Supplementary Online Content


eMethods. Supplementary methods

eTable. Comparison of neuropsychological performance between patients and controls

eFigure 1. Ten common resting-state networks identified in the ICA analysis of the resting-state fMRI data of all the subjects

eFigure 2. ROI locations used for seed-based connectivity analysis

This supplementary material has been provided by the authors to give readers additional information about their work.
Supplementary Methods

Principal components analysis of cognitive data

Principal component analysis (PCA) was implemented in PASW software. PCA is a dimensionality reduction method that enables a set of components to be extracted from a large amount of data, and where the first principal component accounts for as much of the variability in the data as possible (maximizing its variance).

PCA was used here to obtain a common factor of cognitive outcome. The variables introduced in the decomposition were the scores on the following neuropsychological tests: Letter-Number Sequencing; Digit Span Forward and Backwards; the Trail Making Test (TMT-A/B); the Rey Auditory Verbal Learning Test; the Rey-Osterrieth complex figure; Stroop reading, color-naming, and reading word-color conditions; verbal semantic and phonemic fluencies. The first principal component was used as the subject’s cognitive outcome and it accounted for 50.3% of the total variance in the neuropsychological data.

Amplitude of low frequency fluctuations in fMRI data

The amplitude of low frequency fluctuations (ALFF) was used to obtain a measure of the signal amplitude during resting fMRI in the frequency domain.\(^1\),\(^2\)

Prior to computing individual ALFF maps, resting fMRI data were preprocessed using tools implemented in AFNI (http://afni.nimh.nih.gov/afni) and FSL (http://www.fmrib.ox.ac.uk/fsl) software. These steps included motion correction, brain extraction, spatial smoothing with a Gaussian kernel of FWHM = 6 mm and grand mean scaling. A sample of the original fMRI data was also used to compute registration matrices between individual functional and MNI standard spaces, using a linear registration algorithm (FLIRT tool from FSL).\(^3\)

Resting-state data were then transformed to frequency domain with a fast Fourier transform (FFT) algorithm, thereby enabling us to obtain a 4D image in which each voxel contained the amplitude of the signal across the whole spectrum. Finally, individual ALFF maps were computed as the square root of the sum of the squares of the amplitude at each frequency point for each voxel within the frequencies of interest (0.01 - 0.1 Hz).
Before conducting group statistical analyses, ALFF maps were transformed into Z scores and moved to standard MNI space using the registration matrices obtained previously.

Finally, ALFF maps of all subjects were concatenated and introduced into a permutation-based group analysis using Randomise\textsuperscript{4} from FSL. In this analysis we tested for voxel-wise differences between groups using 5000 permutations. The size of significant clusters was selected using the threshold-free cluster enhancement (TFCE) method.\textsuperscript{5} Difference maps were finally thresholded using correction for family-wise error (FWE) with \( P < .05 \).

\textit{Resting state pre-processing and ICA analysis}

Independent component analysis (ICA), as implemented in MELODIC\textsuperscript{6} from FSL, was applied to the resting fMRI data in order to decompose the data into a set of independent components (ICs) that described common spatio-temporal and independent patterns of correlated brain activity across the whole group of subjects in the study. Before decomposition, fMRI data were preprocessed as follows: removal of the first five scans, motion correction, skull stripping, spatial smoothing with a Gaussian kernel of FWHM=6 mm, grand mean scaling, and temporal filtering (high-pass filter of FWHM=150 s and low-pass filter of FWHM=11.6 s). Functional scans were then registered to the MNI standard template using linear registration with 6 degrees of freedom.\textsuperscript{4} Resampling resolution was set to 4 mm. The number of ICs was then estimated using the Laplace approximation to the Bayesian evidence of the model order.\textsuperscript{6} Within all ICs obtained we identified the common resting-state functional networks,\textsuperscript{2,5,7} and specifically the default mode network (DMN). The selection procedure was performed by visual inspection together with template matching using data available online.\textsuperscript{2,5} Template matching was performed by means of spatial cross-correlation between pairs of maps.

The spatial map of the DMN was then introduced into a dual regression analysis.\textsuperscript{8,9} In this analysis the preprocessed functional data of each subject were first regressed against the spatial IC maps, yielding individual time series associated with the DMN. These time series were then used to regress again the individual preprocessed fMRI data and to obtain individual spatial maps. Spatial maps were finally tested for voxel-wise differences between groups using non-parametric testing with 5000 random permutations.\textsuperscript{4} After family-wise error (FWE) correction, differences with \( P < .05 \) were considered significant.
In all the regions that resulted significant in the comparison we extracted the DMN scores associated with each individual (patients and controls). These scores were further used to study the relationship between connectivity, structure and cognition.

**Seed-based analysis of the DMN**

The peak coordinates of the DMN identified by the ICA were used to create four spherical ROIs representing the main nodes of this network: medial prefrontal cortex (MPFC), precuneus/posterior cingulate (PPC), and left and right parietal cortices (left-PAR and right-PAR). Connectivity maps were created using a procedure similar to that described in Biswal et al. (2010).

For each seed (or DMN node) we used the preprocessed and MNI-registered resting fMRI data to extract seed time series as the average time series within all the seed voxels. Then, for each 4D dataset we obtained a connectivity map representing the correlation between the seed and each voxel in the brain. These maps were transformed into Z scores using Fisher’s r-to-Z transformation.

Finally, Z-maps were tested for voxel-wise differences between groups using non-parametric testing with 5000 permutations.\(^4\) Resulting maps were obtained directly in MNI standard space.

In all the regions of the connectivity maps where significant differences were found between groups, we extracted individual connectivity scores for further statistical analysis.

**Analysis of diffusion MRI data**

Diffusion MRI images were analyzed using FDT (FMRIB’s Diffusion Toolbox), a software tool for analysis of diffusion-weighted images included in FSL. Firstly, data were corrected for distortions caused by the eddy currents in the gradient coils and for simple head motion, using the B0 non-diffusion data as a reference volume. Fractional anisotropy (FA) maps from each subject were then obtained using a diffusion tensor model fit, and registered to MNI space.

A probabilistic tractography algorithm was also applied to the diffusion images. To this end, diffusion parameters were first estimated using the BEDPOSTX tool from FSL, which computes a Bayesian estimation of the parameters (i.e., diffusion parameters and local fiber directions) using sampling techniques and a model of crossing fibers.\(^{10,11}\) The density functions obtained were subsequently used
within PROBTRACKX from FSL to estimate connectivity between the two DMN ROIs (i.e., medial prefrontal ROI and posterior cingulate/precuneus ROI) extracted from the analysis of the resting fMRI data. Previous to tractography, these two ROIs were moved from standard MNI to individual diffusion space, using linear registration (FLIRT). Thus, the entire probabilistic tracking procedure was carried out in each subject’s diffusion space and further registered to the standard MNI template. Using the probabilistic tractography algorithm we obtained individual normalized maps in which each voxel value indicated the probability of having fibers connecting the two regions.

Finally, we computed the average connectivity map for the group of controls and the group of patients separately. The average connectivity map of controls was used, together with the registered FA maps, to estimate fiber integrity of this connection in the whole sample, as the mean FA within the pathway.

**Relationship between cognitive, structural and functional data**

The aim of this analysis was to study the relationship between the results obtained in all the above analyses and to determine how they are related to subjects’ cognitive outcome.
eReferences

eTable. Comparison of Neuropsychological Performance Between Patients and Controls

<table>
<thead>
<tr>
<th>Test</th>
<th>TBI group (mean/SD)</th>
<th>Control group (mean/SD)</th>
<th>Statistic t(p)</th>
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<tbody>
<tr>
<td>RAVLT learning</td>
<td>44.77 (±10.20)</td>
<td>56.14 (±5.22)</td>
<td>4.15 (&lt;.001)</td>
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<td>RAVLT (DR)</td>
<td>43.66 (±9.41)</td>
<td>57.45 (±3.24)</td>
<td>5.74 (&lt;.001)</td>
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<td>ROCF (DR)</td>
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<td>54.48 (±7.75)</td>
<td>2.80 (.008)</td>
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<td>Symbol Digit</td>
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<td>55.72 (±9.28)</td>
<td>3.70 (.001)</td>
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<td>TMTA</td>
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<td>44.81 (±6.31)</td>
<td>3.28 (.002)</td>
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<td>TMTB</td>
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<td>44.24 (±6.90)</td>
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<td>Digits forward</td>
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<td>53.21 (±10.62)</td>
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<td>Digits backward</td>
<td>46.60 (±8.21)</td>
<td>53.98 (±10.65)</td>
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<td>Semantic fluency</td>
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<td>52.74 (±8.14)</td>
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<td>Phonetic fluency (PMR)</td>
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<td>54.36 (±8.02)</td>
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<td>55.45 (±7.88)</td>
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<td>54.26 (±9.18)</td>
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<td>56.34 (±9.06)</td>
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<td>54.56 (±8.19)</td>
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</tbody>
</table>

TBI: traumatic brain injury; RAVLT: Rey auditory verbal learning test; DR: delayed recall; ROCF: Rey-Osterrieth complex figure; CPT: Conners’ Continuous Performance Test. Note: *T* values mean scores.
**eFigure 1.** Ten common resting-state networks identified in the ICA analysis of the resting-state fMRI data of all the subjects

**Common resting-state networks identified**

A. Visual medial

B. Visual occipital

C. Visual Lateral

D. Default Mode

E. Cerebellum

F. Sensorimotor

G. Executive control/salience

H. Auditory

I. Right fronto-parietal

J. Left fronto-parietal

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eFigure 2. ROI locations used for seed-based connectivity analysis