, undertaken using evidence based methods for an exploratory proof of principle study [14,15], that suggested between 10–26 patients would be required to detect a group difference. All patients had sustained a significant previous burns injury (> 15% total body surface area) and been admitted to the burns intensive care unit for invasive ventilation. Patient recruitment, characteristics and cognitive testing have been described in detail by Watson et al. [16] who demonstrated that the patients showed a global cognitive deficit relative to matched volunteers and have a significant decrease in cognition relative to their predicted pre-morbid IQ. They assessed cognitive performance using the well-validated Cogstate® battery of cognitive tests [17] with performance on these tests converted to Z-scores using population means and standard deviations. The median Z-score across the tests was used to represent overall cognition for each participant and it is this metric that has been used for comparing neuroimaging changes to cognitive performance in this study.

2.3. MRI Image acquisition

Magnetic resonance images were acquired using a whole-body 3.0 T Siemens Magnetom Verio MRI scanner (Siemens, Germany) with a 32-channel head coil.

Gradient-echo EPI images for fMRI analysis were obtained with the following parameters: TR= 2.5 s, TE= 25 ms, Slice number= 43, Slice thickness= 3 mm, Image matrix= 74 × 74, FOV= 220x220mm, Flip angle= 90° Bandwidth= 1438 Hz. During the 411 s resting state fMRI acquisition period (165 volumes), participants were asked to remain awake with their eyes open and focused on a fixation cross.

For structural imaging and cortical thickness measurements, T1-weighted magnetization-prepared rapid-gradient echo (MPRAGE) sequences were acquired through the sagittal plane with the following parameters: TR= 1.9 s; TE= 2.49 ms; TI= 900 ms; Slice number= 176, Slice thickness= 1 mm, Matrix= 256 × 256, FOV= 250x250mm, Flip angle= 9°, Bandwidth= 170 Hz.

A single shot spin-echo echo-planar sequence was used for DTI with diffusion gradients along 30 directions: b-values= 0 & 1000 s/mm^2, TR= 7.3 s, TE= 88 ms, Slice number= 58, Slice thickness= 2.5 mm, Matrix= 96 × 96, FOV= 240x240mm, Bandwidth= 1446 Hz.

2.4. fMRI pre-processing and data analysis

Data pre-processing was performed in SPM12 (Welcome Trust Centre for Neuroimaging, University College London, United Kingdom) [18] running in Matlab R2018a (The Mathworks Inc, USA). Pre-processing steps were in line with other similar studies [19]. Briefly, functional volumes underwent realignment, slice-timing correction, registration to Montreal Neurological Institute (MNI) space using the normalised EPI template image in SPM and spatial smoothing (8 mm full width half maximum Gaussian kernel filter). Motion parameters from realignment were evaluated and a motion artefact threshold (translation > 3 mm, rotation > 1°) was employed for exclusion. No participants displayed gross movement sufficient to require exclusion of any volumes. Noise correction was performed using the anatomical component-based noise correction (aCompCor) method implemented in the Functional Connectivity toolbox (CONN) [20] for SPM12. During pre-processing, high resolution T1-weighted anatomical volumes for each subject were segmented into grey matter, white matter and cerebrospinal fluid and normalised to MNI space. BOLD signals from cerebral white matter and ventricles were removed using principal component analysis (PCA) of the multivariate BOLD signal within each of these masks. Finally, BOLD data was band-pass filtered (0.008–0.09 Hz) to reduce low-frequency drift and noise effects.

2.5. Regions of interest (ROI)

As the DMN is a functionally defined network without clear anatomical boundaries, ROIs for the four major subdivisions of the DMN (anterior DMN (aDMN), posterior DMN (pDMN), left temporal-parietal junction (lTPJ) & right temporal-parietal junction (rTPJ)) were created by combining binarised masks

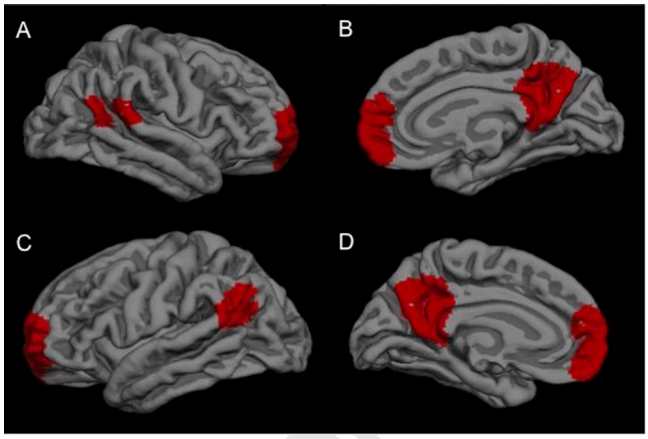

Fig. 1 – Anatomical location of default mode network (DMN) subdivisions derived from an existing meta-analysis of UK Biobank participants, overlaid onto standard space cortical surface. A. Right hemisphere (lateral) showing right temporoparietal junction and anterior DMN. B. Right hemisphere (medial) showing anterior DMN and posterior DMN. C. Left hemisphere (lateral) showing left temporoparietal junction and anterior DMN. D. Left hemisphere (medial) showing posterior DMN and anterior DMN.

of DMN subdivisions (Fig. 1.) derived from 10,000 UK Biobank participants [21] made freely available from Neurovault.org (an online repository of activation patterns generated from peer-reviewed fMRI studies) [22].

2.6. fMRI analysis

The average BOLD time series for all voxels in each ROI was normalised using Fisher's transformation and correlations performed with the other three DMN ROIs, to produce a 4 × 4 correlation matrix. The resulting correlation coefficients were then compared between patients and matched volunteers using a paired 2-tailed t-test. The False Discovery Rate (FDR) [23] was applied to correct for multiple comparisons across the 12 seed-target combinations and the results were thresholded at a corrected p-value of $p < 0.05$.

To examine whether FC between the four DMN subdivisions is related to cognitive performance, the inter-ROI correlation coefficients were correlated with median scores on the Cogstate® battery by calculating Pearson's correlation coefficient. All statistical analyses were undertaken using the R statistical software package [24]. A linear regression model was then created including covariate adjustment for age, sex and NART FSIQ score (a validated method of assessing a subjects predicted pre-morbid IQ). [23,24].

2.7. DTI fractional anisotropy analysis

To investigate for any differences in white matter content between the four DMN subdivisions, the DTI images were used to calculate the mean FA of each of the predetermined ROIs. First, diffusion weighted images were pre-processed

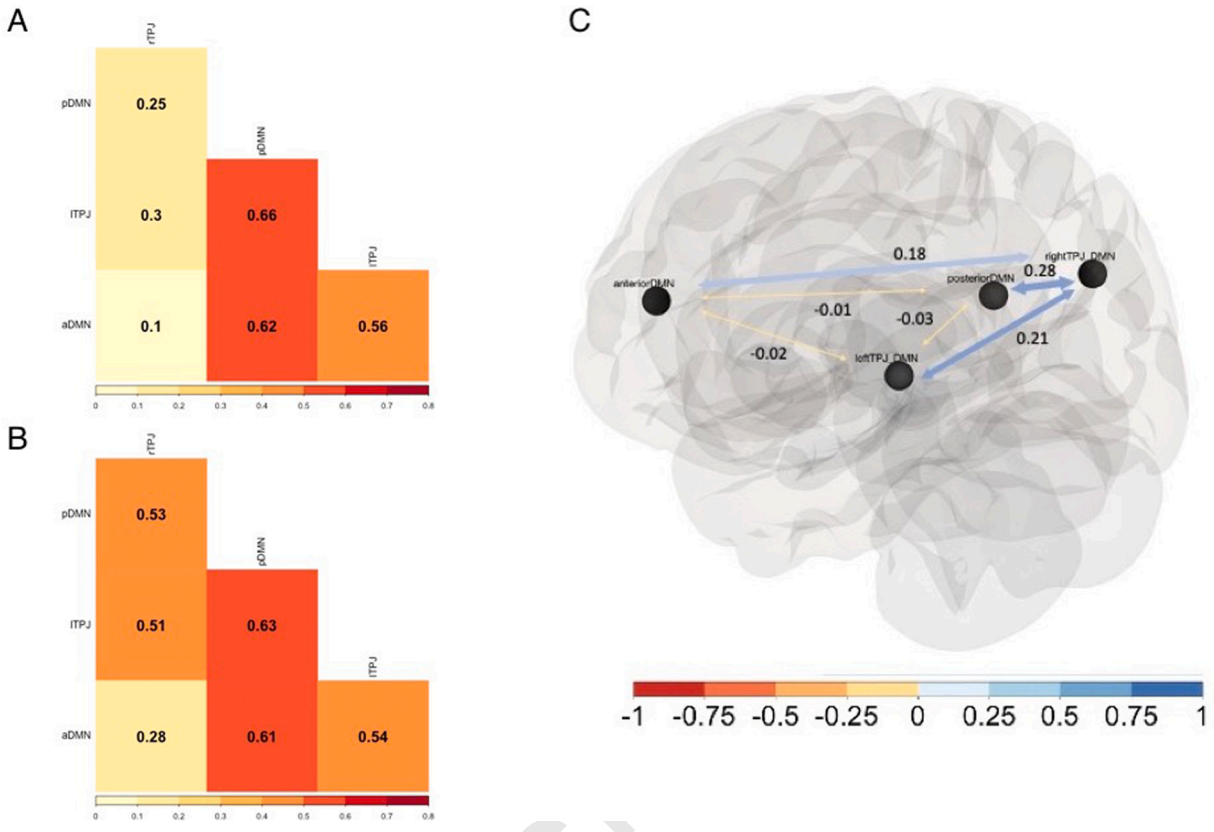

Fig. 2 – Correlation matrix for subregions of the DMN for patients (A) and volunteers (B). Values within each square represent functional connectivity between pairs of subregions. The difference in functional connectivity between patients and volunteers (C) is represented by the thickness and colour of lines connecting DMN ROIs which have been overlaid onto a standard cerebral template. DMN = Default Mode Network, ROI = Region of Interest, rTPJ = Right Temporoparietal Junction, lTPJ = Left Temporoparietal Junction, pDMN = Posterior DMN, aDMN = Anterior DMN.

with the FSL Diffusion Toolbox (FDT) [27]. Pre-processing consisted of eddy-current correction, motion correction and removal of non-brain tissue using the Brain Extraction Tool (BET) [28]. DTIFIT was then used to fit the diffusion tensor model. FA maps were then registered to MNI space before calculation of the mean FA value for each of the four ROIs.

After assessing for normality, the difference in mean FA between the patients and volunteers was compared for each of the four ROIs using a paired 1-tailed t-test. FDR adjustment was applied and significance inferred by a corrected p-value of $p < 0.05$.

2.8. *T1 structural MRI analysis*

All T1 structural scans were processed using Freesurfer v6.0 and underwent a standard processing pipeline. This consisted of skull stripping, white matter segmentation, intensity normalization and surface reconstruction [29]. The four DMN ROIs were then transformed into individual subject anatomical space and used for calculation of CT in the last stage of the traditional Freesurfer pipeline. After assessing for normality, the difference in mean CT, measured in millimeters (mm), between the patients and volunteers was compared for each of the four ROIs using a paired 1-tailed t-test and FDR correction was applied with significance inferred by a corrected p-value of $p < 0.05$.

3. Results

All results are presented as mean(standard deviation) unless otherwise stated.

3.1. *Functional connectivity analysis*

FC matrices were generated separately for patients and volunteers (Fig. 2). FC between rTPJ and pDMN was significantly lower in BICU patients than volunteers (0.25(0.26) vs 0.53(0.28), $t = 2.91$, $p = 0.011$, p-FDR= 0.03). FC between rTPJ and lTPJ was also significantly lower in patients than volunteers (0.30(0.16) vs 0.51(0.20), $t = 3.18$, $p = 0.006$, p-FDR= 0.03). FC between other regions of the DMN (Fig. 2) was not significantly different between patients and controls.

FC between rTPJ and pDMN correlated significantly with cognitive performance (Fig. 3), ($t = 3.70$, $R^2 = 0.33$, $p < 0.001$). A linear model including adjustment for age, sex and premorbid-IQ was also highly significant ($F=8.69$, $R^2 = 0.58$, $p < 0.001$) with post-hoc analysis showing significant associations between cognitive performance and rTPJ-pDMN FC

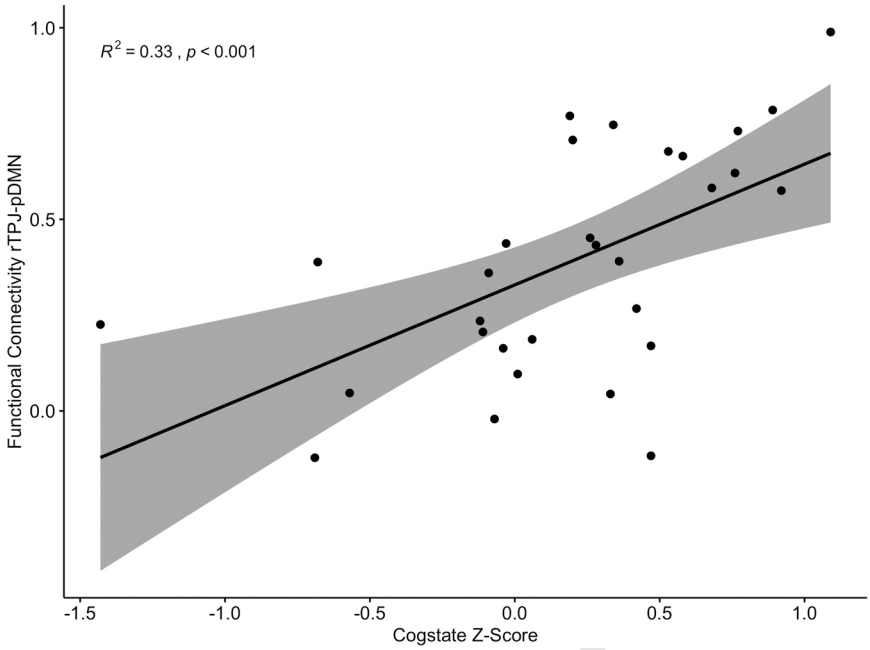

Fig. 3 – Correlation of functional connectivity between the right temporoparietal junction (rTPJ) and posterior default mode network (pDMN) with cognitive performance, as assessed by the median Z-score on the Cogstate® neurocognitive battery. The black line represents the fitted regression line with the surrounding grey area representing the 95% Confidence Interval for the regression line.

(t = 3.40, p = 0.002) as well as premorbid-IQ (t = 3.47, p = 0.002) but not age or sex. FC between rTPJ and lTPJ, which was also significantly different between patients and controls, did not show a significant correlation with cognitive performance (p = 0.180).

3.2. *Fractional anisotropy analysis*

Mean FA values for rTPJ were significantly lower in patients than volunteers (0.16(0.02) vs 0.18(0.02), t = 2.70, p = 0.008, p-FDR= 0.03). Mean FA values for lTPJ were also significantly lower in patients than volunteers (0.18(0.02) vs 20(0.02), t = 2.39, p = 0.015, p-FDR= 0.03). There was no significant difference in mean FA for pDMN between patients and volunteers (0.18(0.02) vs 0.19(0.02), t = 1.45, p = 0.085, p-FDR= 0.11), nor for aDMN (0.16(0.01) vs 0.16(0.01), t = 0.89, p = 0.195, p-FDR= 0.20) (Fig. 4A). Of note, there was no correlation between FC between rTPJ and pDMN and mean FA for rTPJ (R^2 =0.01, p = 0.630).

3.3. *Cortical thickness analysis*

No significant difference in CT was found between patients and volunteers in any of the four sub-regions of the DMN. rTPJ (patients: 2.74(0.14)mm, volunteers: 2.63(0.20)mm, t = 1.61, p = 0.935), pDMN (patients: 2.49(0.15)mm, volunteers: 2.43(0.17)mm, t = 1.12, p = 0.876), lTPJ (patients: 2.58(0.16)mm, volunteers: 2.48(0.15)mm, t = 1.75, p = 0.949), aDMN (patients: 2.55(0.16)mm, volunteers: 2.47(0.11)mm, t = 1.54, p = 0.927) (Fig. 4B.).

4. Discussion

Our study shows that patients previously admitted to the adult burns intensive care unit show decreased functional connectivity between the rTPJ and both the pDMN and the lTPJ regions of the default mode network, when compared to matched volunteers. Functional connectivity between rTPJ and pDMN correlates with cognitive performance, which suggests that reduced connectivity in this network may explain the cognitive impairment seen in these patients. Furthermore, patients showed reduced fractional anisotropy in both rTPJ and lTPJ, whilst there was no difference in cortical thickness. It is therefore possible that white matter changes in these regions contribute to the functional connectivity and cognitive deficits seen in these patients.

Whilst these functional neuroimaging changes are entirely novel, the associated structural neuroimaging changes are in line with previous findings of white matter deficits in other cohorts of intensive care patients experiencing long-term cognitive impairment [30].

That the observed cognitive deficits in adult BICU patients are associated with deficits of the DMN and particularly rTPJ is biologically plausible. The DMN is thought to be involved in high-level cognitive processing [8] and pathologies affecting cognition, including mild cognitive impairment and Alzheimer's disease, are associated with disruption of the DMN [9]. Specific neuroimaging studies of the rTPJ have found it to be involved myriad of higher cognitive functions [31] but particularly the re-orientation of attention [32], whilst its central role in higher cognition is supported by its large expansion in

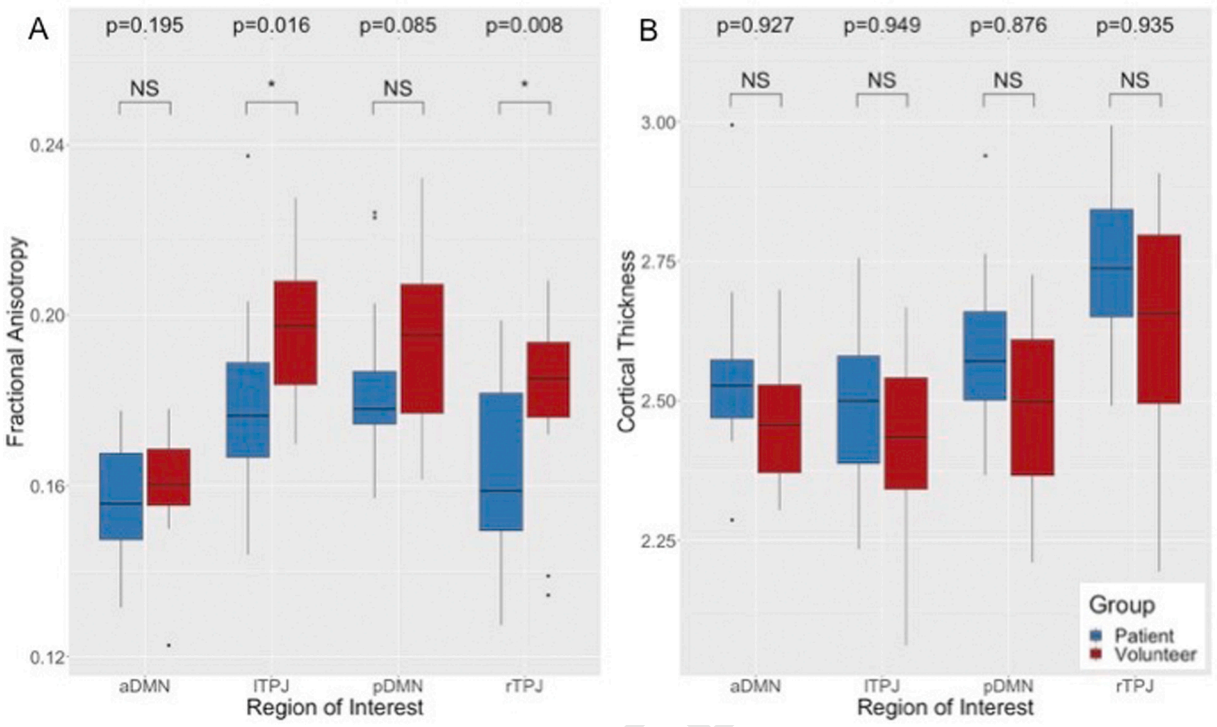

Fig. 4 – Boxplot of the mean difference in fractional anisotropy (A) and cortical thickness (B) between patients (blue) and matched controls (red) for the four subregions of the default mode network (DMN). Statistical comparison is based upon one-tailed paired T-tests. rTPJ = Right Temporoparietal Junction, lTPJ = Left Temporoparietal Junction, pDMN = Posterior DMN, aDMN = Anterior DMN.

humans compared to non-human primates and the fact that it matures very late in human development [33]. Its role in reorientation of attention is also supported by clinical findings, namely that lesions of the rTPJ cause hemi-spatial neglect [34]. Interestingly our previously reported cognitive results show that the patient group had deficits in all specific tests of attention on the Cogstate® battery alongside more inconsistent deficits across a range of other cognitive modalities [16].

Whilst this study has many strengths, it also has several limitations. Firstly, the study only involved a small cohort of fifteen patients and requires replication in larger cohorts. It does however provide a proof of principle that structural and functional MRI changes can be used to identify deficits in patients previously admitted to BICU. Secondly, whilst the patient group was homogenous in terms of pathology and comorbidity, it is worth noting that there was significant heterogeneity in terms of the time between the burns injury and subsequent cognitive testing and neuroimaging. Thirdly, whilst the functional connectivity between rTPJ and pDMN correlated with cognitive performance, we cannot be sure that the functional connectivity deficits are causative in the cognitive deficits experienced by the patient group. Similarly, whilst it seems plausible that white matter changes in rTPJ, as suggested by decreased mean fractional anisotropy but preserved cortical thickness, may contribute to the functional connectivity deficit between rTPJ and pDMN, we also cannot be sure this is directly causative.

Table 1 – Summary of Demographic Information and Injury Profiles.

	Patients	Volunteers
Age	40.9 (14.1)	39.9 (12.9)
Sex	73% Male 27% Female	73% Male 27% Female
Charlson Comorbidity Index	0 (IQR 0-0.5)	0 (IQR 0-0)
International Standard Classification of Occupational Skill Level	SL1 (7%) SL2 (53%) SL3&4 (40%)	SL1 (0) SL2 (49%) SL3&4 (40%) Unclassified (20%)
National Adult Reading Test	108 (11.6)	116 (8.4)
Total Burns Surface Area	32% (IQR 30 – 40)	-
rBaux Score	78.8 (18.2)	-
Mechanism of Injury	Flame (80%) Scald (13%) Electrical (7%)	-
Site of Injury	Home (67%) Workplace (20%) Motorway (7%) Public Area (7%)	-

Data are presented as mean (standard deviation) unless otherwise stated

5. Conclusions

In this small exploratory cohort, we provide the first evidence of fMRI changes in patients previously admitted to BICU.

Indeed, it also represents the first evidence of fMRI changes in any cohort of patients with intensive care related long-term cognitive impairment. Future work should therefore focus on investigating whether structural and functional changes of the DMN can be identified in larger cohorts of patients previously admitted to BICU as well as patients previously admitted to general adult intensive care. If the same structural and functional deficits can be reliably identified, it could be instrumental in directing research into neuro-protective strategies to improve the long-term cognitive outcomes of future intensive care patients.

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CRediT authorship contribution statement

Stuart O'Connor: Formal Analysis, Visualization, Writing – Original Draft, Writing – Review & Editing. **Edward Watson:** Conceptualization, Methodology, Investigation, Project Administration, Writing – Original Draft, Writing – Review & Editing. **Matthew Grech Solars:** Investigation, Formal Analysis. **Mary Finnegan**: Investigation, Formal Analysis. **Lesley Honeyfield**: Methodology. **Rebecca Quest**: Methodology, Investigation. **Adam Waldman:** Methodology, Supervision. **Marcela Vizcaychipi:** Conceptualization, Methodology, Supervision, Project Administration.

Uncited references

[25]; [26].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Authors contributions

Study Conception: EW, MPV, Experiment Design: EW, MPV, LH, RQ, AW Patient Recruitment: EW, Cognitive Testing: EW MRI Data Acquisition: MGS, MF, RQ, AW, MRI Data Analysis: SO, MGS, MF, Writing of Paper: SO, EW.

Review of Paper and Proof Reading: All Authors.

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